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**ABSTRACT BOOK**

*Organised By*



**Malaysian Society of Neurosciences**

Persatuan Neurosains Malaysia

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# Plenaries & Symposia

## PLENARY LECTURE 1

# Diagnosis and Pathology of Inflammatory Myopathies

*Werner Stenzel*

Idiopathic inflammatory myopathies are a group of diseases, clinically summarized as myositis.

During the past years, it has become evident that morphological phenotypes are more variable than described by those of the classical triade: dermatomyositis (DM), polymyositis (PM) and inclusion body myositis (IBM). Of note, these phenotypes describe clinical entities that may inform about prognosis and therapeutic decisions.

In addition, autoantibodies (aABs) can be associated with characteristic types of myositis. This 'association' of autoantibodies with a certain clinical phenotype and a 'morphotype' helps to classify myositis: The combination of clinical and morphological phenotype and the aAB profile allows for a precise identification of myositis subtypes.

This lecture summarizes what is known so far about morphological alterations, which are typical for certain disease entities, and which can therefore be used as biomarkers.

## PLENARY LECTURE 2

# Deficits in axonal transport in ALS and Charcot-Marie-Tooth disease models

**James N. Sleight<sup>1,#</sup>, Andrew P. Tosolini<sup>1,#</sup> and Giampietro Schiavo<sup>1,2,3</sup>**

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<sup>#</sup>equal contribution

Axonal transport is critical for maintaining neuronal homeostasis, function and survival through bi-directional trafficking of diverse organelles and protein complexes. This process has been found altered in several neurological diseases, including Alzheimer's disease (AD), peripheral neuropathies, such as Charcot-Marie-Tooth (CMT), and amyotrophic lateral sclerosis (ALS).

In particular, SOD1<sup>G93A</sup> mice, an established animal model of ALS, display deficits in in vivo axonal transport at pre-symptomatic stages, suggesting that the impairment of this process contributes to disease onset and neurodegeneration, and that rescuing these deficits may alleviate neuropathology. However, the molecular basis of these alterations is currently not known.

Neurotrophic factors mediate neuronal survival through local signalling at nerve termini and long-range signalling via retrograde axonal transport. Boosting neurotrophic factor signalling may thus represent a possible intervention to modify axonal transport and treat neurodegenerative conditions. Given the essential role of axonal transport in neuronal homeostasis, dissecting how neurotrophic factors influence cargo trafficking in healthy and diseased axons is crucial importance to further understanding the pathophysiology of neurodegenerative diseases and to develop effective therapeutic targets.

This presentation will focus on the pathomechanism of ALS and CMT and the complex relationship between these currently untreatable diseases and alterations in long range trafficking and signaling of neurotrophic factors. Our recent findings indicate that these diseases manifest through malfunctioning of the complex interplay between developmental, maturation and survival programs, which has important implications for the timing of effective therapeutic treatments.

**SYMPOSIUM 1 | Inflammatory Myopathy**

# Pathology and Pathogenesis of Sporadic Inclusion Body Myositis

*Werner Stenzel*

The sporadic form of inclusion body myositis (sIBM) is considered one of the most relevant inflammatory myopathies above 50 years of age in Europe and USA, although it is rather rare in some Asian countries.

The clinical presentation of the disease is a 'pure' muscle disease with an insidious onset of proximal leg/hip weakness and consecutive finger/wrist flexor as well as swallowing weakness that progresses slowly.

The pathological hallmarks comprise inflammation, mitochondrial changes, degenerative vacuolar alterations and a severe myopathic picture.

In addition to two prevailing concepts of inflammation and degeneration as basic causative players, some newer concepts have emerged that will be addressed during the lecture. These comprise T cell dysfunction and neoplastic features of so-called LGL lymphocytes, the viral etiology and the role of chaperone genes in pathogenesis.

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**SYMPOSIUM 1 | Inflammatory Myopathy**

# Childhood Inflammatory Myopathies

*Swee-Ping Tang*

Juvenile Idiopathic Inflammatory Myopathies (JIIM) are a heterogenous group of autoimmune muscle diseases in children characterised by muscle weakness and typical skin rashes. JIIM can be classified by clinical phenotypes into Juvenile Dermatomyositis (JDM), Juvenile Polymyositis (JPM), overlap myositis and clinically amyopathic JDM. The autoantibody profiles in children are also similar to adults apart from different proportions; and the commonest myositis specific autoantibodies in childhood are anti-p155/140, anti-MJ and anti-MDA5. Juvenile Dermatomyositis is the commonest JIIM in childhood (80%) and is characterised by typical skin lesions (Gottron's papules and heliotrope) with symmetrical proximal and axial muscle weakness. Additional features may include photosensitive rash (malar rash, shawl sign, extensor linear erythema), small vessel vasculopathy and complicated by calcinosis in 20-47%. Investigations include routine use of muscle enzyme measurement but these may be normal even in active disease. Magnetic resonance imaging (MRI) is a useful aid for diagnosis and for monitoring disease activity. Muscle biopsy should be done in all atypical cases of JDM especially in the absence of skin disease. Measurement of myositis-specific autoantibodies should be done whenever possible. Management should be multidisciplinary and treatment induction should include high dose corticosteroids (oral or intravenous) with methotrexate (MTX), in combination with sun protection and a safe exercise program. Mycophenolate mofetil (MMF) and ciclosporin A can be an option for those intolerant to MTX. Intravenous immunoglobulin may be a useful adjunct for resistant disease as is MMF. Intravenous cyclophosphamide should be considered for severe disease in particular for major organ involvement or extensive ulceration. For refractory disease, rituximab or anti-TNF can be considered.

**SYMPOSIUM 2** | Translational Medicine - Physiology and Therapeutics of Neuromuscular Disorders

## Recent Advances In Botulinum Toxin Therapy in the Neurologic Clinics

**Raymond L. Rosales, MD, PhD***Chair, University Hospital Dept. of Neurology&Psychiatry and Medical Faculty Professor, University of Santo Tomas, Manila, Philippines*

Translating to the clinics the rapidly advancing science of botulinum neurotoxins (BoNT) is as relevant in Neurologic practice. Among others, addressing the BoNT efficacy in muscular hyperactivity, new studies are geared toward formulating the toxin(s) to achieve faster onset and longer duration of action. While perhaps achievable, the associated BoNT adverse event(s) profile should be carefully watched. In Neurology, “stuck in the pharmacologic 3-4 month re-injection rule,” the current BoNT formulations are being re-assessed because of recent developments in spasticity and dystonia clinical trials. Abreast with “disease phenotyping” strategies, pain reduction in dystonia, spasticity has become a potential BoNT target. The effects of BoNT has reached strong recommendations for chronic migraine, and has been explored in neuralgias (trigeminal and post-herpetic) and myofascial pains. It is of specific neuromuscular interest that BoNT is currently being applied, not only in muscle spasms, but also in stiff-person syndrome and tremors, among others. The glandular efficacy, hinged on robust pharmacological autonomic effects of BoNT, are added into the “platter of BoNT application in Neurologic practice.”

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**SYMPOSIUM 2** | Translational Medicine - Physiology and Therapeutics of Neuromuscular Disorders

## Advances of the Basic Science of Gene Therapy in Muscular Dystrophy

**Shin'ichi TAKEDA, M.D., Ph.D.***Executive director**National Center of Neurology and Psychiatry, Tokyo, Japan*

There are progresses in gene therapy approaches to muscular dystrophy including Duchenne muscular dystrophy (DMD). DMD is the most common childhood genetic disease, affecting one among 5,000 newborn boys, causing progressive muscle weakness, heart and respiratory failure and premature death. This disease is caused by the mutations of the DMD gene, and there is no cure exists for this disease, but a number of promising new molecular therapies are being intensively studied. Exon skipping by antisense oligonucleotides (AOs) is a novel method to restore the reading frame of the mutated DMD gene, and rescue dystrophin expression. We have reported that systemic delivery of AOs targeting exon 6 and 8 of the canine DMD gene to CXMDJ, a dystrophin-deficient canine animal model, efficiently restored functional dystrophin proteins at the sarcolemma of these dogs, and improved phenotypes of affected dogs without serious adverse effects (*Ann Neurol.* 2009;65:667-76). We, then, optimized AO sequences, which allow exon 53 skipping of the human DMD gene, together with Nippon Shinyaku Co. Ltd. After numbers of toxicology study of the AOs, NS-065/NCNP-01, we carried an early phase clinical trial of exon 53 skipping among DMD patients, under the approval of Japanese Pharmaceutical and Medical Devices Agency (PMDA). The trial has been successfully completed as an investigator-initiated trial in NCNP hospital without serious adverse events. Following highly effective exon skipping detected by RT-PCR and dystrophin expression examined by immunofluorescence staining and Western blotting (*Sci Transl Med.* 2018), the AOs have been chosen as fast track for approval process both in Japan and in US, then phase I/II trial in Japan and phase II trial in US are carrying by either Nippon Shinyaku Co. Ltd. or NS Pharma, Inc. I would mention other advances in gene therapy approaches to muscular dystrophies in general.

**SYMPOSIUM 2 | Translational Medicine - Physiology and Therapeutics of Neuromuscular Disorders**

# Clinical Trials in Muscular Dystrophies

**J. Andoni URTIZBEREA, MD, MSc***Institut de Myologie, APHP, Filnemus  
PARIS - France*

Muscular dystrophies represent a heterogeneous group of neuromuscular disorders characterised by a dystrophic pattern on the biopsy and variable degrees of CK level elevation. Amongst them, Duchenne muscular dystrophy (DMD) is one of the most common, devastating genetic disorders in childhood. After several decades of ignorance and despair for both families, caregivers and scientists, the discovery, in 1987, of dystrophin, the defective protein causing the disease, has brought much hope to all. Although the function of the protein and its regulation remain only partially known, a great deal of advances have been made over the past fifteen years and are now being translated into therapeutic interventions. Three complementary, curative approaches have been used to tackle muscular dystrophy: gene therapies, cell therapy and pharmacology. Very few have reached the clinical stage yet but their rationale and the potential for clinical applications sound more and more exciting.

Ataluren, for instance, is a molecule developed by PTC Therapeutics exclusively targeting patients with stop mutations in the DMD gene (that is some 13% of the total DMD pool of patients). This drug was approved both by FDA and EMA and is now marketed in a growing number of countries. Another approach is based on antisense oligonucleotides susceptible to generate a therapeutic exon skipping. Only one of them, eteplirsen, is officially approved and sold by Sarepta Therapeutics in the US. Many other promising approaches are still in the pipeline and will lead to another series of clinical trials. Among these, delivery of a functional micro-dystrophins by means of a recombinant adeno-associated viral vector looks very promising.

Nevertheless, many challenges are all stakeholders, clinicians, patients and payers: the quality of some clinical trials, the modest efficacy of all these medications and above all the limitations in access.

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**MSN CHAPTER SYMPOSIUM | Stroke**

# Stroke Classification and Localisation

**Dr Khairul Azmi Ibrahim**

Stroke can be classified into two main types: ischaemic or haemorrhagic stroke. These two main classification allow further classification into subtypes. Several phenotypic and aetiological ischaemic stroke classification have emerged during the last three decades to permit comparison of results in stroke researches and for assessing prognosis and for optimizing stroke treatment. The Oxfordshire Community Stroke Project (OCSP) stroke classification and the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) stroke classification remains the two most popular ischaemic stroke classification. However, both ischaemic stroke classification is far from perfect. This is partly due to the fact that stroke is a heterogenous disease with more than 150 causes. And the aetiology of ischemic stroke is often multifactorial and therefore an ideal ischemic stroke classification should both comprise all underlying pathologies that could potentially concur to an index event and emphasize the most likely etiological and pathophysiological mechanism. This lecture discuss the commonly used ischaemic stroke classifications and how it can help doctors to better understand the pathophysiology of stroke and help them with the therapeutic decision making in daily practice.

## MSN CHAPTER SYMPOSIUM | Stroke

# Non-Vitamin K Antagonist Oral Anticoagulants for the secondary prevention of Ischemic Stroke: In the Perspective of Neurologist

**Associate Professor Dr. Hoo Fan Kee**

Neurology Unit,

Department of Medicine,

Faculty of Medicine and Health Sciences

Universiti Putra Malaysia, Serdang, Malaysia

Atrial fibrillation is the leading complication for ischemic stroke. 20% of the patients suffered from a permanent disability. Oral anticoagulant is indicated for non-valvular atrial fibrillation if CHA<sub>2</sub>DS<sub>2</sub>-VASc  $\geq 2$  in a male, 3 in a female. NOAC is recommended in preference to a VKA if the patient is eligible for NOAC. The evidence is limited with regards to the timing to start OAC post stroke as the No prospective studies are available. Patients with a TIA or stroke within the past 7–30 days were excluded from the randomized NOAC trials. ESC AF 2016 guidelines recommended the rule of '1-3-6-12 day rule' for initiation of OAC in a post-stroke patient.

## MSN CHAPTER SYMPOSIUM | Stroke

## Acute Stroke Management

**Law Wan Chung**

### Presentation 1

Stroke is commonest neurological condition which causes significant morbidity and mortality. Stroke incidence is increasing particularly in developing country such as Malaysia. Acute stroke management with reperfusion therapy is the most effective treatment for acute ischemic stroke (AIS). However, it is not widely available in developing country.

Recent advances in perfusion therapy for AIS increases reperfusion treatment window and improves outcome. Patient selection with appropriate neuroimaging allows more patients to access the therapy.

Reperfusion treatment for AIS is important and effective aspect of stroke management. Every AIS patient should be offered reperfusion therapy as a standard of care.

### Presentation 2 (Case presentation is by Dr Zaw Win Moe, my physician)

A patient with advance cancer whom became confuse and stuporous during admission associated with some jerky movement.

## MSN CHAPTER SYMPOSIUM | Neuroimmunology and Neuroinfection

# Neurometabolic Disorders

*Prof Datin Dr Norlinah Mohamed Ibrahim*

Neurometabolic neurological disorders are neurological syndromes associated with metabolic disturbances either due to genetic mutations or acquired. The acquired neurometabolic disorders are the consequence of biochemical disturbances affecting various parts of the brain, particularly the basal ganglia and other vulnerable structures within the brain. These syndromes are often partially reversible, depending on the aetiology. Typical examples include hyperglycaemic hyperosmolar state (HHS) and osmotic demyelination syndrome. The genetic neurometabolic syndromes are heterogeneous disorders characterized by genetically caused metabolic defects which give rise to neurological and psychiatric manifestations. They typically present in infancy, childhood or early adulthood. Clinical presentation may be acute or insidious onset and may have episodic or paroxysmal presentation such as the monoamine metabolism disorders (Dopa Responsive Dystonia), GLUT1 deficiency and Pyruvate dehydrogenase deficiencies. Recognizing and identifying these genetic neurometabolic syndromes can be challenging, as their phenotype is rather heterogeneous, with mixed movement disorders. The age of onset, the clinical manifestation and the presence of imaging findings may help in accurately identifying and treating these conditions. Wilson's disease, a metal storage disorder due to abnormal copper metabolism should be recognized and treated appropriately to prevent long term sequelae. Recognizing the unique phenotypic features will enable accurate diagnosis, such as the diurnal fluctuation of dopa responsive dystonia, the paroxysmal episodic events in GLUT1 deficiency, dystonic ophistotonus of PKAN and predilection for oromandibular involvement in Wilson's disease and PKAN. This lecture will focus on both acquired and genetic neurometabolic syndromes, with focus on treatable ones, such as Wilson's disease.

## MSN CHAPTER SYMPOSIUM | Epilepsy

# Is it Epilepsy?

*Raymond Azman Ali*

Several paroxysmal disorders may mimic epileptic seizures, and the converse may also occur. Examples of epileptic seizures that may be misdiagnosed as non-epileptic events include frontal lobe and temporal lobe seizures, visual and auditory epileptic auras and non-convulsive status epilepticus. Such events may look like pseudoseizures, psychotic disorders and unexplained coma, respectively, to the inexperienced physician. An epileptic seizure can be defined as an intermittent, stereotyped disturbance of consciousness, behaviour, emotion, motor function, perception or sensation that on clinical grounds results from cortical neuronal discharge. Epilepsy is a neurological disorder characterised by two or more epileptic seizures occurring more than 24 hours apart. Vasovagal attacks occur in the presence of a clear precipitating factor such as pain, emotional stress and crowded areas. They are usually preceded by light-headedness, nausea, ringing in the ear and the vision "going black". Various epileptiform clinical phenomena (e.g. tonic spasms, myoclonic jerks and automatisms) may accompany vasovagal attacks and simulate epileptic seizures. Cardiac syncope is also commonly associated with myoclonic jerks. The diagnosis of psychogenic non-epileptic seizures is now facilitated by video-EEG monitoring. The attacks are seldom stereotyped and are modified according to the relevance or importance of the audience. There is usually no or little post-ictal confusion and drowsiness. Urinary incontinence and self-injury, including tongue biting do not exclude the diagnosis. Tics and other movement disorders may also mimic epileptic seizures. Focal seizures with or without loss of awareness, on the other hand, may mimic pseudoseizures. A good history obtained from a reliable eyewitness is the cornerstone to the diagnosis of epileptic seizures.

## MSN CHAPTER SYMPOSIUM | Epilepsy

# The Staring Child

*Dr Ahmad Rithauddin*

The child with staring episodes is a frequent encounter in the paediatric clinic. Absence seizure is often suspected, but eventual diagnosis of focal seizures with impaired consciousness and non-epileptic staring are not infrequently made. Children with typical childhood absence epilepsy display characteristic seizure semiology and EEG changes, and share similar neurocognitive profile, response to treatment and long term prognosis. Other forms of epilepsies with absence seizures show more variable features, and may require longer treatment. Advances in genetics, electrophysiology and functional imaging have resulted in a better understanding of the pathophysiology of absence seizures, but these have not yet translated into better treatment modalities.

## MSN CHAPTER SYMPOSIUM | Epilepsy

# Treatment of Epilepsy

*Lim Kheng Seang*

Correct diagnosis and classification of epilepsy are the keys for successful treatment in epilepsy. First part of the lecture will be on how to choose and start the first antiepileptic drugs (AEDs) appropriately, based on literatures and personal experiences. Second part will be on refractory epilepsy, which is defined as failure of seizures to response to two or more AEDs at optimal dose. It is estimated that 30-40% of people with epilepsy will be refractory. There are many causes of refractory epilepsy, including misdiagnosis, wrong choice of AEDs, inadequate dose of AEDs and underlying pathology. An attempt to reassess the diagnosis and excluding non-epileptic causes, e.g. syncope and psychogenic seizures, should be done. A trial of AEDs at its optimal dose is essential unless the patient develops intolerable side effects. Suitable patients can be referred for newer AEDs and drug trial. For those with refractory focal epilepsy, curative epilepsy surgery might be an option, and thus necessitate referral for pre-surgical evaluation. A seizure freedom rate of 50-70% can be achieved with epilepsy surgery.

**PLENARY LECTURE 3**

# What I have Learnt from Muscle Research – Important Discoveries and Progress in Myology

**Ikuya Nonaka, MD***National Center of Neurology and Psychiatry, Tokyo, Japa*

Around 50 years ago, Japanese Government started to set up “the muscular dystrophy units” in 27 national hospitals to educate and provide medical care to children. When I joined one of the Hospitals, about 80 patients were admitted: most of them were undiagnosed. I started muscle biopsies and delivered them to NCNP for histochemical analysis. There were many problems to get good sample to make a diagnosis.

The best way for muscle biopsies and tissue preparation is illustrated in [https://www.ncnp.go.jp/nin/guide/r1/video\\_e.html](https://www.ncnp.go.jp/nin/guide/r1/video_e.html)

I would discuss what I have learnt from muscle pathology research

- 1) Fixation  
Dip the sample quickly in isopentane cooled by liquid nitrogen or in mixed solution of dry ice and acetone; SHAKE the tissue in solution for 1 min.
- 2) ATPase staining  
Try pre-incubation solution at various pHs (pH 10.5, 10.6, 10.7, 10.8 10.9 and 11.0) , (pH 4.7, 4.6, 4.5, 4.4, 4.3 and 4.2)
- 3) PAS (periodic acid Schiff) staining for glycogen  
Since glycogen particles are washed out during staining for frozen section, please use Epon embedded section,
- 4) Electron microscopy (EM)  
An important way to know pathogenetic mechanism (!),  
Electro-cytochemistry (cytochrome C oxidase: COX EM)
- 5) Detail clinical information is necessary  
Muscle MRI/CT
- 6) Muscle tissue repository

**PLENARY LECTURE 4**

# The role of Muscle Biopsy in the Era of Next Generation Sequencing

**Rahul Phadke**

The advent of Next Generation Sequencing (NGS) technology allows for large-scale genome-wide sequencing that has dramatically accelerated new gene discovery in rare diseases including neuromuscular disorders. There is an ever-increasing transition from implementation of NGS in research laboratories to routine clinical genetic diagnostic laboratories due to availability of robust and reliable sequencing and gene-targeting technologies. This has brought into sharp focus a reappraisal of the current and future role of the muscle biopsy, which for decades has been employed for pathological disease characterisation based on characteristic morphological and protein abnormalities and in directing molecular genetic testing. Of the various NGS approaches, targeted gene panels or virtual gene panels following Whole Exome Sequencing (WES) interrogate groups of disease-causing neuromuscular genes known at the time. Efficient design and implementation of these panels relies on deep phenotyping including well-characterised muscle pathology. Interpretation of new variants identified in one or more known disease-causing genes is aided by the clinicopathological context, and a biopsy can provide tissue for additional functional characterisation including protein studies and mRNA sequencing to understand consequences of splicing variants. Evaluation of archival biopsy material of patients and/or other affected family members can be invaluable in directing NGS gene-panel testing and in interpretation of variants found therein. Muscle pathology may provide crucial evidence for correct disease classification in scenarios of discrepant findings from WES and historical linkage analysis. Muscle biopsy remains an essential tool in the investigation of acquired/inflammatory myopathies and mitochondrial diseases. Bioinformatic tools and in vitro functional analyses are not always reliable tests of variant pathogenicity. Identification of other patients and families with similar disease and mutations in the same gene is essential for validating pathogenicity of novel genes. In this context, deep pathological phenotyping may identify novel muscle pathology signatures, which can then be used to screen biopsies of molecularly undiagnosed cases with similar, previously unrecognised findings. In the future, muscle biopsies are likely to retain a role, largely in variant interpretation of known and novel genes, and evaluation of outcome measures in clinical trials of gene-based therapies for neuromuscular disorders.

**SYMPOSIUM 3 | Paediatric Neuromuscular Diseases**

# Neuromuscular Junction Disorders - Clinical Aspects and Management

**Andrew J. Kornberg***Department of Neurology, Royal Children's Hospital, Parkville Australia*

Neuromuscular junction disorders in childhood are uncommon and include the congenital myasthenic syndromes, as well as autoimmune myasthenia gravis (MG). They may present with fluctuating diplopia, ptosis, gaze paresis and weakness. Complications can include gross motor delay, poor posture, secondary orthopaedic complications, withdrawal from activities, psychological disturbance and respiratory crises.

Autoimmune myasthenia gravis (AMG) has a distinct pathogenesis from transient neonatal myasthenia and the array of congenital myasthenic syndromes (CMS) due to presynaptic, synaptic basal lamina and post-synaptic defects. Onset in infancy, less diurnal fluctuation, positive family history and acetylcholine receptor antibody (AChR) negativity are useful features in distinguishing CMS from AMG.

Autoimmune MG in childhood can be difficult to diagnose as the symptoms can vary greatly and investigations such as repetitive nerve conduction studies and single fibre EMG may be difficult to perform. Acetylcholine receptor antibodies are more frequently negative in childhood in comparison to adults. Children, as adults, are usually treated with immunosuppression but these may have risks in the developing immune system. Thymectomy is used in childhood but special considerations are necessary.

This lecture will detail the presentation, the diagnosis and the therapy of the various neuromuscular disorders including myasthenia gravis and will review the clinical aspects and therapy of these disorders.

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**SYMPOSIUM 3 | Paediatric Neuromuscular Diseases**

# Spinal Muscular Atrophy (SMA) - Update and Treatment

**Yuh-Jyh Jong***College of Biological Science and Technology, National Chiao Tung University, Hsinchu, Taiwan Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan  
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Chung-Ho Memorial Hospital, Kaohsiung, Taiwan*

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative disorder characterized by motor neuron dysfunction resulting in generalized hypotonia and muscle weakness. SMA is caused by deletion and mutation of survival motor neuron 1 (SMN1) gene leading to widespread decreased SMN protein level. A SMN1 copy gene and SMA modifier, SMN2, is intact in all SMA patients but contains a C-to-T variation in exon 7 that affects a splice enhancer and determines exclusion of exon 7 in the majority of its transcript, leading to an unstable protein that cannot compensate for full-length SMN protein. To date, SMA is the leading genetic cause of infant mortality in the world.

A consensus statement on SMA standard of care (SOC), has been widely used throughout the world since 2007. Those SOC recommendations have been updated in 2018 to cover 8 areas for multidisciplinary care including the diagnostic and genetic counseling, pulmonary, acute care management in the hospital setting, orthopedic (spinal curvature, joint contractures, fractures), physical therapy and rehabilitation, gastrointestinal and nutrition, other organ systems involved in SMA, ethical considerations and palliative care.

In the past decade cross-professional investigators have identified different SMN- dependent therapeutic approaches including SMN2 ISS-N1 targeting antisense oligonucleotides, SMN2 targeting small molecules, and gene therapy that show promise in treating SMA. Until recently FDA has approved nusinersen, the first treatment drug for children and adults with SMA in US (December, 2016). However, careful analysis of SMA animal models and patients has revealed some limitations that need to be taken very seriously, including a limited time-window for successful therapy delivery, making newborn screening (NBS) of SMA mandatory.

In this presentation, we will outline the updated SMA treatment strategies and NBS that are currently developing in new SOC and therapeutic era.

## SYMPOSIUM 3 | Paediatric Neuromuscular Diseases

# Pitfalls in Muscle Biopsy Diagnosis of Paediatric Neuromuscular Disorders

**Rahul Phadke**

Muscle biopsy is a key tool in the investigational algorithm for patients with suspected neuromuscular disease. It is essential to recognise a number of pitfalls and limitations of establishing a biopsy diagnosis. A key, yet under-recognised factor adversely affecting diagnostic yield is improper sampling, handling, processing and staining of samples causing tissue wastage and uninterpretable findings. Formalin fixation adversely affects morphology, enzyme histochemistry and protein immunohistochemistry. Delayed freezing of samples can cause spurious loss of respiratory chain enzyme activity, particularly complex IV. Application of antibodies for protein immunoanalysis without knowledge of characterisation, quality control and developmental expression may result in false-positive and false-negative interpretations. Fetal and perinatal samples should be interpreted with caution. Given the overlapping gene-phenotype associations in inherited congenital primary neuromuscular diseases, interpreting muscle morphology without knowledge of the clinical phenotype and investigations can be misleading. Structural abnormalities such as cores are non-specific and can occur in neurogenic, metabolic and myasthenic diseases in addition to congenital core myopathies. Significant overlap may be seen in congenital muscular dystrophies with secondary inflammation and paediatric-onset immune necrotising myopathies with dystrophic changes in biopsies. Pathology in myofibrillar/protein aggregation myopathies can be remarkably patchy. Distinction between myopathic versus neurogenic fibre-type grouping can be challenging in biopsies from proximal sites especially in cases of distal SMA. Specific structural pathology in congenital myopathies can evolve over time and be absent in younger biopsies. A histologically normal biopsy does not exclude a neurometabolic/mitochondrial/myasthenic defect. Failure to recognise the milder end of the phenotypic spectrum, update the knowledge of extending phenotypes in known genes and those associated with novel genes are causes of missed diagnoses. To avoid serious misdiagnoses and maximise diagnostic yield that can contribute in directing molecular genetic testing, it is essential to review the biopsy findings in a multidisciplinary set up.

## SYMPOSIUM 3 | Paediatric Neuromuscular Diseases

# Pompe Disease in China: A Report from the Pompe Registry

**Yuying Zhao<sup>1</sup>, Zhaoxia Wang<sup>2</sup>, Jiahong Lu<sup>3</sup>, Xuefan Gu<sup>4</sup>, Yonglan Huang<sup>5</sup>, Zhengqing Qiu<sup>6</sup>, Yanping Wei<sup>6</sup>, Chuanzhu Yan<sup>1</sup>**

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**Background** :Pompe disease is a rare, progressive, autosomal recessive lysosomal storage disorder caused by mutations in the acid  $\alpha$ -glucosidase gene (GAA). This is the first report of Chinese patients from the global Pompe Registry. Chinese patients enrolled in the Registry (ClinicalTrials.gov, NCT00231400) between Jan 2013 and 2 Sep 2016 were included and grouped by infantile onset (IOPD; onset of disease at age  $\leq$ 12 months with cardiomyopathy), or late onset (LOPD; presentation after 12 months of age or presentation at  $\leq$ 12 months without cardiomyopathy) Pompe disease. Data analyses were descriptive. Results: Of the 78 Chinese patients included, 84.6% had never received enzyme replacement therapy (ERT). For IOPD (n=5), age at symptom onset and diagnosis was 3.3 (SD=1.67) and 6.1 (2.15) months, and for LOPD (n=59) was 14.9 (12.35) and 22.1 (10.08) years, which is younger than LOPD patients from the rest of the world (28.4 [18.86] and 34.9 [20.03], respectively). The most common diagnosis methods for LOPD were enzyme assay (79.7%) and/or DNA analysis (61.0%). Chinese LOPD patients appeared to have worse lung function versus patients from the rest of the world, indicated by lower forced vital capacity (37.2 [14.00]% vs. 63.5 [26.71]%) and maximal expiratory and inspiratory pressure (27.9 [13.54] vs. 51.0 [38.66] cm H<sub>2</sub>O, and 29.4 [12.04] vs. 70.5 [52.78] cm H<sub>2</sub>O). Conclusions: Compared with patients from the rest of the world, Chinese patients with LOPD appeared to have younger age at symptom onset and diagnosis, lower lung function, and the majority have not received ERT.

**MSN SYMPOSIUM | Neurology in Internal Medicine-Case Presentations**

# Osmotic Demyelination Syndrome

**Dr. Yuen-Kang Chia**

Osmotic Demyelination Syndrome (ODS) is a devastating condition which can lead to severe neurological deficits and even mortality. Classically it is caused by rapid over correction of hyponatremia. However, many has reported that ODS can occur in conditions without rapid sodium correction and with normal or even hypernatremia. Theoretically it can be prevented but in real life it still can occur with careful preventive measures. Once it has occurred, supportive care is the mainstay of treatment. However, there are reports on methods to reduce the damage, by re-lowering the sodium, usage of steroid, IVIG and plasmapheresis.

Here I would like to share the experience in treating 5 cases of ODS from Hospital Queen Elizabeth, Kota Kinabalu, Sabah.

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**MSN CHAPTER SYMPOSIUM | Basic Neurosciences Symposium**

# Stripes and Tremors: Modelling Parkinson's in Zebrafish

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Zebrafish are a popular research model due to their genetic similarity with humans. Humans and zebrafish share around 70% of the same genes, while 84% of human genes known to be associated with human disease have an ortholog gene in zebrafish. Zebrafish embryos develop externally, and due to the embryos being transparent, along with their short development time, their genetic makeup can be easily manipulated and their subsequent changes and perturbations can be observed.

One research area into human disease that benefits from these zebrafish qualities is Parkinson's Disease. Parkinson's Disease (PD) is a chronic, age-related progressive neurodegenerative disorder that results in movement disorders such as involuntary tremors and dystonia. Our lab utilizes toxin models, morpholino knockdowns and transgenic zebrafish to help us model and understand PD. The toxin models involve immersing zebrafish larvae in water containing either methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or Rotenone. Gene expression profiles after MPTP and rotenone exposure showed changes in th1, gfap, and sod2 levels suggestive of neurodegeneration consistent with PD. MPTP and rotenone exposure was also shown to affect th-positive cell numbers in the diencephalic region of the zebrafish larval brain which is homologous to the human substantia nigra.

Neurotrophic factors are associated with degenerative conditions such as PD. To help us decipher the roles of neurotrophic factors in PD, neurotrophic factor genes were knocked down using oligonucleotide morpholinos. Recently, Tg(dat:EGFP) zebrafish have also been utilized to visualize dopaminergic neurons in live larvae to record neuronal changes in response to neurotoxins and gene knockdowns.

## MSN CHAPTER SYMPOSIUM | Basic Neurosciences Symposium

# Neurodegenerative Diseases: A Central Role of the Blood-Brain Barrier

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Blood-brain barrier (BBB) formed by cerebral microvascular endothelium regulates molecular exchange between blood-brain interface, providing optimum microenvironment for neuronal function, and acts as brain's first line of defence. BBB dysfunction is associated with pathologies of the central nervous system (CNS), seen either as a cause or consequence of neurological disorders. One event which is linked to neurodegeneration is cerebral hypoperfusion. The damaging effects of cerebral hypoperfusion on the BBB have not been well-documented. Here, we sought to understand the BBB function in cerebral hypoperfusion using two-vessel occlusion rat model. Spatiotemporal profiling of the BBB permeability to exogenous tracers demonstrated a marked extravasation of Evans blue dye in the frontal cortex, posterior cortex and thalamus-midbrain following induction of cerebral hypoperfusion, indicating vulnerability of these brain regions towards hypoxia insult. Ultrastructural analysis reveals damages to cerebral microvascular endothelial cells and astrocytes reflected from increased pinocytotic vesicles and formation of membrane invaginations in the endothelial cells and swelling of the astrocytes' end-feet. Proteins that are involved in mitochondrial energy metabolism, transcription regulation, cytoskeleton maintenance and signalling pathways were found to be differently expressed on cerebral microvessels. Having demonstrated the involvement of the BBB in cerebral hypoperfusion which is the common initiating factor for the development of neurological disorders, this shows that not only the BBB needs to be taken into account in CNS drug delivery strategies, it is also a therapeutic target in its own right. The underlying logic is that if BBB dysfunction can be reduced, halted or reversed, this could be valuable therapy in conditions in which neuronal damage is secondary to, or exacerbated by, BBB damage.

## MSN CHAPTER SYMPOSIUM | Basic Neurosciences Symposium

# Rodent Model of Chronic Ethanol

**Jaya Kumar Murthy**

To date, various chronic alcohol rodent models have been experimented to mimic human condition of alcoholism. Liquid diet technique is one of the most relevant methods that could induce behavioural and biochemical changes comparable to chronic alcoholism, which include marked increase in blood ethanol level and manifestation of withdrawal symptoms upon cessation of ethanol intake. In line with this objective, we have formulated a modified liquid diet (MLD) containing low fat cow milk powder, maltodextrin, sucrose and ethanol, which was fed to male Wistar rats for 28 days. For the first 7 days, MLD without ethanol was given, and from day 8-27, ethanol was gradually introduced (2.4 % for 3 days, 4.8 % for 3 days and 7.2 % for 14 days). On day 28, ethanol was withdrawn from the diet to manifest abstinent-related physical symptoms and assessed for 12 hours. Parameters such as serum ethanol level, daily ethanol intake and changes in body weight was assessed as well. We noticed marked increase in manifestation of various withdrawal symptoms such as agitation, tremors, abnormal gait, stereotyped behaviours and tail stiffness during the 12 hours of abstinence observation period. Administration of acute ethanol (2.5 g/kg, 20 % v/v) profoundly attenuated the withdrawal score. Ethanol withdrawal-induced hypolocomotion also was seen in animals when tested in open field. Upon molecular investigations, we found significant increase in protein and gene expressions of glutamate receptor such as metabotropic glutamate receptor subtype 5 (mGlu5) which denotes central hyperexcitability during the withdrawal state.

## MSN CHAPTER SYMPOSIUM | Basic Neurosciences Symposium

# Neurobiology of Kratom on abuse liability

**Zurina Hassan<sup>1</sup>, Nurul H.M. Yusoff<sup>1</sup>, Sharif M. Mansor<sup>1</sup> and Christian P. Muller<sup>2</sup>**

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Mitragyna speciosa Korth or Kratom has some promising results to be developed for the treatment of opioid dependence. The major active constituent of kratom, mitragynine is also taken as a pure preparation or as an ingredient of 'legal' or 'herbal high' preparations in the western world. Here, we describe abuse liability of mitragynine tested using conditioned place preference (CPP) procedure and potential neural pathways associated with mitragynine rewarding properties. An unbiased 3-chamber CPP paradigm was employed, which consisted of 3 phases; pre-conditioning (2 days), conditioning (8 days), and CPP test. Pre-conditioning test was performed to assess initial individual preference for each CPP chamber. Groups of rats were conditioned with mitragynine (10 mg/kg), combination of mitragynine and naloxone (0.1, 0.3 and 1.0 mg/kg) or baclofen (1.25, 2.5 and 5.0 mg/kg) or vehicle paired with a distinctive chamber. On alternating days, rats were given vehicle and paired with another distinctive chamber. After 8 conditioning sessions, they were given a preference (CPP) test with full access to the entire apparatus under the influence of either naloxone, baclofen or vehicle. Mitragynine-conditioned animals showed CPP as demonstrated by an increased amount of time spent in the drug-associated chamber during CPP test relative to pre-conditioning test. Rats given both naloxone and mitragynine during conditioning did not exhibit CPP. In contrast, mitragynine-conditioned animals given naloxone on the CPP test day produced CPP. These findings indicate that naloxone blocks the acquisition, but not the expression of mitragynine-induced CPP. The administration of baclofen (2.5 and 5.0 mg/kg) 30 min prior to mitragynine injection inhibited the acquisition of mitragynine-induced CPP. In addition, the administration of baclofen (2.5 and 5.0 mg/kg) to the mitragynine-conditioned animals 30 min prior to the CPP test blocked the expression of CPP responses. These findings showed that activation of GABAB receptors by baclofen suppressed the acquisition and expression of CPP effects produced by mitragynine. Mitragynine-induced CPP effects are dependent on the activity of opioidergic and gabergic systems during acquisition and expression phases.

Paper Number: 32

## Two Cases of Laminopathy (LMNA) Presenting with Variable Phenotypes

*Kiran Polavarapu*

Case 1:

Clinical findings: A 38-year-old man, born to consanguineous parents presented during March 2016 with weakness and thinning of right lower limb with altered gait from early childhood and congenital right ankle contracture. The illness was non-progressive till 33 years of age when he developed mild progressive weakness of left upper limb and generalized loss of muscle mass. Patient also has palatopharyngeal weakness with cataracts. There was premature loss of all teeth over last 5 years. Examination revealed a slender habitus, complete heterotopia, bat ears, edentulousness, frontal greying of hair. Serum CK was mildly elevated (362 IU).

Muscle MRI: Asymmetrical fatty infiltration of Vastii and posterior thigh muscles with sparing of rectus femoris and hypertrophy of Gracilis and Sartorius, Severe fatty infiltration of Soleus and medial Gastrocnemius.

Muscle biopsy: Myopathic features with rimmed vacuoles, intracytoplasmic inclusions with protein aggregates on MGT, and also stained faintly for Desmin.

Genetics: LMNA gene heterozygous frameshift mutation in exon 2: c.369delG;p.E124Rfs\*3 (Novel pathogenic).

Case 2:

Clinical findings: A 20-year-old man diagnosed to have dilated cardiomyopathy for 5 years was evaluated during June 2016. From the same time he noticed progressive limb girdle weakness along with bilateral foot drop and low back and neck stiffness with difficulty in bending forwards and difficulty in raising his head off the bed. Examination revealed a thin built man, mild bifacial weakness, mild left sided ptosis, nuchal and spine rigidity, asymmetrical scapular winging, wasting of arm and shoulder muscles with foot drop gait. Tendon reflexes were absent except for sluggish ankle jerks. CK was 2070 IU/L.

Muscle MRI: Lower limb muscles showed severe involvement of posterior thigh and adductor muscles, sparing of rectus femoris, gracilis and sartorius, severe affection of posterior leg muscles with tibialis anterior.

Muscle biopsy: Biceps muscle showed Variation in fibre size, rounding and internalized nuclei, numerous fibres showed presence of vacuoles containing basophilic material, atrophic fibres with clumped nuclei, mild fibrosis, certain vacuoles were rimmed by red granular material. The basophilic material were unstained on HE. A few moth eaten fibres were present.

Genetics: LMNA gene heterozygous missense mutation in exon7:c.G1318A;p.V440M (reported pathogenic).

Paper Number: 46

## Girl With Myopathy and Cardiomyopathy

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Case Report

A 13 year old girl born to consanguineous parentage with normal developmental milestones presented with bilateral ptosis since birth. It was non progressive, non-fluctuating till 10 years of age. For last 3 years, there was progressive worsening in ptosis. History of failure to thrive from birth and following an episode of fever, developed exertional dyspnea and pedal edema for which she was diagnosed to have dilated cardiomyopathy. She had respiratory insufficiency. No family members had any similar illness. On examination, she had thin slender habitus, elongated facies, high arched palate, hypermobility of distal joints. She had right precordial bulge, heaving apical impulse and bilateral inspiratory crackles. She had bilateral ptosis, full extraocular movements except terminal restriction. She also had jaw weakness and facial weakness. There was generalized hypotonia of all limbs with winging of scapula. The neck had contractures, and the flexor power was 3/5 (MRC grading). The upper limb proximal and distal power was 4+/5 except finger extensor-3+. Power in the lower limbs was 4+ and the dorsiflexion was 4/5. All the deep tendon reflexes are sluggish. She had a mild waddling gait. The creatine kinase was 347 U/L. Lactate- 16.1U/L. The liver enzymes were elevated (Alkaline phosphatase- 277 U/L; SGOT- 245 U/L; SGPT- 196 U/L). The nerve conduction studies and evoked potentials were normal. There was no decrement on repetitive nerve stimulation. Muscle biopsy of the tibialis anterior revealed myopathic features with subsarcolemmal granular deposits, vacuolated fibers with red stained inclusion bodies and occasional rimmed vacuoles on modified Gomori stain. The vacuolated fibers were negative for PAS, DESMIN, MAG and few COX deficient fibers. There was no deficiency of all four complexes by mitochondrial assay studies. Electron microscopy revealed distortion of myofilamentous pattern, presence of small rods and subsarcolemmal Z-band aggregates. Genetic testing in the proband revealed a novel homozygous nonsense pathogenic mutation in DES gene [NM\_001927] in exon 1 c.C448T p.R150X. After 6 months of follow up, the child developed acute bullous lesions in the right chest, sepsis followed by cardiac failure and death.

Paper Number: 48

## A 7-Month-Old Boy with Motor Development Delay and Hypotonia

**Wen-Chen Liang<sup>1</sup>, Li-Wen Chen<sup>2</sup>, Min-Ling Hsieh<sup>2</sup>, Yi-Shan Tsai<sup>3</sup>, Yuh-Jyh Jong<sup>1,4,5</sup>**

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*Departments of Pediatrics<sup>2</sup> and Diagnostic Radiology<sup>3</sup>, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan*

*<sup>5</sup>Department of Biological Science and Technology, College of Biological Science and Technology, National Chiao Tung University, Hsinchu, Taiwan*

A 7-month-old baby boy was referred to the hospital due to delayed motor milestone and failure to thrive. His body weight gain stopped since age 5 months and he remained 6 kg weight since then. Physical examination showed cardiac heaves, hypotonia and mild tachypnea. He presented with head lag and could not roll over at age 7 months. Chest x-ray revealed cardiomegaly so that complete cardiac survey was done and suggested dilated cardiomyopathy. Due to hypotonia, weakness and slightly elevated CK level, muscle biopsy was done and showed excessive lipid accumulation in muscle fibers. Metabolic profiling was done and displayed no abnormal findings (normal free carnitine and acylcarnitines levels).

Final diagnosis: Barth syndrome (genetically confirmed)

Paper Number: 17

## Episodic Muscle Weakness for 17 Years, and Aggravated for 3 Years

**Chuanzhu Yan**

*Laboratory of Neuromuscular Disorders and Department of Neurology of Qilu Hospital, Shandong University, Jinan, China.*

A 25-year-old man began complaining for episodes of muscle weakness in four limbs since the age of 7 years. Episodes occurred about once a week, lasting from several hours to a day and more frequently in Falls and Winter. The episodes were triggered by rest after exercise, prolonged sitting, and cold. Bulbar, respiratory and sphincter muscles were not affected. In between the episodes, his muscle strength was normal. However, myotonia in eyelids, hands, and masticatory muscles could be induced by repetitive exercise and cold. Within 3 years later, he developed persistent weakness and daily transient stiffness in bilateral lower limbs. Now, he cannot walk more than 20 meters on his own. Family history indicates episodic paralysis affected his mother once.

Neurologic examination:

He is awake, alert and interactive. The examinations about cranial nerves, tendon reflex, sensory and coordination are unremarkable. Motor strength: Facial muscles normal. Neck flexion and extension 4+/5, sternocleidomastoid 5/5, deltoids 4+/5, biceps 4/5, triceps 5/5, wrist extension and flexion 5/5, finger extension and flexion 5/5, iliopsoas 2/5, quadriceps femoris 4/5, tibialis anterior 5/5, gastrocnemius 5/5. Motor tone normal. No muscle atrophy. Reflexes (-) symmetrical. Pyramidal tract sign: (-).

Laboratory and electromyography Examination:

Laboratory studies gave normal results for electrolyte. CK increased to 1247 U/L. Electromyography indicated myogenic changes with myotonic discharge. Long exercise test showed CMAP decreased up to 49%.

Muscle biopsy:

Cryosections of left biceps: H&E, Gomori trichrome, NADH-TR, SDH, COX, S/C, PAS, ORO, ATPase, immunostains (Dystrophin-Rod, dystrophin-C, dystrophin-N, dysferlin,  $\alpha$ -sarcoglycan,  $\beta$ -sarcoglycan,  $\gamma$ -sarcoglycan,  $\delta$ -sarcoglycan, caveolin 3, emerin, laminA/C, ACP, MHC-1, CD<sub>34</sub>, SMA)

H&E staining involved marked variation in fiber size. Internal nucleated fibers increased up to 80%. Over 15% of the muscle fibers contained internally placed capillary "bundles". Vacuoles scattered in partial fibers. Oil red O staining indicated moderate increased droplets. No decrease in MGT, COX or SDH activities.

Immunohistochemical staining: No specific protein deficiency.

Impression: Myogenic pattern.

Paper Number: 122

## A Patient with Exercise Intolerance and Walking Disturbance

Shuang Cai

The patient is a 41-year-old male presenting with walking disturbance and post-exercise lower limb numbness and myalgia for one and a half year. Since August 2016, he started to feel myalgia after exercise and the symptom relieved with a short break. Since October 2016, he started to feel numbness of the lower limbs spreading upwards and had unstable walking. The symptoms aggravated, and in October 2017, he could only walk for 30 meters before an intermittent break. Frequent diarrhea was also complained during the disease course. No myoglobinuria was observed. There was no consanguineous marriage or family history. On physical examination, he had normal muscle strength. There was tenderness of both calves. Tendon reflexes were normal in the upper limbs and reduced in the lower limbs. Sensation of pinprick, vibration and position were reduced in bilateral legs and feet. Romberg's sign was remarkably positive. Normal alternation and finger-to-nose test were observed. CK was 809U/L in November 2017 and elevated to 2305U/L in January 2018, while LDH was 326U/L and 455U/L respectively. EMG and NCV showed myogenic changes and multiple peripheral neuropathy preferentially involving the sensory axons of the lower limbs. Muscle MRI revealed edematous signals of bilateral calves. CSF protein was slightly elevated to 570mg/L, while the cell counts, glucose and chloride were within normal limits. The screen of ANA, ENA, tumor markers, thyroid function, EKG, UCG and brain MRI were all normal.

Paper Number: 128

## A 69-Year-Old Man with a 1-Year History of Progressive Leg Weakness

Jantima Tanboon, MD<sup>1,2</sup>; Masashi Ogasawara, MD<sup>2</sup>; Ichizo Nishino, MD, PhD<sup>2</sup><sup>1</sup>Department of Pathology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand<sup>2</sup>Department of Neuromuscular Research, National Center of Neurology and Psychiatry (NCNP), Tokyo, Japan**Chief complaint:** Progressive leg weakness for 1 year**Present illness:** A 69-year-old Japanese man noticed leg weakness after a 1-km walk. By the end of the year, he could only walk for 20 steps.**Past history/underlying disease (s):** HT, DM, rectal cancer S/P surgery last 4 years.**Family history:** No parental consanguinity. No history of neuromuscular diseases.**Physical examination:** Good consciousness**Skin:** No Gottron's sign, No Heliotroph rash, No mechanic hands

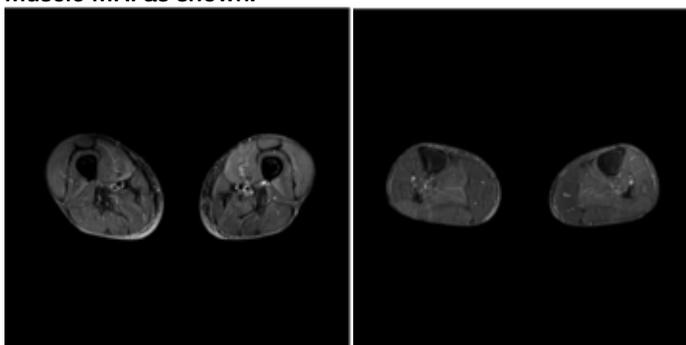
Bilateral proximal lower extremity muscle atrophy, calf muscle hypertrophy

MMT (of 5 MRC scale): Symmetrical proximal muscle weakness

Neck flexion/extension 4/4, shoulder abduction/adduction 4/4, elbow flexion/extension 4/5, Hip flexion/extension 4/4, knee flexion/extension 4/5, wrist flexion/extension 5/5, finger flexion/extension 5/5, ankle flexion/extension 5/5

**Laboratory investigations:**

CK 536 U/L

**Muscle MRI as shown:**

Muscle biopsy is taken from left deltoid. What is your diagnosis?

Paper Number: 131

## Fever and Myalgia After an Island Holiday

**CY Tan, KJ Goh, Wong KT, N Ramli, Tan CT**

*University of Malaya, Kuala Lumpur*

DLM was a participant in a church camp in Pangkor Island in January 2012. About 9 to 11 days after returning from the Island to Kuala Lumpur, Madam DLM developed fever which was associated with moderately severe myalgia the back, arms and legs. No muscle swelling was observed. Many of her companions at the camp also developed similar symptoms.

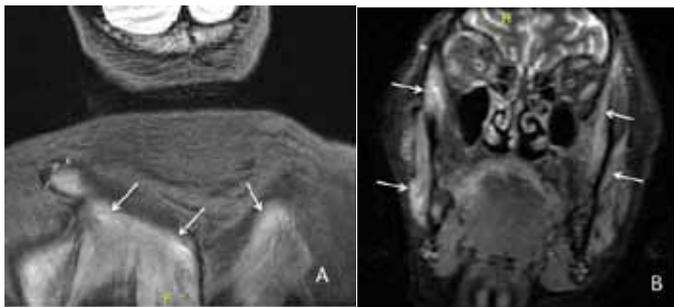
She had an underlying history of Type II diabetes mellitus with chronic renal impairment. There was no family history of any neuromuscular disease. She was admitted to hospital where she was treated symptomatically and her fever resolved

10/2/12: WBC 6.8 x 10<sup>9</sup>/L (eosinophil 0.31 x 10<sup>9</sup>/L, 4.6%), Hb 10.9 g/L, Platelet 240,000/μL, urea 13.0 mmol/L, creatinine 432μmol/L, AST 33 (15-37), ALT 29 (30-65), creatine kinase 57 U/L (normal 26-192).

Myalgia persisted and she presented again in April 2012 with worsening of her myalgia

14/4/2012: WBC 6.2 x 10<sup>9</sup>/L (eosinophil 0.27 x 10<sup>9</sup>/L, 4.3%), Hb 11.1 g/L, Platelet 344,000/μL, urea 20.0 mmol/L, creatinine 351μmol/L, AST 89 (15-37), ALT 167 (30-65), creatine kinase 2015 U/L (normal 26-192).

MRI muscle: Showed asymmetrical myositis involving the masseter and temporalis, trapezius muscles and Lt sternocleidomastoid noted. Figure A. Coronal STIR of back muscle showed high signal intensities affecting Lt and Rt trapezius muscles (arrows). Figure B. Coronal STIR of neck showing high signal intensities affecting both muscles of mastication (arrows)



Muscle biopsy was carried out over the L medial gastrocnemius muscle.

Paper Number: 129

## A 53-Year-Old Woman with 20 Years History of Proximal Myopathy

**Chen Fei Ng**

NA, 53-year old Malay ethnic woman, presented 20 years ago with bilateral proximal lower limb weakness. She had no bulbar symptoms. There was no significant family history. Clinical examinations revealed muscle power of 2/5 in the proximal lower limb and generalised hyporeflexia. There was no cutaneous features of vasculitis or dermatomyositis. Serum CK was 2098 u/L. Muscle biopsy of the right vastus lateralis (year 1999) was suggestive of inclusion body myositis.

She was started on tapering course of oral prednisolone 60mg daily in 1999. Throughout the follow-up, she was given a few courses of oral prednisolone, and the addition of azathioprine 150mg daily. She was later switched to mycophenolate mofetil 500mg bd due to poor response. Over the 20 years, there was no significant improvement and it slowly progressed to involve her proximal upper limb. There was no long flexors weakness. CK in January 2018 was 495 u/L. MRI of the LL showed inflammatory changes in the tibialis anterior and posterior, soleus and distal part of gastrocnemius bilaterally. There were also minimal inflammation in the vastus lateralis, gluteus maximus and deltoid. Chronic fatty infiltration was seen in proximal gastrocnemius.

Muscle biopsy of the left biceps was done (year 2017).

Muscle biopsy  
G118/99  
16676/2017

Paper Number: 21

# Longitudinally Extensive transverse Myelitis (LETM) mimickers of Neuromyelitis Optica Spectrum Disorders (NMOSD): Clues to Diagnostic Recognition

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<sup>2</sup>Department of Radiology, Hospital Kuala Lumpur

## Background:

Longitudinal extensive transverse myelitis (LETM) is a frequent manifestation of NMOSD. However, there are other causes of LETM which are important to recognize from a diagnostic and therapeutic point of view.

We report two cases of LETM

Case 1: Spinal cord infarct secondary to left vertebral artery dissection

Case 2: High cervical spinal dural arterio-venous fistula

## Case 1

A 14-year-old boy, presented with sudden onset of upper and lower limbs weakness preceded by short-lived chest pain, which occurred after two episodes of short distance running.

Neurological examination showed flaccid paraplegia with areflexia and sensory level at T2. Upper limbs power graded as MRC 4/5 with symmetrical reflexes. Plantar responses were equivocal.

Autoimmune screening including serum aquaporin 4 antibody were negative. Normal echocardiogram and coagulation profiles. CSF analysis was normal with absent oligoclonal bands.

MRI spine showed longitudinally extensive anterior spinal cord lesion with presence of 'Owl's eyes' signs. MRA showed irregularity and pseudo-dilatation of the V3 and V4 segment of left vertebral artery. Cerebral angiogram was normal (Figure 1 in poster).

## Case 2

A 50-year-old Chinese male presented with progressive lower limbs weakness for 3 months with painful paresthesia, urinary and bowel retention.

Neurological examination revealed spastic paraparesis with sensory level at T6. Serum NMO Ig G was negative. Normal CSF analysis. Initial MRI spine showed T2 intramedullary hyperintensities from medulla to C7. His weakness worsened even after completing immunotherapy. Repeat MRI/MRA spine revealed long segment hyperintense cervical cord lesion with cord expansion and anterior serpiginous T2 flow voids. CTA and spinal angiogram showed dural fistula at left C1 level with a likely feeding artery from meningeal branch of left vertebral artery (See Figure 2 in poster).

## Conclusion:

Presence of atypical clinical history such as age of onset with possible trigger, unusual temporal history of the disease and associated symptom onset, atypical presentations with flaccid lower limbs (e.g. case 1), lack of response to immune mediated therapies and persistently negative biomarkers (e.g. anti AQP4 antibodies) supported by neuroimaging interpreted by neuro-radiologist gives clues to alternative diagnoses of LETM other than NMOSD.

Paper Number: 22

# The Usefulness of Perfusion Imaging in Acute stroke with Low Non-Contrast CT ASPECTS for Reperfusion Therapy

*Chen Fei Ng, Syazarina Syaris Osman, Wan Asyraf Wan Zaidi, Ching Soong Khoo, Shahedah Koya Kutty, Rabani Remli, Norlinah Mohamed Ibrahim, Hui Jan Tan, Wan Nur Nafisah Wan Yahya*

## Objectives:

The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) has been widely used in the assessment of acute ischemic stroke to guide reperfusion therapy. Earlier studies showed that baseline non-contrast CT (NCCT) ASPECTS of  $\leq 7$  predicted functional dependence and symptomatic intracerebral haemorrhage in patients who underwent thrombolysis. Perfusion imaging such as CT perfusion may be more accurate to evaluate established infarct and salvageable penumbral tissue.

## Method:

We described a case of right middle cerebral artery (MCA) infarct with low baseline NCCT ASPECTS, who was successfully thrombolysed with intravenous alteplase based on significant penumbra on CT perfusion.

## Results:

A 66-year old man with no known medical illness presented with sudden onset of left-sided body weakness and slurred speech for 2 hours. He was a heavy smoker for 30 years. On examination, he had left hemiparesis, left lower facial palsy, left homonymous hemianopia, neglect and dysarthria. The initial National Institute Health Stroke Scale (NIHSS) was 15. NCCT ASPECTS was 3. CT angiogram and CT perfusion of the brain were done to stratify further for reperfusion therapy. CT angiogram showed chronic stenosis at M1 segment of the right MCA but no large vessel occlusion. However, CT perfusion revealed a significant penumbra of  $>50\%$  with small infarct core. He was given intravenous alteplase at 3 hours. On the second day, his NIHSS improved to 5 and the repeated CT brain did not show intracranial haemorrhage. He was discharged home 4 days later with modified Rankin scale of 2.

## Conclusion:

NCCT ASPECTS may overestimate infarct core as cortical swelling may represent penumbral tissue. Perfusion imaging, such as CT perfusion is more reliable in guiding patient selection for reperfusion therapy.

Paper Number: 28

# A Randomized Double-Blind Placebo-Controlled Trial Of Probiotics for Constipation in Parkinson's Disease

**Kah Kian Chong<sup>1</sup>, Shen-Yang Lim<sup>1</sup>, Mohamad Addin Azhan A Manap<sup>1</sup>, Jia Lun Lim<sup>1</sup>, Soon Chai Low<sup>1</sup>, Sanjiv Mahadeva<sup>2</sup>, Ai Huey Tan<sup>1</sup>**

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**Background:** Constipation is the commonest gastrointestinal symptom in Parkinson's Disease (PD), affecting up to 70% of patients, and causes significant impairment in quality of life. However, there is a paucity of randomized clinical trials (RCT) to evaluate the efficacy of treatments for constipation in PD. This study aims to investigate the effects of probiotics on constipation in PD.

**Methods:** This is a randomized, double-blind, parallel-group, placebo-controlled RCT. PD patients fulfilling ROME-IV criteria for functional constipation were recruited consecutively and randomized to receive either 4 weeks of probiotic capsules containing strains of Bifidobacterium, Lactobacillus and Enterococcus; or identical-appearing capsules containing (inactive) maltodextrin. Data regarding patient demographics, clinical status (including MDS-UPDRS), body mass index, medications, dietary intake, and physical activity (SIMPAQ) were collected. The primary outcome was the change in the average number of spontaneous bowel movements during the last 2 weeks of the treatment phase, compared to the 2-week pretreatment phase, as recorded by stool diary. Secondary outcomes included changes in the constipation severity scale (adapted from ROME-IV criteria), stool consistency (Bristol stool scale), and quality of life scale related to constipation (PAC-QOL). Adverse effects were recorded. Sample size calculation revealed that 36 patients were required in each arm to achieve clinical superiority with alpha of 0.05 and power of 0.80.

**Results:** To date, 67 patients have been recruited. Interim intention-to-treat analyses were performed on 43 patients who have completed the study and 2 drop-outs. There were no significant between-group differences in age, gender, BMI, physical activity, PD duration, total MDS-UPDRS, and PD medications. Spontaneous bowel movements per week (the primary endpoint) increased significantly in the treatment group ( $1.10 \pm 1.70$ ) compared to placebo ( $-0.26 \pm 0.79$ ,  $P=0.005$ ). Total ROME-IV, PAC-QOL and stool consistency also improved significantly ( $-3.53 \pm 2.67$  vs.  $-0.77 \pm 2.73$ ,  $P=0.002$ ;  $-21.47 \pm 19.61$  vs.  $-2.58 \pm 13.22$ ,  $P=0.001$ ;  $-0.41 \pm 1.11$  vs.  $0.27 \pm 0.77$ ,  $P=0.021$ ), with higher rates of satisfaction with treatment in the treatment group (55.6% vs. 24%,  $P=0.031$ ).

**Conclusions:** This interim analysis showed significant improvements in bowel frequency, stool consistency, constipation severity scale, and quality of life in patients receiving probiotic treatment. To date, patient enrollment and retention have been satisfactory, with no significant adverse events reported.

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Paper Number: 40

# Sequential Intermittent Plasmapheresis as Induction and Maintenance Therapy in the Management of Asian Patients with Neuromyelitis Optica Spectrum Disorder

*Jie Ping Schee*

## **BACKGROUND :**

Plasmapheresis is an effective therapy for acute attacks of neuromyelitis optica spectrum disorder (NMOSD). Benefits of intermittent plasmapheresis as maintenance therapy have been reported as well. This study explores the efficacy of a novel protocol i.e. sequential intermittent plasmapheresis (SIP) in the management of patients with corticosteroid-refractory NMOSD.

## **METHODS :**

Through retrospective review of medical records, we identified all NMOSD patients in Hospital Kuala Lumpur who had been treated with SIP namely an induction phase of monthly plasmapheresis for 3 months with or without the subsequent maintenance phase of 3-monthly plasmapheresis for 9 months. We explored these patients' demographics, clinical and para-clinical characteristics including neuroimaging. Comprehensive outcome measures of this study included improvement in Expanded Disability Status Scale (EDSS), lower limb motor power in Medical Research Council (MRC) scale, visual acuity in Visual Outcome Scale, and relapse rate. Statistical analysis was conducted through SPSS® Statistics Version 20 and statistical significance was set at  $p < 0.05$ .

## **RESULTS :**

SIP was initiated for 14 adult Malaysian patients whose NMOSD attacks were refractory to intravenous methylprednisolone, namely 4 patients with transverse myelitis and 10 patients with concurrent transverse myelitis and optic neuritis. 10 patients (71%) were female. 13 patients (93%) were AQP4-IgG positive. 6 patients (43%) completed both induction and maintenance phases, 6 patients (43%) completed induction with no maintenance phase, and 2 patients (14%) completed induction phase followed by incomplete maintenance phase. SIP led to statistically significant improvement in EDSS at immediately after, 1 month, 6 months and 1 year after the first cycle. Improvement in limb power immediately after the first cycle and subsequent continuous improvement until 1 year after the first cycle of SIP was statistically significant as well. The 10 patients with optic neuritis demonstrated statistically significant improvement in visual acuity at 6 months after the first cycle. Improvement in relapse rates both within the SIP duration and within 2 years after the completion of SIP was statistically significant.

## **CONCLUSIONS :**

Sequential intermittent plasmapheresis as induction therapy with or without the subsequent maintenance phase improves the overall disease outcomes and prevents relapses in adult patients with steroid-refractory NMOSD.

Paper Number: 70

# Kuala Lumpur Regional Integrated Stroke Intervention System – Stroke Thrombolysis Registry (KRISIS - STR ) Audit 2009 – 2017 : Improvement of Door-to-needle time

*Wn Asyraf Wan Zaidi*

## **Introduction :**

Hyperacute stroke treatment with intravenous recombinant tissue plasminogen activator (r-tPA) is a very time-dependent therapy. Treatment delay must be avoided in order to achieve good therapeutic outcome. It is very important for a stroke capable centre to audit the timeliness of the thrombolytic treatment to deliver the treatment efficiently and lower the risk of adverse event.

## **Methodology :**

We conducted a retrospective study, the data was extracted from our KRISIS – STR from 2009-2017. The information collected including patient demographics, stroke severity, door-to-needle, onset-to-needle and treatment outcome measured by modified Rankin scale (mRS). We analysed the door-to-needle (DNT) and onset-to-needle to two group ( 2017 and before 2017).

## **Results :**

A total of 156 patients underwent reperfusion treatment from 2009-2017. Intravenous r-tPA were given to 146 ( 93.6%) patients and 10 (6.4%) patients underwent mechanical thrombectomy. In 2017, 33 (6.7 %) out of 491 patients were treated with intravenous thrombolysis. We treated higher National Institute of Health Stroke Scale (NIHSS) in 2017 with mean of 14 (4-31) in comparison with before 2017, mean of 12 (1-26), ( $p = 0.042$ ). The DNT in 2017 mean was 101 minutes ( SD = 40 ) and before 2017 was 127 minutes ( SD = 55 ), ( $p = 0.168$ ). Around 18.2% patients were treated within 60 minutes from arrival in 2017 as compared to 4.3% in 2016. Patients arrived faster in 2017 with onset-to-needle time mean of 200 minutes ( SD = 73 ) and before 2017 the mean was 214 minutes ( SD = 51 ), ( $p = 0.141$ ). The mRS upon discharge mean was the same with mean of 2 ( SD = 2 ), ( $p = 0.082$ ). From 2009-2017, 61.6% of patients treated achieved favorable outcome upon discharge and only 7.5% suffered intracerebral hemorrhages.

## **Conclusion :**

Although there is an improvement with the DNT in 2017, further work need to be done to identify factors contributing to treatment delay.

Paper Number: 77

# Budget Impact Analysis of Fingolimod for Treatment of Highly Active Relapsing-Remitting Multiple Sclerosis (RRMS) in Hospital Kuala Lumpur (HKL): Hospital Perspective

**Lee MW<sup>1</sup>, Yong YV<sup>2</sup>, Viswanathan S<sup>3</sup>, Tan AL<sup>1</sup>, Cheng KS<sup>1</sup>, Norkasih I<sup>1</sup>**

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## Introduction:

Fingolimod is used for highly active RRMS patients who have failed first-line treatment (ie. interferon beta). Studies have shown the superior efficacy of fingolimod in terms of relapse rates and MRI outcomes, compared to interferon beta. Nevertheless, local data on the impact of Fingolimod treatment to drug budget is scarce.

## Objective:

To evaluate budget impact of Fingolimod treatment in highly active RRMS patients who have failed interferon-beta.

## Methods:

The number of highly active RRMS patients who have not responded to interferon beta was collected from HKL Demyelinating Disease (DD) Database 10503. Epidemiology, frequency of monitoring and clinic visit, market share as well as side effects management were from clinical experts opinion. Relapse rate, non-adherence rate and adverse events were obtained from current literature. Drug cost was obtained from Pharmacy Store, HKL. A budget impact model was developed with a time horizon of 5 years. Current treatment mix is interferon beta and existing fingolimod patients, whereby future treatment mix is interferon beta, new and existing fingolimod patients. Cost inputs included drug acquisition, intervention cost, managing side effects/ complications cost as well as changes in disease-related costs; (hospitalization and clinic visits). Number of patients taking fingolimod was projected to increase gradually with 2 new patients each year.

## Results:

With the current treatment mix, the total cost of treatment in year 1 is RM2,007,880 and year 5 is RM3,205,722. Based on a forecast uptake of 2 new Fingolimod patients each year, the total budget was estimated at RM 3,452,090 in year 5. The net budget impact was estimated to be RM246,368 in year 5. The total 5-year cumulative incremental cost was estimated to be RM694,255.

## Conclusion:

The present analysis showed that, despite lower relapse and non-adherence rate compared to interferon beta, fingolimod had an incremental impact on the hospital drug budget. There is a desire need for strategies to make Fingolimod affordable for Malaysians.

Paper Number: 79

# Case Series of Atypical Guillain-Barré Syndrome (GBS) and Concomitant Neurological Illness: Clinical Interpretation Above Diagnostic Criteria

**Andy Ko TY<sup>1</sup>, Teo Yan<sup>1</sup>, Liong CC<sup>1</sup>, Wong TM<sup>1</sup>, Chang FT<sup>2</sup>, Hiew FL<sup>3</sup>**

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## Background:

There are various clinical phenotypes and electrophysiological subtypes of Guillain-Barré Syndrome (GBS), making clinical diagnosis challenging and prognostication process uncertain. Currently available clinical diagnostic criteria and classification were based on clinical phenotypes, requiring clinician ruling out GBS mimics. However, this can be challenging in the context of concomitant presentation with another neurological illness or the lack of clinical suspicion.

## Methods:

We described 3 cases of GBS with either atypical presentation or with concomitant neurological pathology and their respective neurophysiological features from a secondary hospital in Sarawak, Malaysia.

## Results:

First subject was a 60-year-old lady with background uncompensated Hepatitis B-related liver cirrhosis and diabetes mellitus, presented with classical form of GBS with concomitant statin induced myopathy following recent antecedent gastroenteritis. She was started on atorvastatin 3 months prior. Clinically, she had predominant proximal weakness with generalised areflexia. Maximum creatinine kinase was 26470 U/L. Lumbar puncture (LP) did not reveal albuminocytological dissociation. However, nerve conduction study (NCS) showed axonal subtype polyneuropathy. Statin therapy was withheld, and a trial of 5 days course intravenous immunoglobulin (IVIg) showed remarkable recovery with ability to ambulate without support on discharge. Second subject was young gentleman in his 20s' with underlying Hepatitis C, presented with recent history of progressive areflexic lower limb paraparesis with sensory level at T10 dermatome. MRI whole spine and CSF study were unremarkable. NCS demonstrated axonal motor sensory subtype polyneuropathy. Similarly, he improved remarkably to full MRC score following a course of IVIg. Our third subject, 67-year-old lady with background hypertension, presented with 3 days history of acute asymmetrical generalised weakness, affecting predominantly the left. Examination showed left facial upper motor neuron weakness, generalised areflexia and diffused sensory deficits. CT brain demonstrated a recent right lacunar infarct. CSF study revealed albuminocytological dissociation and NCS confirmed demyelinating subtype polyneuropathy. Despite IVIg therapy, she developed respiratory muscles weakness, requiring prolonged mechanical ventilation. Multiple complications ensued, with her eventually succumbed to severe sepsis related to prolonged hospital stay.

## Conclusion:

GBS can have atypical presentation and complicated by other neurological pathology. High index of suspicion supported by specific diagnostic tests may improve diagnostic accuracy and treatment outcome.

Paper Number: 85

# Acute Parkinsonism in Young Adult Following Streptococcal Infection: Possible Adult Variant of PANDAS

*Shahedah Koya Kutty*

## **Background:**

Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection (PANDAS) is a group of disorders recently recognized as a clinical entity in children. It is however rarely described and investigated in adult. To date, there is paucity of literature of post streptococcal related acute parkinsonism and dyskinesia or PANDAS variant among adult.

## **Method:**

A case of 18 year-old woman, who presented with acute parkinsonism after streptococcal tonsillitis.

## **Result:**

Our patient was a previously well, 18 year-old Malay lady, who presented with a two months history of intermittent fever, associated with sore throat and sudden onset of behaviour changes. She has been found to be more quiet and respond slowly to questions and commands in the preceding one week prior to admission. Mild intermittent resting tremor was seen on her right hand and right leg. She had reduced facial expression, significant bradykinesia and diffuse rigidity with asymmetry. Deep tendon reflexes were normal and plantar responses were equivocal. The remainder of her neurological examination was unremarkable. Medical and family history was non-contributory. Her vitals were within normal limits. Her blood counts, viral screenings and anti-NMDAR were unremarkable. Her lumbar puncture revealed an opening pressure of 10 cm CSF with normal constituents. The ASO titer was raised up to 400IU/ml. Electroencephalogram (EEG) shows mild encephalopathy changes and MRI brain shows normal finding.

She was initially treated with IV Ceftriaxone 2 g twice daily for total a week and later IV methylprednisolone 1g daily for 3 days. She was also given Tab clonazepam 0.5mg OD, 25/100 mg of carbidopa/levodopa at one tablet three times for her extrapyramidal symptoms. Immune globulin (IVIG) was started on her in view of poor response to the above treatment, which later resulted in significant and rapid clinical improvement. Upon the clinic follow up at 3 months, her tremor, bradykinesia, and rigidity resolved.

## **Conclusion:**

This case underscores the importance of recognising post-streptococcal infection as an aetiology of acute parkinsonism in young adults, to avoid treatment delay. As illustrated in our case, the prognosis is good with immunomodulatory therapy.

Paper Number: 109

## Evaluation of Secondary Prevention in Older Survivors of Ischemic Stroke: Data from Malaysia Stroke Registry

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**Introduction:** The risk of recurrent stroke is known to be greatest in the first 6 months following an initial presentation. Hence, secondary prevention measures is essential part of stroke care. Despite this, older patients often receive less aggressive secondary prevention strategies contrary to the evidence that most of these strategies can be effective in the elderly.

**Objective:** to evaluate the impact of age on receiving the secondary prevention medications at the time of hospital discharge. Pre specified secondary prevention drug classes studied were antiplatelet, lipid lowering agent and antihypertensive.

**Method:** In this study, records of acute ischemic stroke patients from Malaysia National Stroke Registry were retrospectively examined. Patients were divided into 2 groups: those who were less than 80 years of age and those who were 80 years old and more.

**Result:** There were 8947 of < 80 years old and 755 of ≥80 years old patients registered in Malaysia National Stroke Registry from July 2009 to December 2017. Male represented 56.1% of patients in young group and 43.9% in older group. Compared to young age, older age were less likely to receive antiplatelet (87.9% vs 91.8%; p=0.001) and anti-hypertensive drugs (45.4% vs 50.4%; p=0.009). Factors associated with antiplatelet prescribing identified in older age were lacunar stroke (OR 3.06; 95% CI 1.35, 6.90) , good Modified Rankin Scale upon discharge (OR 1.28; 95% CI 1.04, 1.57) and male (OR 1.64; 95% CI 1.04, 2.58) whereas underlying diabetes mellitus (OR 1.51; 95%CI 1.09, 2.09) ,atrial fibrillation (OR 2.30; 95% CI 1.31, 4.02) and unclassified stroke (2.09;95%CI 1.12,3.90) were the factors associated with antihypertensive prescribing.

**Conclusion:** After hospitalization for ischemic stroke, there was an age disparity in antiplatelet prescribing contributed by OCSF classification, MRS upon discharge and gender as well as antihypertensive drug prescribing which associated with underlying DM and AF and also OCSF classification.

Paper Number: 111

## Phenotypic Characteristic of Families with Spinocerebellar Ataxia (SCA) 3 in Malaysia

**Noorasyikin Mohamed Arifin**

**Objective:** To describe phenotypic characteristics of genetically confirmed SCA 3 patients in neurology unit PPUKM

**Methods:** 15 patients from 7 families tested positive for ATXN 3 were recruited. Patients were assessed for onset and duration of illness. Clinical phenotypes i.e. cerebellar signs, ocular movement disorder, pyramidal and extrapyramidal signs, peripheral nerve dysfunction, cognitive dysfunction and other related disorder such as dysphagia and incontinence were also analyzed. Objective evaluation using scale for the assessment and rating of ataxia (SARA) and quality of life (QoL) score using EQ5D-3L were also performed.

**Results:** All 15 patients had at least 3 generations with family history of similar neurological abnormalities. Youngest patient registered was 16 years old and oldest was 59 years old with median age of 36.0 years (IQR 33.0-39.0). The shortest duration of disease was one year and longest was 11 years with median 4.0 years (IQR 2.0-6.0). First presentation in all patients was progressive gait instability and currently 7 (46%) were wheelchair dependent. Median time to wheelchair in 7 patients were 12 months (IQR 12-24). Total of 11 (73%) patients had appendicular ataxia and 14 (93%) patients had dysarthria. In terms of ocular movement abnormalities, 10 (67%) subjects presented with nystagmus whereas 7 (47%) had ophthalmoplegia and diplopia. The median of duration of illness to onset of ophthalmoplegia was 12 months (IQR 6-21). Nine (60%) patients had pyramidal signs. Only 3 (20%) patients had signs of parkinsonism, 2 (13%) had dystonia and one patient (6.7%) had cognitive dysfunction. There was a marked heterogeneity among siblings with SCA 3 manifested in variable neurological signs. Median SARA scale was 12.5 (IQR 8.5-19.0) and median QoL score was 60.0 (IQR 40.0-80.0).

**Conclusion:** SCA 3 phenotype is similar to that described in the literature with progressive ataxia plus pyramidal syndrome, parkinsonism and ataxia.

Paper Number: 116

# Reliable Change Index (RCI) in Assessing Mindfulness-Based Intervention for People with Epilepsy (PWE)

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## Background

Mindfulness-based interventions (MBI) are proven to significantly reduce psychiatric symptoms and promote good mental health among the neurological population. The efficacy of MBI for epilepsy however, have yet to be thoroughly investigated.

## Objectives

The efficacy of MBI in PWE was examined in Studies 1 and 2. The primary aim is to investigate its clinical significance via the Reliable Change Index (RCI) and the magnitude of a treatment effect over a control using the number-needed to treat (NNT) approach.

## Method

Study 1 was conducted in Hong Kong. Total 60 drug-resistant epilepsy were randomly allocated to the mindfulness (MT) or social-support group (SS) to receive a four 2.5-hour biweekly sessions. The 2nd study was a preliminary study conducted in Malaysia, with 9 epilepsy patients participated in the mindfulness trial to receive a six 2.5-hour weekly sessions. Primary outcomes included depression and anxiety. Secondary outcome was on quality of life. Jacobson's methodology was used to determine the RCI in outcome measures. The calculation of NNT was based on patient's baseline risk and the average control patient in the trial.

## Results

In studies 1 and 2, post-treatment assessments showed that patients in the MT group experienced greater reduction in depressive and anxiety symptoms ( $p < .05$ ). Contrary to Study 1, the MT group in Study 2 found an improvement in quality of life (QOL) ( $p < .05$ ). RCI in studies 1 and 2 showed that the improvement in QOL was statistically reliable ( $40.0 \approx 66.7\%$ ). The extent of gains were reflected in levels of depression ( $43.3 \approx 55.6\%$ ) and anxiety ( $33.3 \approx 44.4\%$ ). NNT analysis showed 5 epilepsy patients would have to receive MBI over four 2.5-hour biweekly sessions.

## Discussion

Mindfulness therapy is effective in reducing psychological distress and improving quality of life in PWE. Our findings showed two important clinical significance that the: (i) amount of change that has occurred in the MT group was large enough to be meaningful and (ii) improvement of scores (RCI) were not due to imprecision of measuring tools. Implementation of a psychological therapy requires consideration on the length and success rate of the therapy, our NNT measure therefore offers psychobehavioural scientists to consider this intervention.

Paper Number: 127

# Impact of Pre-stroke Angiotensin-Converting Enzyme Inhibitors (ACEi) on pneumonia During Acute Stroke: An Asian Perspective

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## Introduction:

Stroke-associated pneumonia imposes significant morbidity and mortality for acute stroke care. The use of ACE inhibitors (ACEi) has been shown to reduce the risk of post-stroke pneumonia. However, little is known about the role of pre-stroke ACEi usage on pneumonia during acute stroke episodes, which led to the conduct of this study.

## Methods:

This prospective observational study involved reviewing 11,398 patients admitted to 15 Malaysian public hospitals with acute stroke from 1st January 2010 thru 31st December 2016. Data on demography, WHO stroke classification, clinical assessment and Glasgow Coma Scale (GCS) at presentation, stroke recurrence, stroke-related pneumonia and outcomes were extracted from the Malaysian National Neurology Registry. Descriptive analyses and multivariable logistic regressions were performed to evaluate the pre-stroke ACEi effect on stroke-related pneumonia and clinical outcomes.

## Results:

More than half (56%) of patients were male, with an average age of  $62.5 \pm 12.47$  years. About 78.5% had first-ever stroke and nearly 80% were ischaemic stroke. Up to 14.6% had stroke-related pneumonia during hospitalization, with one-fifth of total mortality being attributable to stroke-related pneumonia. About 15.9% were prescribed on ACEi before their first-ever stroke, compared to 27.1% with recurrent event. Adjusting for demographics, GCS at presentation, stroke recurrence and classifications, diabetes and smoking status, patients on ACEi prior to acute stroke had lower risk of developing pneumonia (OR=0.74, 95%CI 0.63, 0.86;  $p < 0.001$ ) and lower risk of succumbing to stroke-related pneumonia (OR=0.66, 95%CI 0.45, 0.96;  $p = 0.032$ ), compared to their counterparts without ACEi. Subgroup analyses observed similar effects on reduction in occurrence of pneumonia (OR=0.687, 95%CI 0.56, 0.84;  $p < 0.001$ ) and pneumonia-related mortality (OR=0.60, 95%CI 0.37, 0.99;  $p = 0.045$ ) among patients with first-ever stroke, but not in those with recurrent stroke ( $p = 0.317$  and  $p = 0.309$ , respectively). Besides, pre-stroke ACEi also observed a reduction in all-cause mortality during acute stroke (OR=0.65, 95%CI 0.51, 0.83;  $p < 0.001$ ).

## Conclusion:

This study demonstrated that ACEi prior to first-ever stroke may confer protective effect against stroke-related pneumonia and associated mortality during acute stroke event. It may be worth for a prospective trial to confirm its potential beneficial effect among patients with high risk for stroke.

NMRR registration number: 08-1631-3189

Paper Number: 97

# Determining Optimal Early Rehabilitation After Stroke (AVERT-DOSE): A Multi-Arm Covariate-Adjusted, Response-Adaptive Randomised Controlled Trial

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## Background and Aims

In 2015, we completed the landmark, international RCT of early rehabilitation (The Lancet, 2015). We determined that too much training early interferes with stroke recovery and that most patients may be responsive to therapy if the right dose can be found (Neurology 2016). The aim of this study is to define the optimal early intervention regimens for people with mild and moderate stroke severity.

## Method

We will use a multi-arm, dose-finding, Covariate-Adjusted, Response-Adaptive (CARA) Randomised Clinical Trial (Figure 1) in two specified mild and moderate stroke severity strata. We will test three separate rehabilitation intervention regimens in each strata against a pre-specified control to identify the intervention regimen that results in fewer disabled patients at 3 months post stroke (mRS 0-2). A sample size of 2,572 patients will allow us to independently observe pre-specified effects in these two strata with power 80% and significance threshold of  $p=0.025$ . All analyses will be intention-to-treat. Patients with mild to moderate stroke will be recruited using our global trials network in Australia, New Zealand, Singapore, Malaysia, India and United Kingdom.

## Results

The trial protocol is in final stages of development with site identification underway.

## Conclusion

AVERT-DOSE will establish clear, definitive, early intervention protocols, that will ensure that stroke patients receive best evidence care, both here and in developing health service systems.

**If you are describing a clinical trial or clinical trial results, including any ongoing trial, please indicate the trial registration number in the following box. If this does not apply to you please indicate: N/A**

Protocol under development

Keywords

acute stroke

rehabilitation

response-adaptive

dose

cost effectiveness

Paper Number: 1

## Development of Chronic Model of Epilepsy induced Cognitive Dysfunction in Zebrafish

*Mohd Farooq Shaikh*

**Background:** Epilepsy is a neurological disorder associated with repeated unpredictable epileptic seizures. Impairment of the cognitive performances such as learning and memory is frequently observed in epileptic patients. Anti-epileptic drugs (AEDs) are efficient to the majority of patients. However, 30% of this population seems to be refractory to the drug treatment. These patients are not seizure-free and frequently they show impaired cognitive functions. The major problem associated with conducting studies on epilepsy-related cognitive function is the lack of easy, rapid, specific and sensitive in vivo testing models. For investigating the cause and pathology of human disease animal models are considered as a useful tool. It is better known that such models can never represent the complete pathology that is observed in human diseases. However, by using a number of different techniques and parameters in the zebrafish, we can incorporate the unique feature of specific disorder to study the molecular and behavior basis of this disease. In the view of current literature, the goal of the study was to develop a zebrafish model of epilepsy induced cognitive dysfunction.

**Methods:** For chronic epilepsy induced cognitive dysfunction model, we tried to inject different chemo-convulsion such as PTZ (kindling) or kainic acid (KA) followed by three-axis maze analysis for cognitive behavior. A single dose administration of kainic acid (KA) or repeated administration of pentylenetetrazole (PTZ) for 10 days successfully induces kindling effect in zebrafish and also worsen the memory function in three axis maze model.

**Results:** Repeated administration of PTZ at 80 mg/kg of low dose can induce kindling like effect and worsen the memory function at Three-axis maze model. Kainic acid at 3mg/kg dose produce chronic epilepsy and affect the cognitive function when compared to control fish.

**Conclusion:** Therefore, combination of behavioral, neurochemical and gene expression information, makes this zebrafish a useful tool for future research and discovery of newer and safer AEDs.

Paper Number: 9

## An MRI Study of Gray Matter Volume and Neural Tractographic Connectivity in the Brains of Regular Ketum Users

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Ketum is a popular herb used in traditional medicine that has recently gained attention nationwide due to widespread use for its psychoactive properties. Dose dependent opioid and stimulant-like effects have been observed in mice studies and raise concerns about any abuse potential and negative cognitive and behavioral effects arising from chronic use. There is a lack of data of ketum use in humans and structural and functional studies are needed to elucidate the presence or absence of possible dangers of ketum use. We present the first investigation of brain volume and neural tractographic connectivity in the brains of 7 regular ketum users computed from MRI neuroimages. We compare against 7 healthy controls to identify regions of interest that could be linked to susceptibility or causality from regular ketum use. We find significant volume reduction in the pallidum (31%) and putamen (18%) of ketum users but no other significant differences in whole brain, white or cortical gray matter volume. Using brain network analysis, we find no significant difference in structural connectivity, node strengths nor brain network properties between the ketum and control groups. However, we find evidence of reduced node weights and greater diversity of connections between brain nodes of ketum users. Our preliminary findings show no major deficiencies in brain neuroanatomy in regular ketum users aside from significantly reduced gray volume in the subcortical regions but future studies with larger cohort size are necessary to confirm the presence of more subtle differences, if any.

Paper Number: 20

## Changes in Electroencephalography (EEG) Spectral Power in Frontal and Parietal Cortices in Freely Moving Rats Elicited by Mitragynine from *Mitragyna Speciosa*

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Kratom (*Mitragyna speciosa*) is a widely abused herbal drug preparation in Southeast Asia. It is often consumed as a substitute for heroin, but imposing itself unknown harms and addictive burdens. Mitragynine is the major indole alkaloid of kratom that has recently been reported to induce morphine-like behavioural and cognitive effects in rodents. The changes in brain activity of its user either acute or repetitively remained unreported. Here, we investigate the effects of mitragynine treatment in freely moving rats using electroencephalography (EEG) activity. Rats were administered with mitragynine (1 and 30 mg/kg) after 7 days of electrode implantation surgery. Morphine (5mg/kg) and Methamphetamine (1mg/kg) were used as positive control. Brain activity was recorded 1 hour after acute and repetitive exposure of mitragynine. We found that mitragynine triggered changes of brain activity in both low and high doses. Animal treated with mitragynine (1 mg/kg) produced EEG synchronization characterised by continuous large-amplitude synchronized activity, with no prominent changes in specific power density both in acute and repetitive studies in recorded regions. Mitragynine (30 mg/kg) produced an EEG desynchronization characterised by a general decrease in amplitude of all the frequency bands (0-50 Hz) with prominent upsurge of theta power (4.75-6.75 Hz) after acute administration, and decreased of delta power (1.25-4.5 Hz) after repeated administration only at frontal cortex. These results suggest that mitragynine elicited a biphasic (synchronization and desynchronization) changes of brain waves affecting specific frequency bands and region depending on the dose.

Paper Number: 47

## Anti-TRPM4 Antibody Improves Hippocampal Long-Term Potentiation Deficit in Chronic Cerebral Hypoperfused Rats

Nurul Aqmar Mohamad Nor Hazalin<sup>1,3</sup>, Liao Ping<sup>2</sup> and Zurina Hassan<sup>1</sup><sup>1</sup> Centre for Drug Research, Universiti Sains Malaysia, Malaysia<sup>2</sup> Calcium Signaling Laboratory, National Neuroscience Institute, Singapore<sup>3</sup> Faculty of Pharmacy, Universiti Teknologi MARA, Puncak Alam Campus, Malaysia

**Background:** Transient receptor potential melastatin 4 (TRPM4) is a calcium-activated, non-selective cation channel. Activation of TRPM4 following hypoxia/ischemia leads to oncotic cell death. As hippocampus is one of the brain regions most vulnerable to cerebral hypoperfusion, damage to the neurons can lead to the synaptic dysfunction. Therefore, the present study aims to evaluate the effect of single administration of anti-TRPM4 antibody on the long-term synaptic plasticity in chronic cerebral hypoperfusion (CCH) induced rats.

**Methods:** Male Sprague Dawley rats (200-250 g) were subjected to permanent bilateral occlusion of common carotid arteries (PBOCCA) or sham-operated surgery. Immediately after surgery, the rats were given single loading dose of anti-TRPM4 antibody (0.5 µg/g body weight each) intraperitoneally. Electrophysiological recordings were conducted under urethane anaesthesia 28 days after the surgery

**Results:** The results demonstrated that CCH resulted in inhibition of hippocampal LTP formation without affecting the basal synaptic transmission. Interestingly, treatment with anti-TRPM4 antibody significantly rescued the impairment of LTP in PBOCCA rats.

**Conclusions:** The present findings suggest a novel role for TRPM4 expressed in adult hippocampus in restricting synaptic plasticity after CCH. The potential of anti-TRPM4 antibody to improve neuronal plasticity represent a promising role of this antibody-based therapeutic in targeting ion channels to treat various neurological diseases which warrant further investigation.

Paper Number: 52

## Mitragynine (Ketum)-induced Memory Impairment of Swiss Albino Mice in the IntelliCage<sup>®</sup> System

*Nurul Iman Wan Ismail*

**Background:** *Mitragyna speciosa* (Ketum) is a traditional medicinal plant in the northern region of Malaysia and southern region of Thailand. Ketum leaves have been recreationally consumed as a substitute to opium due to their stimulant and euphoric effects, hence subject to addictive liabilities. Mitragynine, a major constituent of Ketum leaves, has recently been reported to impair cognitive performance in rodents, although mechanisms remain unclear. The present study aimed to identify the effect of mitragynine sensitisation on mice spatial learning and reversal learning, and the possible involvement of cannabinoid (CB1) receptor.

**Methods:** Male Swiss albino mice were subjected to a 28-day chronic regimen with mitragynine (5-25mg/kg, ip, n=6), or mitragynine + NIDA-41020 (CB1 receptor antagonist, 20mg/day, oral, n=6). Control group received Tween-20 vehicle (1ml/kg, ip, n=6). The automated home-cage IntelliCage<sup>®</sup> social learning system was used to observe the effect of mitragynine sensitisation on mice spatial learning (Day 15 to 21) and reversal learning (Day 22 to 28).

**Results:** Mitragynine-sensitised mice exhibited failure to perform operant learning task and to acquire the water-rewarded corner ( $p < 0.05$ ) and spatially-shifted corner ( $p < 0.05$ ) relative to the vehicle-control group. However, place learning and reversal learning deficiencies seen in mitragynine-sensitised mice were significantly ameliorated with the administration of NIDA-41020.

**Conclusions:** These findings implicate the role of brain CB1 receptors in the spatial learning deficit associated with chronic mitragynine use. Future studies to deliberate the underlying neuronal basis are warranted, particularly in relation to emerging Ketum use and misuse.

Paper Number: 68

## Evaluating the Effect of Mitragynine, the Main Indole Alkaloid of Ketum in Relieving Abdominal Pain During Menstruation

*Noorul Hamizah Mat*

**Background:** Several testimonials about the effectiveness of ketum in relieving premenstrual syndrome has been reported by ketum users in the United States. The opioid-like effects of ketum is the main reason for its consumption. Therefore, the study was aimed to evaluate the analgesic effects of mitragynine, the main indole alkaloid of ketum by evaluating its effectiveness in relieving menstrual symptoms, particularly the abdominal pain in rats mimicking human symptoms and to investigate the effective dose of mitragynine in relieving abdominal pain.

**Methods:** Female Sprague Dawley rats were pretreated intraperitoneally with either mitragynine (1, 5, 10, 12.5, 15 or 30 mg/kg) or vehicle (20% Tween 80) 30 minutes prior to 2% acetic acid administration (i.p.) and the writhing behaviour was recorded for 60 minutes. Writhing was presented as contraction of abdominal muscles which was accompanied by behaviour such as pronounced stretching of the hind and fore limbs, arching of the back as well as twisting and turning the dorsoabdominal muscles after induction with acetic acid. The number of writhing frequencies were averaged every 5 minutes interval and the total percentage of inhibition was evaluated by comparing with vehicle.

**Results:** All mitragynine doses were found to significantly reduced writhing behaviour ( $p < 0.0001$ ) except for 1 mg/kg. Mitragynine (15 and 30 mg/kg) demonstrated 100% inhibition in writhing behaviour compared to vehicle ( $p < 0.0001$ ), which indicated that no pain perception was experienced by the rats.

**Conclusions:** This study suggested that mitragynine has a potential as an anti-analgesic property with 15 mg/kg is the effective dose to develop this effect. Thus, mitragynine can be potentially developed as a new pain killer for relieving menstrual symptoms.

Paper Number: 103

## Pipeline Image Processing in Cerebral Small Vessel Disease (CSVD) for White Matter Integrity Determination Among Asymptomatic Individuals

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Cerebral small vessel disease (CSVD), in its asymptomatic or silent spectrum, is often found as incidental finding from magnetic resonance imaging (MRI) brain scanning. Diffusion tensor imaging (DTI) in combination with MRI brain scanning is an emerging neuroimaging method that can identify CSVD or white matter hyperintensities. Several methods exist for this purpose, with no specific gold standard in place to optimize the use of DTI in CSVD. This study aimed to compare their reproducibility and reliability in the assessment of white matter ischemic integrity in asymptomatic CSVD by using several combinations of pipelines processing. Upon consent, 48 subjects who met the study inclusion/exclusion criteria were recruited from the Clinic of Family Medicine at Hospital USM underwent MRI brain scanning. The images of the MRI brain scanning were further analyzed using several sets of DTI pipeline processing software involving different combinations of pipelines. The software used in variable combinations included DSI Studio, MRI converter, Fiber Tracking, MedInria 2.2, MedInria 1.9, Matlab, FSL, MRTrix, TrackVIs and Free Surfer. We found few parameters that can be used to compare the reproducibility and reliability between the combination of DTI software pipelines processing such as visualization, detection of white matter hyperintensities (WMH), tractography, the finding of WMH region of interest (ROI), tract statistic, and availability of WMH atlas. Later, such data can be used to optimize and develop a specific profile for CSVD disease spectrum for each of the tested DTI software pipelines processing.

Paper Number: 114

## Japanese Encephalitis Virus Can Infect Sensory and Autonomic Neurons: Evidence from in Vitro and in Vivo Studies

**Kum Thong Wong**

**Background:** Japanese encephalitis virus (JEV) is well known to infect neurons in the central nervous system (CNS). We investigated if peripheral sensory and autonomic neurons could likewise be susceptible to JEV infection.

**Methods:** Murine organotypic culture systems for dorsal root ganglia (DRG) and intestinal autonomic ganglia (IAG) were developed by harvesting the appropriate tissues from 1-day-old ICR mice. After careful dissection, the approximately 1x3mm fragments were infected with JEV/Nakayama strain (106CCID50/ml, volume 4ml/Petri dish) and incubated over a 5-day period on membranes at the air-medium interfaces with Neurobasal medium. Tissue fragments were harvested at 1, 3 and 5 days-post infection (dpi) for histopathological analysis. The in vivo experiment was done using a 2-week-old ICR mouse model, which was infected via the left hindlimb footpad with the JEV/Nakayama strain (106CCID50/ml, volume 20µl). All mice (n=6) were observed over several days, humanely euthanized near the terminal stage of infection, and tissues collected for histopathological analysis. Viral antigens and viral RNA were detected in infected tissues using specific immunohistochemistry and in situ hybridization assays, respectively.

**Results:** The DRG and IAG organotypic cultures were viable and were able to support viral infection. Both viral antigens and RNA were localized in neuronal bodies as early as 3 dpi and were very prominent by 5 dpi. All the mice succumbed to infection, and predominantly neuronal viral antigens/RNA were found in the DRG, peripheral sensory nerves, intestinal autonomic ganglia, brain and spinal cord.

**Conclusions:** Apart from the CNS neurons, sensory and autonomic neurons could be infected by JEV, suggesting that infection of peripheral neurons could potentially contribute to the pathogenesis of JE.

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Paper Number: 51

## FHL1-related Clinical, Muscle MRI and Genetic Features in Six Chinese Patients with Reducing Body Myopathy

*Zhaoxia Wang*

Reducing body myopathy (RBM) is a rare X-linked myopathy characterized pathologically by the presence of reducing bodies. The causative gene for RBM has been identified as FHL1, which encodes the four-and-a-half LIM domain protein 1 (FHL1). RBM has been reported in various ethnic populations, but not in Chinese populations. We present the clinical, muscle magnetic resonance imaging (MRI) and genetic features of 6 Chinese RBM patients (5 male and 1 female) from unrelated families. We divided the patients into 2 groups according to their age of onset. The late-onset group consisted of 3 male patients who had juvenile or early-adulthood onset, and the early-onset group consisted of the other 3 patients (2 male and 1 female) who had symptoms starting in early childhood. In addition to limb muscle weakness, a feature common to both groups was pronounced axial muscle involvement, with a rigid spine in 5 patients and dropped head in 1 patient. However, disease progression was more rapid in the early-onset group than in the late-onset group. Muscle MRI revealed fatty infiltration predominantly in the postero-medial muscle of the thigh and the soleus muscle of the calf, sparing the gluteus and sartorius muscles in 5 patients. Oedema appeared in the early-onset patients. Muscle pathology demonstrated the presence of reducing bodies distributed in small groups within muscle fibres. Molecular analysis revealed FHL1 mutations, including 3 novel (c.386G>A/p.C129Y, c.446\_448delACT/p.Tyr149del, and c.745T>C/p.C249R) and 3 reported mutations. To the best of our knowledge, this is the first report of RBM in the Chinese population. Our findings expand the genetic spectrum of FHL1-related RBM.

Paper Number: 55

## Congenital Muscular Dystrophies in the Mainland China: Clinical and Molecular Spectrum of a Multi-Center Cohort

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**Background:** Congenital muscular dystrophies (CMDs) are clinically and genetically heterogeneous conditions. We aimed to determine the relative frequency and clinical and genetic spectrum of CMD in a large multi-center cohort in the Mainland China.

**Methods:** A cohort of patients suspected to have CMD was ascertained from the databases in 9 centers between 2003 and 2017. Patients were screened with a combination of immunohistochemical analysis and genetic analyses based on the clinical findings.

**Results:** The study includes 361 patients, mutations were identified in 244 of the 361 (67.6%). The cohort was subdivided into diagnostic categories based on the most recent classifications on CMDs. The most common forms were those with laminin a2 deficiency (38.2%) followed by those with  $\alpha$ -dystroglycan glycosylation deficiency (26.9%) and collagen VI deficiency (20.9%). The forms of congenital muscular dystrophy related to mutations in LMNA and SEPN1 were less frequent (11.3% and 2.7%, respectively).

**Conclusions:** Our study provides for the first time the distribution for each of the major diagnostic categories of CMD in a large multi-center cohort of Mainland China. The study also reflects the diagnostic progress in this field with an accurate classification of the cases according to the most recent gene discoveries.

Paper Number: 56

# Exon 4 Deletion in LAMA2 is the Most Frequent Mutation in Chinese Patients with Laminin $\alpha$ 2-Related Muscular Dystrophy

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**Background:** We aimed to describe pathogenic copy number variations (CNVs) within the LAMA2 gene in a large cohort of patients with LAMA2 MD in the Chinese population and develop a modified next generation sequencing (NGS) assay for LAMA2 variant detection and identification.

**Methods:** High-resolution LAMA2-targeted array-based comparative genomic hybridization (a-CGH) microarray and NGS-based CNV profiling were used to analyze 114 individuals with LAMA2 MD, including 96 who were LAMA2 mutation-positive and 34 who had intragenic rearrangements. Mutational mechanisms of CNVs were investigated based on the sequence characteristics of breakpoint junctions.

**Results:** Causative CNVs were identified in all 29 probands and confirmed by analyzing the patients' parents, including compound heterozygous CNVs (26 patients) and homozygous CNVs (3 patients). In total, eighteen distinct LAMA2 CNVs were detected, all of which were only found in the Chinese population. We estimate that the overall frequency of CNVs in LAMA2 was 19.3%. Exon 4 deletion was detected in 10 alleles of eight patients, accounting for nearly 27% of all CNVs. All of them were shown to have the same haplotype and sequence at the breakpoint junction, suggesting that the exon 4 deletion represents a founder mutation in the Chinese population and is a mutation hotspot. Replication-based mechanisms, such as FoStES/MMBIR, may explain the majority of LAMA2 intragenic CNVs; two LINE elements located in intron 9 and intron 12 suggested potential intragenic-rearrangement hotspots within LAMA2. We present a modified NGS assay for LAMA2 variant detection and identification; the assay allows 85.7% of CNV breakpoint junctions to be identified directly alongside sequence information, which also overcomes false-positive rate using MLPA and spurious calls generated during array experiments.

**Conclusions:** We provide a novel perspective on the copy-number mutational spectrum in LAMA2; we demonstrate that the exon 4 deletion represents a founder mutation in the Chinese population and the exon is a mutation hotspot. Moreover, we provide a novel experimental approach for the detection and sequencing of the CNV breakpoints using NGS.

Paper Number: 57

## A New Titinopathy: Recessive TTN Variants Cause a Novel Form of Early-Onset Multi-Minicores Disease without Cardiac Involvement

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**Background:** Titin, encoded by the gene TTN, is involved in not only maintaining the structure of cardiac and skeletal muscles, but also in their development, extensibility, elasticity, as well as signaling events. Congenital multi-minicores disease (MmD) with fatal dilated cardiomyopathy (DCM) reported to date has been attributed to homozygous or compound recessive truncating mutations in the C-terminal (M-band) of the titin protein. Our aim was to delineate the phenotype and determine the genetic defects in two female siblings with an early-onset multi-minicores disease without cardiac involvement.

**Methods:** Clinical and myopathological evaluation of the two affected children, whole exome sequencing and minigene studies were performed.

**Results:** Both children presented with congenital muscle weakness and no structural or functional heart abnormalities on the latest follow-up. Skeletal muscle biopsies showed predominance of type 1 fibers and multi-minicores lesions (foci of mitochondria depletion and sarcomere disorganization). Skeletal muscle ultrastructural studies confirmed the presence of multiple foci of sarcomere disruption and mitochondria depletion. We identified compound heterozygous TTN variants (c.15496+1G>A and c.18597\_18598insC, p.Thr6200Hisfs\*15) corresponding to the Ig domain of the proximal I-band. Minigene analysis confirmed exon skipping of Exon 52.

**Conclusions:** I-band titin mutations cause a novel form of early-onset multi-minicores disease without cardiac involvement. Our finding expands the existing spectrum of known TTN variants and phenotypic manifestations and suggest that pathogenic variants of I-band titin may not cause dysfunction in cardiac muscles but cause a severe congenital defect in skeletal muscles.

Paper Number: 76

## Novel Recessive DNAJB6 Mutation Causes Severe Myofibrillar Myopathy and Compromises DNAJB6 Function

Fangyuan Qian

**Background:** Myofibrillar myopathy (MFMs) is a progressive muscle disease characterized by the disintegration of muscle fibers with the formation of protein aggregates. So far, only heterozygous missense mutations in DNAJB6 have been associated with autosomal dominant myofibrillar myopathy, limb-girdle muscular dystrophy type 1E and distal myopathy.

**Methods:** We performed whole exome sequencing in a 72-year-old Chinese man affected by MFM with distal lower extremity weakness and respiratory failure. The consanguineous family members of the patient were also investigated the genetic basis of this complex phenotype. Additionally, we investigated the pathogenicity of the causal mutation and possible mechanism in biopsy muscle using immunofluorescence, quantitative real time PCR, and western blot analysis, and filter-trap assay in cell transfection experiments.

**Results:** A homozygous mutation in exon 9, c.695\_699del (p.V232Gfs\*7) in of the DNAJB6 gene which affected DNAJB6a isoform exclusively was identified in the proband, while whose five non-myopathic family members were heterozygous mutation. Muscle pathology showed cytoplasmic inclusions and rimmed vacuoles. Bioinformatics analysis demonstrated that the mutation caused the nuclear localization signal loss of DNAJB6a. Immunofluorescence, quantitative real time PCR and western blot analysis showed the absence of DNAJB6 expression in nucleus and highlighted multiple fibers with subsarcolemmal accumulation, perinuclear aggregates and sarcoplasmic inclusions. Desmin, p62, and LC3b showed moderate to strong colocalization with DNAJB6 in the myofibrillar aggregates, and the rimmed vacuoles were strongly TAR DNA-binding protein 43(TDP-43)-positive. Furthermore, immunofluorescence analyses and filter-trap assay demonstrated that the c.695\_699del (p.V232Gfs\*7) mutation possessed a decreased effect on the anti-aggregation function of DNAJB6 protein.

**Conclusions:** This is the first report of Chinese patients with DNAJB6 myofibrillar myopathy. Our new findings may expand the molecular spectrum of DNAJB6 mutations and also emphasize the pathogenic role of DNAJB6a dysfunction in MFMs. Our data suggest that the novel mutation of DNAJB6 may play the pathological role in MFMs by decreasing its anti-aggregation function.

Paper Number: 86

# Genetic and Clinical Findings in a Chinese Cohort of Patients with Collagen VI-Related Myopathies

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**Background:** Collagen VI-related myopathy, caused by mutations in the genes encoding collagen VI, represents a clinical continuum from Ullrich congenital muscular dystrophy (UCMD) to Bethlem myopathy (BM). Here we studied the clinical, pathological and genetic characteristics of 60 Chinese patients with collagen VI-related myopathies.

**Methods:** Clinical data of probands and their family members were collected and muscle biopsies of 26 patients were analyzed. COL6A1, COL6A2 and COL6A3 exons were analyzed by direct sequencing or exon trapping and next generation sequencing (NGS). Mosaicism was detected and quantified by personal genome machine amplicon deep sequencing for mosaicism (PASM), which involves amplicon resequencing.

**Results:** Sixty patients were characterized by delayed motor milestones, muscle weakness, skin and joint changes with forty UCMD and twenty BM. Muscle biopsies revealed dystrophic changes and immunohistochemical/immunofluorescence studies showed completely deficiency (CD) of collagen VI or sarcolemma specific collagen VI deficiency (SSCD). We identified 62 different pathogenic variants in these 60 patients, with 34 were first reported while 28 were previously known; 72 allelic pathogenic variants in COL6A1 (25/72, 34.7%), COL6A2 (33/72, 45.8%) and COL6A3 (14/72, 19.4%). Among them, 39 were de novo, 25 autosomal recessively inherited, 7 maternally dominantly inherited, and 1 of unknown. Among these mutations, 34 (54.8%) are reported here for the first time and 28 (45.2%) were previously described. These variants were mostly distributed in COL6A1 and COL6A2, and 52/72 were in the triple helical domain (THD) and were mostly missense and splicing variants. We also found one case of somatic mutation in a parent by gDNA sequence chromatograms. The validation of mosaicism by PASM indicated a lower proportion of the mutant allele in the related parent.

**Conclusions:** Here we provide clinical, histological and genetic evidence of collagen VI-related myopathy in 60 Chinese patients. The mutations we identified underscore the importance of the THD in the assembly and function of collagen VI. NGS is a valuable approach for diagnosis and accurate diagnosis provides useful information for genetic counseling of related families.

Paper Number: 88

# Phenotype-Genotype Analysis of Chinese Patients with early onset LMNA-Related Muscular Dystrophy

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**Background:** The correlation between phenotype and genotype of Chinese patients with early onset LMNA-related muscular dystrophy was analyzed.

**Methods:** The clinical and pathological data of 42 Chinese patients with early onset LMNA-related muscular dystrophy were collected and analyzed. LMNA gene mutation analysis was performed by direct sequencing or next generation sequencing. Mosaicism was detected and quantified by personal genome machine amplicon deep sequencing for mosaicism (PASM), which involves amplicon resequencing.

**Results:** Totally 56 patients attending Peking University First Hospital between 2007 and 2018 were clinically diagnosed with LMNA-related muscular dystrophy and in 42 patients of 41 family mutations were identified in LMNA. Seventeen patients were diagnosed with Emery-Dreifuss muscular dystrophy (EDMD) and twenty five were diagnosed with LMNA-related congenital muscular dystrophy (L-CMD). Muscle biopsies from 15 patients (6 EDMD, 9 L-CMD) who did muscle biopsy revealed muscular dystrophy changes and six biopsy specimens from these 9 L-CMD cases exhibited inflammatory changes as well. We identified 19 novel and 10 known LMNA gene mutations in the 42 patients. All LMNA mutations occurred de novo except one EDMD patient who inherited from her father (displayed the same symptoms as his daughter). There were no hot-spot mutations in our cohort and c.745C>T occurred in seven L-CMD patients. Seven known mutations showed identical phenotype as reported cases, but 3 mutations (c.116A>G, c.94\_96delAAG, c.1489-14\_1489-7del) exhibited differently. Two patients with c.116A>G were EDMD while reported cases showed as L-CMD. Two patients with c.94\_96delAAG were diagnosed with EDMD and this mutation was reported both EDMD and L-CMD. The mutation c.1489-14\_1489-7del caused exon 9 deletion, and reported patients with exon 9 deletion resulted in dilated cardiomyopathy or LGMD and the mouse model showed Hutchinson-Gilford progeria syndrome. However, this patient presented as L-CMD and exhibited no symptoms of dilated cardiomyopathy or progeria. We also found somatic mosaic variant in the parent of four probands by PASM, indicating a lower proportion of the mutant allele in the related parent.

**Conclusion:** LMNA-related muscular dystrophy has different severity of symptoms and disease progression. Genotype-phenotype relationships remain unanswered and some mutations show different phenotype and further investigation is required.

Paper Number: 89

## Novel SEPN1 mutations cause SEPN1-related myopathy in Chinese Patients and diagnostic clues

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**Background:** Clinical manifestations, muscle pathological features and genetic characteristics in 5 Chinese SEPN1-related myopathy patients were summarized and analyzed in order to improve its diagnosis.

**Methods:** Clinical data of the probands and the parents were collected and analyzed. Skeletal muscle biopsies were performed to the probands for pathological diagnosis. Genomic DNA was extracted from peripheral blood leucocytes, and the SEPN1 gene was detected by exon trapping and next generation sequencing (NGS) and Sanger sequencing.

**Results:** Five patients presented with delayed motor development, muscle weakness, hypotonia, and a myopathic face, high palatine arches. All could walk independently, with poor running and jumping, and neck extensor weakness, rigid spine, lordosis or scoliosis. Symptoms of respiratory involvement were present in all patients and they often had upper respiratory tract infections and pneumonia. Four patients suffered severe pneumonia, pulmonary hypertension, respiratory failure. Lung function test showed moderate restrictive ventilation dysfunction in patient 2, 3 and 4. Polysomnography suggested hypoxia in all patients, and the minimum of oxygen saturation was 80%, 75%, 75%, 65% and 64%, respectively. Serum CK level was normal or mildly increased. Muscle biopsy indicated chronic myopathic changes in patient 2 and 5, and NADH staining presented small areas of reduced oxidative enzyme reactivity as well. Muscle MRI of proband 1, 3 and 4 showed diffuse fatty infiltration of gluteus maximus and thigh muscle. SEPN1 gene analysis detected with unreported compound heterozygote mutations. And mutations in exon 1 of SEPN1 were easily missed by NGS, which should re-analyze NGS data or detect exon 1 by Sanger sequencing.

**Conclusions:** Five cases of SEPN1-related myopathy are genetically identified and genetic counseling of the family can be possible. Patient who has delay in motor milestone with cervicoaxial weakness early in life, spinal stiffness, progressive respiratory insufficiency, early nocturnal hypoventilation, should be considered SEPN1 mutation.

Paper Number: 83

## GNE myopathy in Chinese population: hotspot and novel mutations

Wenhua Zhu

**Background:** To investigate the clinical features, pathological characteristics, and genetic profiles of GNE patients and genotype-phenotype correlation in China.

**Methods:** We summarized the clinical records of 46 patients diagnosed as GNE myopathy among which detailed molecular analyses were performed. The clinical and mutational profile of 54 previously reported Chinese patients were also reviewed.

**Results:** A total of 21 novel mutations, including a gross deletion spanning exon 1-2 and a retrotransposon insertion were found in our cohort, enlarging the spectrum of GNE mutations. The most frequent mutation in Chinese population was D207V, which accounts for 25.5% of total alleles (51/200). The age of onset was much later in the patients carrying D207V compared to other patients, indicated the less deleterious effect of D207V on enzyme activity.

**Conclusions:** GNE myopathy may be overlooked in China with a relatively milder phenotype due to a less deleterious common mutation.

Paper Number: 84

# Clinical and pathological features in Chinese patients with hereditary inclusion body myopathy

*Yutong Zhang*

**Background:** The objective of the following study was to investigate the clinical and pathological features in Chinese patients with hereditary inclusion body myopathy(h-IBM).

**Methods:** In this report, we describe 102 affected individuals in Chinese PLA general hospital with the clinical and pathological diagnosis of h-IBM. We additionally conducted a review of 44 patients with the diagnosis of distal myopathy with rimmed vacuole (DMRV), oculopharyngeal distal myopathy (OPDM), Welander distal myopathy (WDM) published in the Chinese literature. The search was performed by two authors independently. All the references of the selected articles were hand-searched for relevant studies not captured by electronic searches. The last search was updated in March 2018. Then we systematically analyzed the clinical and pathological characteristics of h-IBM in the Chinese population.

**Results:** The information of 146 patients were collected in this study. Reviews of the clinical features in Chinese population indicate that DMRV is the most common pattern (89%), Inclusion body myopathy with Paget disease of the bone and/or frontotemporal dementia (IBMPFD) and WDM is relatively rare (8% each). Most patients underwent an open muscle biopsy. The pathological manifestations showed that the majority of the rimmed vacuoles were located in the center of the atrophic muscle fibers, and were round or oval with the basophilic granules in the rimmed vacuoles being coarse granules, compared with the pathological features of s-IBM patients. The proportion of mononuclear cell invasions in the muscle fibers was smaller in h-IBM patients.

**Conclusions:** this is the first large report on h-IBM in Chinese population which includes a total of 146 patients (58 sporadic cases and 56 familial cases from 13 families) with the diagnosis of DMRV, OPDM, IBMPFD and WDM respectively. Here we emphasized the clinical and pathological features and indicated that h-IBM patients in Chinese have heterogeneous clinical and pathological features compare with the cases in other countries.

Paper Number: 72

# MADD in an adult Thai patient, harboring mutations in ETFDH gene

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## Background

Adult-onset multiple acyl-CoA dehydrogenase deficiency (MADD) is a rare autosomal recessive disorder, frequently caused by mutation in ETFDH gene. Most cases respond well to riboflavin therapy (RR-MADD). Chronic myopathic symptoms, including progressive weakness, myalgia and exercise intolerance, are the main clinical manifestations. Subacute presentation is relatively uncommon and may mimic acquired myopathies, especially polymyositis. Diagnosis and treatment of adult-onset MADD is frequently delayed.

## Methods

The authors described clinical presentation, electrophysiology, MRI, muscle pathology, genetic study and treatment outcome of an adult Thai patient with MADD.

## Results

A 40-year-old Thai woman presented with 2-month history of progressive generalized muscle weakness without myalgia. Bulbar weakness developed two weeks, prior to admission. The weakness was significant that she required nasogastric tube feeding. Her past medical illness and family history were unremarkable. On examination, she was alert. She had normal extraocular movements. Strength of the neck and proximal muscles was MRC grade II/V. Strength of the distal muscles was MRC grade III-IV/V. She had no muscular atrophy. Lab showed serum CPK of 1979 U/L(25-170), AST of 248 U/L(5-35), ALT of 894 U/L(0-40) and LDH of 688 U/L(125-220), otherwise unremarkable. Ultrasonography showed diffusely increased hepatic parenchymal echogenicity, consistent with a fatty liver. Nerve conduction study was normal. Needle EMG showed non-irritable myopathy. Left deltoid biopsy clearly revealed markedly increased lipid droplets in muscle fibers. Diagnosis of adult-onset MADD was provisionally made and riboflavin was promptly started on the 5th day of admission. The patient showed rapid resolution of all symptoms within one week. MRI of the muscles, two months later, showed mild muscle atrophy of the posterior compartment of both thighs. Single riboflavin therapy has been continued. No acute or chronic deterioration has developed during the course of follow-up of two years. Subsequently, genetic study revealed compound heterozygous missense mutations in ETFDH; NM\_004453.3: c.[250G>A];[524G>A], p.[Ala84Thr];[Arg175His].

## Conclusions

The authors reported an adult-onset MADD who presented with subacute myopathy. Electrophysiological and pathological findings led to the correct diagnosis. Therapeutic trial with riboflavin provided significant advantages, prior to genetic confirmation.

Paper Number: 8

# A case of MELAS syndrome: epileptic patient with lactic acidosis, acute cortical blindness, and mild myopathy

*Si Tri Le, MD. Minh Le, MD. Thang Ba Nguyen, MD. PhD*

## **Background:**

Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) syndrome is a mitochondrial disorder which is maternally inherited or of sporadic occurrence, and which presents features that are included in the components of the disorder name. The weakness due to myopathy described as exercise intolerance is often mild and misdiagnosed easily. A diagnosis could be made by mitochondrial DNA mutation analysis for some typical cases in Vietnam.

## **Case presentation:**

A 20 years old male was admitted to the University Medical Center because of acute onset total blindness. Clinical examination disclosed mild quadriparesis and pes cavus deformity without muscular atrophy. His past medical history demonstrates refractory generalized epilepsy, septic shock with severe lactic acidosis one year prior. Through family history, his grandmother and mother have had deafness as the same age of thirty. Laboratory test shows high NT-proBNP, increase of lactic acid in blood and CSF, brain MRI indicate bilateral DWI high-intensity lesions in the occipital lobes and EMG shows myopathic pattern MUPs. Our patient was diagnosed MELAS syndrome by mitochondrial DNA mutation analysis of blood which demonstrates the mtDNA mutation at nucleotide position 3243 in the gene (MTTL1) encoding for tRNA. During the follow-up visits, his blindness was recovered and the seizures are controlled by two antiepileptic drugs including carbamazepine and levetiracetam.

## **Conclusion:**

MELAS syndrome, a rare disease which is mostly inherited from the mother, could affect multiple organs. The diagnosis could be made by mitochondrial DNA mutation analysis for typical cases. Without current specific therapy, supportive treatments for this syndrome include antiepileptic drugs, supplements (vitamins, arginine, coenzyme CoQ10), neurologic and cardiologic consultancies.

## **Discussion:**

MELAS syndrome is a rare multisystem disorder in which signs of myopathy are usually mild. In typical case, mitochondrial DNA mutation analysis of blood, urine sediment, buccal mucosa, skin fibroblast plays a major role in the definite diagnosis. However, muscle biopsy which is an underused or unavailable diagnostic tool in Vietnam, is still a valuable primary diagnostic approach of metabolic myopathies.

Paper Number: 12

# Mitochondrial cytopathy the great mimicker

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## Background:

Mitochondrial cytopathy greatly mimics myasthenia gravis because of almost similar clinical presentation.

## Case report:

We report a case of a patient who presented with bilateral ptosis without diurnal variation & diplopia since 1998. She denies any symptoms of diplopia, dysphagia, dysarthria, limb weakness & shortness of breath. She was treated in our clinic with pyridostigmine since 1998 with clinical response but she still has residual ptosis. She also had bilateral tarsorrhaphy done in 2007.

Her mother had similar ptosis & did not seek medical treatment. She has 3 children and 2 of her children has similar ptosis. Her daughter has bilateral ptosis noted since early 30s and her son has bilateral ptosis since age 29.

On examination, she had bilateral ptosis, orbicularis oculi weakness with reduced range of movement for all direction of bilateral eyes & also eyelid fatigability. Her neck flexion power was 4/5, extension 5/5; bilateral upper & lower limbs proximal power were 5/5. There was no retinitis pigmentosa on fundoscopy.

Acetylcholine receptor antibody assay (28/5/2005): 0.10nmol/L (negative). Nerve conduction study (6/6/2005) showed no significant decremental response on 3Hz repetitive stimulation test. Single fiber electromyography negative. Modified tension test (30/10/2007): negative.

Lactate 1.0mmol/L (normal: 0.5-2.2mmol/L), Creatinine kinase 132U/L (normal: < 170U/L). Electrolytes were normal. She was not keen for muscle biopsy.

## Discussion points

A detailed history of presentation & family history coupled with examination of family members of the index case is crucial to aid in the diagnosis. Our case mimics myasthenia gravis clinically & was treated with pyridostigmine.

## Conclusion:

Persistent progressive ptosis warrants detailed family history taking & examination of other family members for presence of bilateral ptosis, especially when investigations are negative for myasthenia gravis. A muscle biopsy would be greatly helpful in confirming the diagnosis.

Paper Number: 67

# Mitochondrial toxicity of telbivudine: a case presenting with unusual longstanding neuromyopathy

*Chamaiporn Taychargumpoo*

**Background:** Telbivudine, a thymidine  $\beta$ -L nucleotide analogue, has been a treatment option for chronic hepatitis B virus (HBV) infection due to its effectiveness and good tolerability. However, there were several reports of neuromuscular adverse events with yet unclear pathophysiological mechanism.

**Methods:** The authors described clinical features, electrodiagnostic findings and muscle histopathology of a case with telbivudine-associated neuromyopathy. Comprehensive genetic analysis to find predisposing mitochondrial disorders was also employed. Previous reported cases were reviewed.

**Results:** A 77-year-old woman with HBV infection (HBV viral load of 80,478 copies/ml and negative HBeAg) developed 8-year-course of bilateral incomplete ptosis, painless proximal muscle weakness and distal sensory loss. Weakness and ptosis started one year after receiving telbivudine (600 mg/d). Serial serum creatine kinase (CK) ranged from 600 to 3000 U/L (25-170 U/L). Electrodiagnostic study revealed non-irritable myopathy and concurrent sensorimotor axonal polyneuropathy. Other potential causes of polyneuropathy were also excluded. Left biceps biopsy was compatible with mitochondrial myopathy. Comprehensive mitochondrial and nuclear gene analysis revealed no pathologic variant. Three months after discontinuation of telbivudine, her muscle strength and CK level returned to baseline. However, polyneuropathy was still persisted. Among 27 patients, from 16 previous studies, who developed telbivudine-associated myopathy, ptosis and unusual long course of myopathy have not been reported. Additionally, development of neuropathy without concomitant interferon usage was uncommon. Absence of predisposing mitochondrial disorder in this case gives emphasis to the direct mitochondrial toxicity of telbivudine.

**Conclusions:** The authors presented a case of telbivudine-associated mitochondrial neuromyopathy with very long clinical course, mimicking an inherited mitochondrial disorder. Physicians should be aware of various clinical presentations of this acquired mitochondrial disorder.

Paper Number: 11

# Myasthenia gravis (MG) associated with premature ovarian failure (POF) - a coincidence or cause-and-effect relationship?

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## Background:

To report two rarely-described cases of MG associated with POF and review other similar published cases.

## Methods:

We describe two women with MG, who presented initially with secondary amenorrhoea. A comprehensive literature review was performed using PubMed. Six reports involving seven patients between 1980 and 2017 were found and analyzed.

## Results:

The first case was a 23-year-old nulliparous woman, who presented with eyelid drooping, easy fatigability and lower limb weakness for almost 2 years, preceded by cessation of menses. The second case was a 35-year-old woman (Para 1), who had amenorrhoea (7 months) prior to bilateral ptosis (3 months). Both women were positive for anti-acetylcholine receptor antibodies, repetitive nerve stimulation and single-fibre electromyography tests. Both had hypoestrogenemia with post-menopausal range of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. In the first case, her menses resumed with hormone replacement; and myasthenic symptoms improved with pyridostigmine and azathioprine. The second case resumed menstruating and myasthenic symptoms improved with thymectomy, hormone replacement and pyridostigmine.

From the literature review and our current study, there are nine patients with MG associated with POF. The median age is 27 years old. Two developed myasthenic symptoms and amenorrhoea simultaneously; two were diagnosed with MG first; and five had amenorrhoea before myasthenic symptoms. Three patients had positive anti-ovarian antibodies (AOA); one was positive for anti-LH antibodies; two had positive ovarian biopsies; and three had neither biopsies nor serum AOA done. One had a spontaneous pregnancy after thymectomy and hormone replacement; one started menstruating after thymectomy and plasma exchange; one resumed menstruating after hormone replacement; one resumed menstruating after thymectomy and hormone replacement; one had a myasthenic crisis due to hormone replacement; one had worsening of MG during menstruation; two were amenorrhoeic despite thymectomy; one was unable to conceive despite attempts of induction of ovulation.

## Conclusions:

We conclude that there is a possible link between MG and POF, which are both of autoimmune etiology. This is based upon presence of autoantibodies; and resolution of amenorrhoea after thymectomy or immunotherapy in some cases. Further studies are required to strengthen this link.

Paper Number: 18

# Guanosine diphosphate-mannose pyrophosphorylase-B gene mutations causing limb-girdle muscular dystrophy overlapping with congenital myasthenic syndrome

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**Objective** To report four cases of patients with secondary  $\alpha$ -dystroglycanopathy caused by guanosine diphosphate-mannose pyrophosphorylase-B (GMPPB) gene mutations and review the literature aiming to analyze the clinical manifestations, muscle image, molecular pathology and genetic characteristics of the disease. **Methods** The medical history, physical examination, electromyography and other clinical data of four patients with secondary  $\alpha$ -dystroglycanopathy from two families were collected and retrospectively reviewed from 2009 to 2017. Case 1 (proband of pedigree 1) and case 2 (proband of pedigree 2) were then further analyzed with muscle imaging, muscle pathology and targeted next generation gene sequencing (NGS). **Results** Four patients came from two families (three from the same pedigree), two males and two females, with an onset age of 17-18 years. All four cases presenting as limb-girdle muscular dystrophy overlapping with congenital myasthenic syndrome characterized by evident proximal limb weakness in early adulthood and fluctuating muscle weakness. They all had delayed motor milestone and did not perform well in physical education since childhood. Serum creatine kinase was elevated markedly (1 877-5 275 U/L). Myogenic changes on electromyography and marked attenuation on 3 Hz repetitive nerve stimulation were observed in all patients. Muscle MRI showed prominent involvement of bilateral hamstrings in case 1 and case 2. Muscular dystrophic patterns were demonstrated on muscle biopsies. Targeted NGS revealed two compound heterozygous missense mutations in GMPPB for each case. Case 1 carried c.860G>T (p.R287L)/c851T>C (p.V284L). Case 2 and his both affected sisters (case 3 and case 4) carried c.1097A>G (p.N366S)/c.589G>T (p.V197F). All of these mutations were novel variants and pedigree analysis suggested that the two mutations were from parents. Compared with normal control, immunohistochemistry and western blot showed significantly decreased expression of  $\alpha$ -dystroglycan in the muscle tissue from case 1 and case 2. **Conclusions** Mutations in GMPPB can lead to dysfunction both in muscle and in neuromuscular transmission causing overlapping between LGMD and CMS phenotypes. Cholinesterase inhibitors can partly improve the symptoms of myasthenia in such patients.

Paper Number: 41

# Adult Onset Limb Girdle Myasthenia Due To A Possible Founder Mutation In A Rare Gene

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## Background

Mutations in GMPPB (GDP-mannose pyrophosphorylase B) results in congenital muscular dystrophies (CMD) and Limb girdle muscular dystrophies. Recently, variants in GMPPB were reported to cause congenital myasthenic syndrome (CMS).

## Methods

10 patients from 4 south Indian families with late onset limb girdle syndrome are described. Evaluation included clinical phenotyping, biochemistry, repetitive nerve stimulation and muscle biopsy. 6 patients underwent genetic testing.

## Results

All were born to consanguineous parents. Family 1: A 50-year-old man had onset at 42 years with progressive proximal limb weakness and after 2 decades is still ambulant. His 3 younger siblings are affected with onset in 4th decade and similar illness. Family 2: A lady aged 35 was symptomatic for 5 years. Similar illness in elder sister. Family 3: A lady aged 32 had history of progressive fatigable limb girdle weakness with hypertrophied calves for 10 years. Family 4: A lady aged 45 developed fatigable limb girdle and jaw weakness from 28 years of age, diurnal and seasonal fluctuations. Her elder sister and maternal cousin also had similar illness. Pyridostigmine and Salbutamol were started in family 3, and showed significant improvement. RNS showed decrement response in all tested patients. CK levels were elevated in all (650-4547 U/L). Muscle biopsy in 4 patients was suggestive of muscular dystrophy.

Genetic analysis performed in 6 patients revealed identical missense mutation c.1000G>A (p.Asp334Asn) in exon 9 of GMPPB gene. This mutation was previously reported in compound heterozygous form in 2 patients of Asian origin (Pakistan and India). However, the phenotype described was CMD with CNS involvement. While, all our patients had homozygous mutation, a milder slowly progressive phenotype consistent with Limb girdle myasthenic syndrome. This indicates the milder effect of the mutation which may require a different mutation to cause severe phenotype. This variant has not been reported from other geographical regions. The allele frequency of c.1000G>A among south Asians is 0.0005 and has zero frequency in other populations in ExAC database.

## Conclusion

This report further expands the emerging phenotypic spectrum of GMPPB associated dystroglycanopathies and indicates a probable South Asian founder mutation with milder effect in its homozygous form.

Paper Number: 62

## The first Korean case of COLQ-mutant myasthenic syndrome

*Jin-Hong Shin*

The COLQ gene encodes a collagen-like strand that anchors acetylcholinesterase upon MuSK molecule at the endplate of neuromuscular junction. Homozygous or compound heterozygous mutation in this gene causes reduction in acetylcholinesterase activity, which in turn leads to an overloading of cations at the synaptic space. It is also pathogenically similar to anti-MuSK myasthenia gravis. Many cases could have been missed before the advent of next generation sequencing, as the clinical presentation is often non-specific.

A 34-year-old woman presented with one year of progressive limbs weakness. She has not suffered difficulties in her daily activity before, though she had not been good at sports since her childhood. She first noticed weakness in her both legs when she stands up from squatting. She also felt difficulty raising heavy objects, which she could manage. The weakness progressed in a few months that she could not keep up with the walking pace with her friend. In 6 months, she could not stand up from sitting on a chair, nor walk without aid. Repetitive nerve stimulation test revealed marked decremental response on her trapezius muscle, indicative of postsynaptic neuromuscular transmission defect. Needle electromyography showed low amplitude, short duration MUPs and rapid recruitment in several muscles, while nerve conduction study was unremarkable. Muscle imaging as well as muscle pathology showed mild myopathy. Blood chemistry findings were all within normal limits. Custom panel myopathic genes detected compound heterozygous mutation in COLQ, c.1195+1G>A (rs755782087) and c.1354C>T (p.R452C, rs368932156), which was reported to be pathogenic in Japanese patients with congenital myasthenic syndrome. She started to take bambutrol 10mg qd, which significantly improved her limbs weakness.

Here we report the first Korean case of congenital myasthenic syndrome by COLQ mutations. Higher level of awareness is required for this ultra-rare disease, as some forms of congenital myasthenic syndromes including COLQ-mutant one can be alleviated by use of beta agonist.

Paper Number: 94

## Analysis of abnormal lipid metabolism in children with ocular myasthenia gravis

*Xiushan Ge*

**Objective** Investigate the abnormal lipid metabolism in children with ocular myasthenia gravis (OMG) before glucocorticoid treatment. **Methods** The total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C) and low density lipoprotein cholesterol (LDL-C) were measured in 61 patients, from neurology department of Capital Institute of Pediatrics, with OMG before the treatment of corticosteroids from January 2017 to May 2018. **Results** There were 18 males, (5.7±4.3) years old, range from 11 months old to 15 years old, and 43 females, (4.3±2.7) years old, range from 11 years old to 1 year old. The proportion of dyslipidemia was 23% (14/61), male and female were 22.2% and 23.3% respectively. There was no significant difference between the sexes. In the patients with abnormal lipid metabolism, 57.1% (8/14) was LDL-C abnormality, 28.6% (4/14) was TG metabolism abnormality, 7.1% (1/14) was TG and LDL-C abnormal metabolism, 7.1% (1/14) was TC and HDL-C metabolic abnormalities. **Conclusion** There is a high proportion of abnormal lipid metabolism in children with OMG before glucocorticoid treatment, and the increase of LDL-C is the main disorder. The mechanism needs further study.

Paper Number: 3

## Elucidation of various inflammatory pathways in experimental paradigms of STZ-induced diabetic neuropathy

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**Background:** Diabetic neuropathy affects more than 50% of diabetic patients. Rutin has been demonstrated in number of pharmacological activities including anti-diabetic, anti-oxidant and anti-inflammatory activities. **Materials and Method:** Streptozotocin (STZ, 55 mg/kg) was administered intraperitoneally (i.p.) to overnight fasted rats. Naive and diabetic rats were randomly selected and divided into eight groups of six animals in each group. Rutin (100 and 200 mg/kg, i.p.) and Nimesulide (5 and 10 mg/kg, i.p.). All the behavioural parameters (Measurement of body weight, Mechanical allodynia, Cold allodynia, Mechanical hyperalgesia, Thermal hyperalgesia) were performed on day 0, 2nd, 4th, 6th and 8th week. On last day (of 8th week), blood was collected retro-orbitally and mean nerve conduction velocity was assessed. The animals were then sacrificed sciatic nerves were isolated for further biochemical estimations, TNF-alpha and caspase-3 activity estimated by ELISA. **Results:** Rutin (100 and 200 mg/kg) for 8 weeks significantly protected all the behavioral alterations, oxidative damage and change in mean nerve conduction velocity induced by STZ. Further, combination of Rutin (100 and 200 mg/kg) with Nimesulide (10 mg/kg) significantly reversed all the behavioural, biochemical and changes in nerve conduction velocity as compared to their effect per se in STZ-induced diabetic neuropathy. **Conclusion:** The present study suggests the protective effect of Rutin against STZ-induced diabetic neuropathy. Study further provides an evidence that rutin produces better effect in combination with nimesulide against STZ-induced diabetic neuropathy.

Paper Number: 5

## Meralgia Paresthetica Treatment with Acupuncture: a case series

**Yun Jin Kim***Xiamen University Malaysia, Sepang, Selangor, Malaysia*

**Background:** Meralgia paraesthetica (MP) is a fairly common condition resulting from entrapment of the lateral femoral cutaneous nerve (LFCN). The purpose of this case series report is the improvement after treatment with acupuncture about a patient with meralgia paresthetica.

**Methods:** We treated the 10 patients with acupuncture treatments in 2015 to 2017. All patients' consultant rheumatologists in one of Malaysia private hospital to referred, and taken the lumbar spine MRI scans to diagnosis. During acupuncture treatment we are use evaluating with VAS score. We are used acupuncture locations are ST31, ST33, ST32, GB31, ST37, ST39, and LR9.

**Results:** After 5 months of treatments, the VAS scores for all 10 patients improved by at least 50%. In the flowing investigation (varying from 3 to 12 months), improvement nearly 70 to 80%.

**Conclusion:** The various symptoms appear in the meralgia paresthetica such as numbness, paresthesia, and pain in the anterolateral thigh, which may result from either an entrapment neuropathy or a neuroma of the lateral femoral cutaneous nerve (LFCN). Acupuncture treatment for meralgia paresthetica resulted in satisfied, also more basic/clinical research of meralgia paresthetia is needed.

Paper Number: 10

## Myokymia of Lower Limbs and Abdomen : a Case Report

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**BACKGROUND:** Myokymia, a form of involuntary muscular movement, may occur in particular region or may affect the body generally. Treatment of myokymia depends upon the cause.

**OBJECTIVE:** To describe a case of myokymia of lower limbs and abdomen.

**METHODS:** A case report.

**RESULTS:** A 18-year-old man has had painful cramps in his lower limbs and fasciculations in the certain muscles after strenuous exercise. Myokymia can be detected when the muscle is at rest and during sleep. The affected muscles were rectus abdominis and the muscles of legs, especially rectus femoris. Excessive sweating occurred on his face and back. There was no evidence of wasting and weakness. Spinal MRI was normal. The total CPK level was slightly high. Nerve conduction velocities were within normal ranges. In needle EMG, myokymic discharges were recorded at rest (consisted of doublets and triplets). Myotonic discharge was not observed. Tests to detect antibodies against voltage-gated potassium channels (VGKC) are not available in Vietnam. According to these data, he was diagnosed as Transient Focal Myokymia. However, his symptoms had not improved with either bed resting or Phenytoin. Consequently, Carbamazepine 200 mg daily was administered and his symptoms resolved over the next few days. He remained taking carbamazepin everyday for 2 weeks and he could work in the fields normally. Then, he stopped using this drug and his myokymia occurred whenever he did hard works. He has been taking carbamazepine until now and his myokymia have not reoccurred.

**CONCLUSION:** Focal myokymia that develops after strenuous exercise usually resolves spontaneously as we know it. However, carbamazepin can be effective in treating these patients.

Paper Number: 19

## Prolonged Exercise Test in Patients with History of Thyrotoxicosis

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### Background:

Thyrotoxic periodic paralysis (TPP) is characterised by recurrent episodes of reversible, severe proximal muscle weakness associated with hypokalaemia and hyperthyroidism. TPP is common in Asians and is a secondary hypokalaemic periodic paralysis, with clinical and electrophysiological characteristics similar to primary hypokalaemic periodic paralysis. Prolonged exercise test (PET) is an easy, non-invasive test evaluating abnormal muscle membrane excitability in periodic paralyses. Results of PET studies in TPP patients on their thyroid status have been variable with one study showing normalization of response while another did not. We aim to evaluate patients with history of thyrotoxicosis with PET and correlate it with the thyroid status.

### Methods:

We prospectively recruited 35 patients with history of thyrotoxicosis (regardless of whether they had TPP) from Endocrinology Clinic. Of the 35 patients, 18 were hyperthyroid, 17 euthyroid or hypothyroid. The thyroid status was determined biochemically from the latest thyroid function test. All patients underwent PET as described by McManis. Compound muscle action potential (CMAP) amplitudes post-exercise were compared against pre-exercise amplitudes and recorded as percentage of mean baseline CMAP amplitude.

### Results:

Compared to 17 euthyroid or hypothyroid patients, significant time-dependent declines in CMAP amplitudes at 20 minutes (88.3±11.9% vs 96.7±5.2%; p=0.012), 25 minutes (88.8±12.9% vs 96.4±8.6%; p=0.047) and 30 minutes (88.1±13.0% vs 97.1±10.3%; p=0.030) after exercise were observed in hyperthyroid patients. The calculated mean greatest decrement from immediate post exercise CMAP amplitudes were 22.5±13.0% in hyperthyroid patients and 15.5±13.0% in euthyroid/hypothyroid patients.

### Conclusion:

CMAP decrement on PET was significantly greater in hyperthyroid patients compared to euthyroid/hypothyroid patients even without a history of TPP. Muscle membrane excitability is highly influenced by thyroid hormone level. TPP results from increased levels of thyroid hormone activity in genetically susceptible patients.

Paper Number: 31

## Clinical characteristics and treatment outcome of childhood onset chronic inflammatory demyelinating polyneuropathy

*Woojoong Kim*

**Backgrounds:** Chronic inflammatory demyelinating polyneuropathy (CIDP) is a clinically heterogeneous group of sensory and motor peripheral neuropathy, presumed to occur due to immune related reactions. Because childhood CIDP is very rare, there are very few published studies to help clinicians in treating refractory cases. Aim of this study is to investigate the clinical features and treatment outcome of childhood CIDP.

**Methods:** Clinical features and treatment outcomes of 14 cases of childhood CIDP (mean age =  $8.6 \pm 3.8$  years old) followed up for more than a year (mean duration =  $47.7 \pm 29.6$  months) were analyzed. Patients were initially treated with either intravenous immunoglobulin (IVIg) (78.6%) or steroids (21.4%). Plasmapheresis was considered when both treatments were proven ineffective.

**Results:** In contrast to adult CIDP, which commonly showed insidious onset with monophasic courses, patients from this study manifested more frequently with subacute onset ( $n=10$ , 71.4%) and polyphasic course ( $n=8$ , 57.1%).

In the monophasic group ( $n=6$ , 42.9%), plasmapheresis ( $n=5$ ) showed a better treatment response (good 80%, partial 20%, none 0%) compared to IVIg ( $n=6$ ) (good 0%, partial 50%, none 50%) and steroids ( $n=5$ ) (good 0%, partial 40%, none 60%), especially in progressive phases. In the polyphasic group ( $n=8$ ), IVIg ( $n=8$ ) (good 50%, partial 37.5%, none 12.5%) and plasmapheresis ( $n=4$ ) (good 0%, partial 100%, none 0%) showed comparable treatment responses. Six polyphasic patients (75%) were refractory to first line treatment and received immunosuppressant; All four patients who received cyclosporine achieved significant disease control. The overall long-term outcomes were favorable, with 6 patients (42.8%) showing minimal symptoms and no relapse within 6 months.

**Conclusions:** This study results suggest that administration of plasmapheresis in progressive monophasic course and cyclosporine in refractory polyphasic course may be effective in childhood CIDP.

Paper Number: 42

## Characterization of Chronic Moderate-Severe Contusion Spinal Cord Injury Muscle Properties

*Kok, HJ, Oster JC, Conover, CF, Barton, ER, Yarrow, JF*

Spinal cord injury (SCI) is a medically complex and life-disrupting condition that is associated with low quality of life. Patients with chronic SCI display extensive muscle atrophy and neuromuscular impairment that impedes functional recovery. Therefore, it is important to understand the chronic neuromuscular adaptations to SCI in order to generate future therapeutic strategies. For this study, 4-month old male Sprague-Dawley rats were randomized to receive T9 laminectomy (SHAM) or T9 laminectomy plus moderate-severe contusion SCI. Basso-Beattie-Bresnahan (BBB) locomotor rating scores were measured weekly. The soleus, a slow-oxidative postural muscle, was harvested at 2 weeks, 1 month, 2 months, or 3 months post-surgery ( $n=3$ /group at each timepoint) and was immunofluorescently labeled with anti-laminin and anti-Myosin Heavy Chain Types I and IIa, to assess fiber-type distribution and muscle fiber cross-sectional area (CSA), and with anti-neurofilament, to evaluate muscle-nerve bundle morphology. Immediately after surgery, SCI animals exhibited near-complete hindlimb paralysis and they did not regain the ability to perform hindlimb weight-supported stepping at any point during the study (i.e.,  $BBB < 9$ ); however, some improvement in hindlimb muscle mobility was observable throughout the study. Body mass, soleus mass, BBB score, and median CSA were significantly lower ( $p < 0.01$ ) in SCI versus SHAM, at all post-surgery timepoints. A slow-to-fast fiber-type shift was observed in SCI animals, with a progressive ~20% decrease in the number of type I fibers, ~8% increase in type IIa fibers, and ~5% increase in hybrid type I/IIa fibers at each consecutive time point, along with the emergence of unstained type IIx/b muscle fibers (~30% of total) at the 3-month timepoint. In addition, muscle fiber splitting was present in SCI animals at the 2-month timepoint, as well as reduced neurofilament staining in SCI muscle-nerve bundles. These changes imply that the deterioration in motor ability accompanying SCI produces muscle atrophy, progressively impairs muscle oxidative capacity via denervation-reinnervation cycles, and contributes in muscle pathology.

Paper Number: 53

# Comparison of dual-energy X-ray absorptiometry and bio-electrical impedance analysis—measured fat mass in myopathy and control subjects

*DW Namgung*

## Background

Myopathy is accompanied by fatty replacement of the skeletal muscle as the disease progress. There are several imaging techniques available to measure fat mass. Dual energy X-ray absorptiometry (DEXA) has been widely compared to other techniques such as CT or MRI for assessing body composition and accepted as validation tool. Bio-electrical impedance analysis (BIA) has performed frequently as a non-invasive and easily accessible method of measuring body composition. Although previous validation study showed excellent agreements in estimating fat mass between DEXA and BIA, no such study has been conducted in myopathy patients. The present study aimed to investigate the correlation of DEXA and BIA-measured fat mass in myopathy and control groups

## Method

A cross-sectional analysis was conducted in 9 myopathy and 9 control subjects at Gangnam Severance Hospital, Seoul, Korea. We measured arm, leg, trunk and total fat mass by DEXA and BIA. Spearman correlation coefficients were calculated to examine the relation of each BIA-measured fat mass with the corresponding DEXA-measured fat mass in myopathy and control subjects. For each region, differences between BIA and DEXA were compared by using Wilcoxon's signed-rank test.

## Results

High correlation was observed between both techniques in total fat mass ( $r=0.883$ ,  $p=0.002$  and  $r=0.983$ ,  $p<0.01$  for myopathy and control subject, respectively). In segmental fat mass quantification for myopathy subjects, excellent agreements between two methods were demonstrated for the left arm ( $r=1.000$ ,  $p<0.01$ ), right arm ( $r=0.943$ ,  $p=0.005$ ), left leg ( $r=0.943$ ,  $p=0.005$ ), right leg ( $r=0.928$ ,  $p=0.005$ ) and trunk fat mass ( $r=0.943$ ,  $p=0.005$ ). All regional fat mass differences were observed significantly ( $p<0.05$ ) except for trunk fat measured by DEXA and BIA.

## Conclusion

In the present study, all BIA-measured regional and total fat mass were strongly correlated with their corresponding DEXA measures ( $r>0.883$ ) for myopathy subjects. Regional fat mass differences between both techniques were significant, but our sample size was small. Although BIA is valuable tool and can easily assess body composition, its accuracy measuring fat mass remains unclear in myopathy patients so further investigation is recommended.

Paper Number: 71

## Incidence of Spinal Muscular Atrophy (SMA) in Malaysia

*Gaik Siew Chng***Background :**

Spinal muscular atrophy is one of the leading genetic causes of infant mortality and represents a significant healthcare burden. With the development of promising novel therapies and clinical trials, comes the need for an improved understanding of its epidemiology and access to specialized care. The estimated worldwide incidence of all types of SMA is around 10 in 100,000 (1 in 10,000) live births. This study aimed to investigate the incidence of genetically confirmed SMA in Malaysia.

**Methods :**

Data over 10-year period from 2007 – 2016 was gathered from Institute for Medical Research (IMR), which is responsible for the majority of all SMA tests in the country. PCR-Restriction Fragment Length Polymorphism (PCR-RFLP) was used from 2007-2012 to detect homozygous deletion of SMN1 gene in SMA patient. This was replaced with Multiplex Ligation-dependent Probe Amplification (MLPA) to identify SMN1 and SMN2 dosage from 2013-2017. Information obtained from the request form included age, gender, ethnicity and clinical phenotype of the patient and stratified to SMA subtypes I - IV.

**Results :**

There were 249 cases of SMA homozygous deletion out of total 1076 requests for SMA gene testing from 2007-2016. This provides an estimate median incidence of 4.9 per 100,000 live births [range 3.46 - 6.54 per 100,000 live births] ( $\approx$  1 in 20 000). The most common subtype is SMA type 1 which constitutes 51.8%, types II/III 46.6% and type IV 1.6%. The gender distribution is almost equal. In terms of ethnicity, Malays seem to dominate with 69.9%. Majority of SMA genetic testing was done before the age of 1 year old.

**Conclusions :**

SMA incidence in Malaysia is lower than that of European or worldwide incidence. Patient and clinical registries for SMA are not available in Malaysia and will be warranted to estimate SMA prevalence rate in Malaysia. This study is a step forward in understanding the epidemiology of SMA and need for follow-up study to determine the number of patients that are ready to participate in trials for new and innovative therapies.

Paper Number: 78

## Devastating Ischemic Monomelic Neuropathy After Plastic Zip Tie Handcuffs, A Message For Security Agencies

*Ahmed Wali*

**BACKGROUND:** Ischemic monomelic neuropathy (IMN) is a well known entity following compression, casts or tourniquet use predominantly in upper limbs. One of the devastating forms is increasingly reported after tying hands of suspects/accused persons with plastic zip handcuffs by security agencies. This is especially increasing in number in countries who are war torn or coping with terrorism after 9/11.

**BACKGROUND:** To increase awareness among physicians and security agencies to recognize IMN early, take measures to prevent this rapidly developing neuropathy and discourage the use of plastic handcuffs for suspects/accused in their arrest process or inside correctional places.

**METHODS:** We report a case of a 22 years old male who was arrested by law enforcement agency as a suspect. His hands were tied with plastic zip handcuffs from behind for 36 hours continuously. The patient developed numbness in few minutes followed by weakness in 2 hours of bilateral Median, Ulnar and Radial innervated muscles. He complained for the above symptoms but was not relieved. 36 hours after cutting the zip tie he was unable to flex forearms and move his hands muscles properly. Examination revealed normal bulk and tone while there was decrease pin prick in distal forearm and hands dermatomes. Finger flexion and abduction had Medical Research Council (MRC) 2/5 power while forearm flexion was 3/5 and extension 4/5.

**RESULTS:** The NCS/EMG revealed asymmetric low motor amplitudes of bilateral Musculocutaneous, Median, Ulnar and Radial nerves with borderline prolonged distal latencies and slow conduction velocities. The sensory potentials of above nerves were non recordable. EMG revealed active denervation potentials with rapid firing rate motor potentials but normal unit configuration in above innervated muscles.

**CONCLUSION:** Plastic zip type handcuffs produces rapid and severe IMN as compared to other means of handcuffs. This can lead to devastating axonal loss in hours and result in long lasting handicap condition for the patients. There is dire need to strongly discourage and or discontinue this type of tie by security agencies.

Paper Number: 93

# Longitudinal outcome of patients with motor neuron disease who underwent muscle biops

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## **Background:**

To evaluate clinical outcome in relation to disease duration and functionality in motor neuron disease (MND) patients who underwent muscle biopsy.

## **Methodology:**

We reviewed muscle biopsies done in our center alongside patient charts (i.e. clinical data, symptoms, laboratory and nerve conduction-electromyography (EMG) studies) for those with pathologic diagnosis of neurogenic atrophy and clinical diagnosis of MND. Hughes Functional Grading Scale (HFGS) was used to assess pre-diagnosis and current functional status.

## **Results:**

18 patients clinically diagnosed with MND who underwent muscle biopsy constituted the population of this study. Of these, 1 patient with clinical diagnosis of Spinal Muscular Atrophy (SMA) was lost to follow-up.

Of the 17 patients included in the study, 11/17 were diagnosed with ALS, disease duration of 2-9 years. Pre-diagnosis HFGS was 1 (able to run) in 1/11, 2 (able to walk 5m independently) in 6/11, 3 (able to walk 5m assisted) in 2/11, 4 (chair or bed bound) in 2/11.

Clinical data showed that at the time of clinical and pathologic diagnosis, 7/11 had bulbar symptoms, 8/11 with bulbar EMG denervation and 3/10 with thoracic paraspinal denervation. A decrease in functional score of 1-3 was noted in 7 patients with one patient expired 5 years after diagnosis (initial HFGS 4).

Six out of 17 patients who were diagnosed with SMA had the following pre-diagnosis HFGS: 1 in 2/6, 2 in 4/6. Decrease of 1-2 HFGS points was seen in these patients with longer disease duration of 2-26 years. In this set of patients, 4 of 6 had bulbar symptoms and EMG denervation and only 1 patient presented with thoracic paraspinal denervation. Later patients were eventually diagnosed with Kennedy disease.

In this study, we also correlate whether pathologic changes such as denervation atrophy and myopathic features can help us prognosticate functional outcome and survival rates.

## **Conclusion:**

Compared to MND of SMA type, the ALS type has expectedly poor prognosis and more rapid progression over the duration of the disease. Bulbar symptoms and their denervation as well as paraspinal denervation indicate poorer prognosis. Significance of teasing out denervation biopsy changes may potentially have value in suggesting outcome prognostication in MND.

Paper Number: 27

## Yield of Muscle Biopsy in patients with findings of Myopathy on Electrodiagnostic testing

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**Introduction:** Evaluation of neuromuscular diseases includes a detailed clinical assessment, blood testing, electrodiagnostic studies (EDS), histological examination of tissue and genetic tests. EDS alone are seldom useful to provide a specific diagnosis. Therefore further testing in the form of muscle biopsy or genetic tests is required. Despite the advances in molecular testing, muscle biopsy remains an important diagnostic tool especially for certain inflammatory myopathies and in areas where genetic testing is unavailable.

**Methods:** Electromyography (EMG)/Nerve conduction studies (NCS) performed for suspected myopathy over 5 years from 2011 – 2016, at the Neurophysiology department of the Aga Khan University Hospital, Pakistan, were reviewed. Based on inclusion criteria, records of 58 patients were retrospectively reviewed for clinical, laboratory and histopathological data.

**Results:** After an EMG/NCS diagnosis of myopathy, the frequency of muscle biopsy testing was 10.1%. The median age of the patients was 26.5 years. The clinically suspected diagnosis of the patients was categorized into hereditary myopathy (15, 25.9%) and acquired myopathy (18, 31%). The positive predictive value of emg was calculated to be 77.2%. Out of the 58 patients, 28 (48.2%) had an abnormal muscle histopathology whereas 20 (34.4%) revealed normal findings. Factors significantly influencing an abnormal outcome of biopsy included moderate to severe elevation of creatine kinase (> 2000), presence of denervation changes and severe myopathy on EMG.

**Conclusion:** Even though the overall yield of muscle biopsy testing may not be very high in our setting due to numerous factors including unavailability of special techniques, stains or expertise, certain factors can help improve the diagnostic yield. Clinicians should encourage muscle biopsy testing, especially in cases with a strong clinical, laboratory and electrodiagnostic suspicion and absence of genetic testing for the suspected myopathy.

Paper Number: 4

## Characteristic findings of brain MRI in myotonic dystrophy

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### Objectives/Background:

Myotonic dystrophy type 1 (DM1) is a progressive multi-systemic disease with potential brain involvement. White matter lesions (WML), dilated Virchow-Robin spaces (DVRS) or ventricular enlargements (VE) on brain MRI, adding to findings of diffuse brain atrophy and bone thickness, have been previously reported in DM1. However, the pathophysiological mechanism of abnormal MRI findings is unclear. The aim of this study is to implement a cross-sectional research for brain MRI abnormality, and survey relevance to atherosclerotic change or CTG repeat size in DM1.

### Materials and Methods:

Medical records of genetically diagnosed patients with DM1 who had brain MRI and routine examinations including cardio ankle vascular index (CAVI) and ankle brachial pressure index (ABI) from 2016 to 2017, were retrospectively investigated. MRI findings were reported by one medical specialist of radiologist: temporo-insular subcortical hyper-intense lesions (TIH), WML classified to four grading according to the criteria by Fazekas, DVRS and VE assessed by Evans index were evaluated.

### Results:

Eighty-five patients were participated (female 37, male 48). The mean age of patients was 45.3 +/- 11.3 years (+/- SD). The mean number of CTG repeat was 1074 +/- 612. The mean CAVI was 6.9 +/- 1.1, and the mean ABI was 1.0 +/- 0.1. TIH was showed in 59 of 85 patients (69%). WML with grade II was demonstrated in 14 patients (16%) and grade III was in 12 (14%). DVRS was observed in 14 patients (16%), and VE was in 6 (7%). Severe periventricular WML was observed even in DM1 patients with small size of CTG repeat or young patients without advanced atherosclerotic change. There was no significant difference in CTG repeat, CAVI or ABI value by the presence or absence of TIH, WML, DVRS or VE.

### Conclusion:

WML was not rare in patients in DM1. TIH can be particularly one of specific MRI findings in DM1. But, association of WML and atherosclerotic change or CTG repeat size in DM1 is still obscure. Comprehensive surveys from many areas are necessary for the pathophysiological investigation to the brain involvement in DM1.

Paper Number: 110

# Application of whole exome sequencing in neuromuscular disorders patients in Hong Kong

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## Background:

Neuromuscular disorders (NMDs) are a group of heterogeneous genetic diseases with a board spectrum of clinical presentations which makes accurate diagnosis challenging. Recently, whole exome sequencing (WES) has a remarkable impact on genetic diagnosis in NMDs patients. We aim to investigate the clinical utility of WES in our patient cohort.

## Methods:

We recruited Chinese pediatrics-onset NMDs patients with rare or non-specific phenotype. They had negative genetic findings by traditional approach including targeted gene Sanger sequencing and MLPA. WES and subsequent bioinformatics analysis was performed using the in-house pipeline in our department. First-tier analysis is based on the 443 genes in the genetable of neuromuscular disorders. If negative, open-exome analysis is followed. Rare variants with population frequency  $\leq 0.01$  were interrogated for pathogenicity based on the ACMG guideline. Variant validation and segregation analysis were performed by Sanger sequencing.

## Results:

Fifty patients (male=33, female=17) with median disease onset age at 1 year old were recruited. We identified disease causative genes in 11 cases, giving a diagnostic yield 22% (11/50). Genes included ACTA1, POMT1, COL6A1 (n=2), MTMR2, LMNA, SEPN1, DNM2, TGFB1, MPZ and IGHMBP2. All of them correlates with the phenotype. Four cases with variant of uncertain significance (VUS) found in TTN, TGM6, SCN11A and LAMA2 respectively.

## Conclusions:

Our achieved diagnostic yield is consistent with reported literatures. This demonstrate WES is an effective and promising tool in our NMDs patient cohort. In addition, a follow-up diagnostic plan will be beneficial to the patients with VUS findings. A clinical approach using WES as the first line diagnostic tool should be considered to minimize the repeated invasive testing and shorten the diagnostic odyssey in NMDs patients with diagnostic challenge.

## Acknowledgements:

This project is a collaboration of paediatric neurology team and clinical genetics team, Department of Paediatrics & Adolescent Medicine, the University of Hong Kong. We would like to thank The Society for the Relief of Disabled Children and The Edward and Yolanda Wong Fund for the support.

Paper Number: 6

## Targeted Next generation sequencing for diagnosis of a clinically defined cohort of muscular dystrophies and myopathies

*Kiran Polavarapu*

**Background:** Inherited myopathies and muscular dystrophies are a genetically heterogenous group of neuromuscular disorders which often present with overlapping clinical and pathological phenotypes.

**Methodology:** Patients with clinical features suggestive of Limb girdle muscular dystrophies (LGMD), distal myopathies (DM) and congenital myopathies (CM) were taken up for genetic analysis by Targeted Next generation sequencing (NGS) with a gene panel constituting 53 known muscular dystrophy and myopathy genes. DNA extracted from blood was utilized for library preparation as per Agilent SureselectQXT protocol followed by sequencing on HiSeq Illumina platform.

**Results:** 45 patients were studied with mean age of 21±11.7 (3-49 years) and male/female ratio of 3:2. Broad clinical phenotypes included LGMD: 31 (68.9%), CM: 9 (20%), DM: 5 (11.1%). Majority of cases were sporadic: 33 (73.3%), while family history was present in 12 (26.7%): Autosomal dominant inheritance in 7, recessive history in 3 and suspected X-linked inheritance in 2 families. Serum Creatine kinase was elevated in 82.2% (>5 times: 22, <5 times: 15). Muscle biopsy reports available in 42 patients showed muscular dystrophy in 25 (60.9%). Myopathic features were reported in 17 patients showing varying degree of cytoplasmic inclusions in 9 cases and rimmed vacuoles in 4. Putative disease-causing variants in 17 genes were identified in 31 patients (68.8%) and conclusive diagnosis was possible in 22 (48.88%) where clinical suspicion was supportive, and variants were either reported pathogenic or novel rare variants (MAF=0) recognized as damaging/probably damaging by in-silico predictions. In another 9 cases, variants were identified with uncertain significance/not exactly correlating with phenotype and need to be further characterized. Most common genes affected were CAPN3 (Calpain-LGMD 2A) in 5 patients followed by DYSF (Dysferlin-LGMD2B), EMD (Emerin-EDMD) in 4 cases each, RYR1 (Ryanodine receptor1-CM) in 3 and GMPPB (LGMD 2T), LMNA (LGMD 1B/EDMD) in 2 each. We also identified a homozygous pathogenic GAA mutation (c.1082 C>T; p.P361L) in a rare case of juvenile onset Pompe disease who presented with rigid spine syndrome.

**Conclusion:** Targeted gene panel NGS offers a quick cost-effective strategy with good diagnostic yield in inherited muscle disorders, when complimented with good clinical phenotyping.

Paper Number: 7

## Next generation sequencing for diagnostic confirmation in MLPA negative Duchenne muscular dystrophy patients

*Kiran Polavarapu*

**Background:** Smaller mutations - point mutations, insertion/deletions (INDELs) etc., occur in 20-25% of Duchenne muscular dystrophy (DMD) patients. Next generation sequencing (NGS) offers a cheaper and higher throughput alternative to traditional Sanger sequencing to identify small mutations in DMD patients.

**Methodology:** Clinically suspected/biopsy confirmed DMD children with MLPA (Multiplex ligation-dependent probe amplification) negative for exon deletions and duplications were recruited after obtaining informed consent/assent. Custom probe design for DMD gene was created with a capture size of 2.077Mbp to cover entire gene (exons, introns and promoter regions) at least twice and sequencing performed on NextSeqTM (Illumina).

**Results:** Mutational analysis was performed in 64 MLPA negative DMD children with mean age of 7.87±2.3(range:3-13 years). Family history (X-linked recessive) positive in six cases (9.37%). Muscle biopsy performed in 51 boys (79.7%) showed loss of Dystrophin on immunohistochemistry. NGS identified hemizygous mutations of DMD gene in 58/64 children (90.6%). Nonsense mutations were most common at 54.7%(35/64) followed by frameshift mutations due to small INDELs in 21.9%(14/64). Variants affecting splice-site occurred in 8/63 (12.5%). Missense mutation was identified in one patient. Except for one mutation, all other variants were classified as pathogenic (55) or likely pathogenic (2) as per ACMG guidelines. In total there were 57 unique variants among which 60% (34) were novel and only one mutation (p.Arg539\*) recurred in two unrelated patients. Unlike larger deletions/duplications, small mutations lacked any hot spot regions and more uniformly spread across coding region with exons 30 and 44 having most number of mutations (4 each). In thirteen patients who did not undergo biopsy and clinical suspicion was high, we were able to accurately identify pathogenic mutations. Mutations were not identified in six cases (9.5%), where possibility of deep intronic variants/complex rearrangements should be considered.

**Conclusion:** In this study we describe spectrum of smaller mutations in a large cohort of DMD children from India. Accurate genetic diagnosis is important to identify potential cases who can benefit from mutation specific therapies and NGS offers a valuable diagnostic screening tool before contemplating invasive muscle biopsy in clinically suspected DMD patients.

Disclosure: Funded by DST-SERB (Govt. of India) project: EMR/2014/000943

Paper Number: 13

## Calpainopathy : A Case Report With Clinical And Histopathological Correlation

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### Background:

Limb girdle muscular dystrophies (LGMD) demonstrate heterogeneity of clinical phenotypes and pathogenetic mechanisms. Calpainopathy(LGMD type 2A) is a relatively common type of LGMD.

### Case report:

We report a case of 49 years old female with motor developmental delay since birth. She had proximal myopathy since childhood. She has a nephew diagnosed as floppy baby and was bed bound since birth. No family history of consanguinity.

She had normal cognition with no facial weakness. She had positive Gower's sign, no winging of scapula or scoliosis. There was symmetrical proximal muscle weakness with normal sensation. She had pes cavus and was able to ambulate independently.

Her creatinine kinase level was normal. Her nerve conduction study was normal. Needle electromyography showed evidence of small polyphasic MUPs with early recruitment, consistent with primary muscle disorder. Left deltoid muscle biopsy was conclusive for limb girdle muscular dystrophy, possibly calpainopathy.

### Discussion:

Calpainopathy is caused by mutations in the CAPN3 gene and can be autosomal recessive or autosomal dominant. However, molecular genetic studies are not widely available in Malaysia. Clinically, Calpainopathy is characterized by symmetrical and selective proximal atrophy with no cardiac or facial disturbance and normal intelligence. However, there are some overlapping between clinical presentations of LGMD subtypes. Therefore, muscle biopsy specimen is warranted.

### Conclusion:

High cost of genetic analysis still hinders investigations for LGMD in many parts of the developing world. Consequently, detailed clinical history with examination and muscle biopsy can be employed as important tools for the initial diagnosis and classification of LGMD.

Paper Number: 26

## Pneumothorax associated with Duchenne muscular dystrophy: a retrospective study of the past 10 years

Michio Kobayashi

**Background** Pneumothorax associated with Duchenne muscular dystrophy (DMD) was first reported in 1994, but there have been only a few case reports since then. Therefore, we felt the need to investigate the frequency and risk of pneumothorax secondary to DMD.

**Methods** We retrospectively analyzed the clinical records of DMD/intermediate muscular dystrophy (IMD) patients who were treated at our institution between January 1, 2008 and December 31, 2017. The incidence density was calculated based on onset frequency and total observation period. We also investigated whether there were any differences between patients with and without pneumothorax in terms of body weight, Cobb angle, tidal volume (TV), and inspiratory positive airway pressure (IPAP). **Results** A total of 21 patients were included. The mean and standard deviation of age and observation period were 30.0±7.7 years and 7.3±3.0 years, respectively. The percentage of patients using respirator was 90% (19/21). Pneumothorax occurred in 24% (5/21) of all patients. The mean number of recurrences was 2.2. The events occurred during respirator use in all instances, with 75% (12/16) during pressure control ventilation and 25% (4/16) during volume control ventilation. Follow-up observation alone was carried out in 44% (7/16), pneumothorax was treated with chest drainage and pleurodesis in 31% (5/16) and chest drainage alone in 19% (3/16), and the patient was transferred to another hospital in 6% (1/16). Two patients died of pneumothorax. The incidence density of pneumothorax was 10.6% person-years. The mean and standard deviation of body weight and Cobb angle in patients with pneumothorax were 27.0±5.0 kg and 57.1±18.9°, respectively, with body weight being significantly lower and Cobb angle larger as compared with patients without pneumothorax. There was no difference in IPAP between patients with and without pneumothorax, and TV was lower in those with pneumothorax. **Conclusion** The frequency of DMD/IMD patients with pneumothorax did not differ greatly from that in the previous report, but repeating recurrence and deaths were seen. Therefore, we surmised that treatment may be more difficult than before with the introduction of positive pressure ventilation. Additionally, our findings suggest the importance of weight control and good posture keeping to prevent pneumothorax.

Paper Number: 39

## Mutation pattern in Familial and non-familial forms of Duchenne Muscular dystrophy: a study on a large single center cohort

Atchayaram Nalini

**Background:** There exists only a few reports mentioning the percentage and mutation pattern in familial forms of DMD. In the current study we have attempted to look at the pattern of mutations in DMD patients with and without a positive family history. **Methods:** A retrospective study of DMD children belonging to 55 families registered at our Neuromuscular disorders clinic between October 2012 and January 2018. Detailed clinical history, neurological examination and genetic data were obtained. All children underwent MLPA testing and the negative cases had NGS followed by muscle biopsy and IHC in NGS negative cases. Non-familial cases seen during the same time were analyzed for comparison. **Results:** There were 148 affected patients from 55 families. The familial group comprised of 11.3% (55/537) of the total DMD cohort. Among this group MLPA showed mutation in the DMD gene in 42/55(76.36%), MLPA negative=13/55(23.64%), deletions= 40(95.24%), duplications=2(4.76%). NGS confirmed=11/13[11(19.6%), 8(nonsense), 2(splice variant), 1(frameshift)]; no mutation identified= 2/13. Deletions in hot-spot region= 26/40- 60%), duplications=both are proximal( 2-7 and 21-30). Hot-spot region for deletion=45-52. Out of frame=36(85.71%), in frame=6(14.29%). Most common exon deleted=50(20/40=50%). No mutations occurred beyond exon 54. age at onset was  $2.74 \pm 1.7$ (1-7 in familial and  $3.8 \pm 1.6$  (1-8) in non-familial. There were 458 non-familial cases in this large DMD cohort. The pattern of mutation was: exonic deletions=383/458(83.62 %), hot spot, 45-54 region deletions=273/383 (71.3%), exonic duplications=20/458 (4.36%) spread from exon 2-69, NGS confirmed small mutations= 49/458 (10.7%)[47/456(10.3%) 27(nonsense) 13(frameshift), 6(splice variant), 1(missense)] no mutation= 6/458 (1.31%). No hotspot region for duplications was identified. Most common exon deleted= 50 [185/383 (48.3%)]. **Conclusions:** The familial forms had more MLPA negative cases 14(25%) vs 53(11.6%), more small mutations 11(19.6%) vs 47/456(10.3%), age of onset was earlier in familial group. Overall the incidence of familial forms was low when compared to reports from China and similar to a report from Italy. Our results imply that our cohort had an early accessibility to diagnosis and genetic counseling which possibly prevented further cases of DMD, more easily available specialist care and affordable genetic testing. Also, an increased awareness of DMD and prenatal testing among pediatricians.

Paper Number: 49

## Case Report: Miyoshi Myopathy with Novel Mutation C.463G>T in DYSF Gene

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**Introduction:** Frequency of Miyoshi myopathy is varying in each region, overall about 1-2 per million. Miyoshi myopathy, a distal myopathy phenotype of dysferlinopathy, is due to recessive mutations in DYSF gene encoding dysferlin on chromosome 2p13.2. More than 300 mutations of DYSF gene have been identified, among which about 80 are recurrent mutations according to the UMD-DYSF locus-specific database.

**Case Illustration:** A 26-year-old man was referred with chief complaint of muscle atrophy since three months before admission. At age 20 years, he experienced myalgia and weakness in both legs, which was initially started with difficulty tiptoeing. At age 22, weakness progressed and he became unable to climb stairs and walk independently. At age 24, weakness involved both upper extremities. Although his brother had intellectual disability, there was no similar manifestation in other family members. Physical examination revealed symmetrical muscle weakness in legs and arms, predominantly in distal legs. CK level was 5796U/L (normal range <308U/L), LDH 609U/L (normal range <225U/L). Nerve conduction study was normal and electromyography was compatible with myogenic changes in facial, and upper and lower extremities without spontaneous activities. Muscle histopathology was compatible with muscular dystrophy and dysferlin was absent on immunohistochemistry. Western blot analysis showed marked reduction of dysferlin (0.4%), confirming the diagnosis of dysferlinopathy. Nevertheless, target resequencing analysis in 61 genes known to be causative of muscular dystrophy identified only a heterozygous c.463G>T (p.G155\*) variant which was also confirmed by Sanger-sequencing. Albeit never been reported, this variant is highly likely to be pathogenic considering that it is a nonsense type variant. The unidentified mutation in the other allele may be present in the unsequenced region such as promoter or introns.

**Conclusion:** We identified a case with Miyoshi myopathy. Although the diagnosis was confirmed at the protein level, only a heterozygous nonsense mutation was found in DYSF gene.

Paper Number: 54

## Dysferlinopathy was recovered by readthrough therapy through ataluren

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Dysferlinopathy, the rare muscular dystrophy, is caused by mutations of gene encoding dysferlin which repairs the membrane damages. We found one of the nonsense mutation site on dysferlin is the most common among Korean patients with dysferlinopathy. Therefore, we generated a knock-in transgenic mouse harboring c.2494C>T in exon 24 and flanking introns which has the same mutated site (p.Q832\*) as the dysferlinopathy patients. We generated the dysferlin deficient mice with the dysferlin mutation found diagnosed in Korea dysferlinopathy patients and investigated the effect of ataluren to ameliorate the symptoms of dysferlinopathy.

**Methods:** Prior to starting the experiment, the dysferlin deficient mouse, named dqx, were back-crossed to C57BL/6 over 5 generations. 0.9 mg/ml of ataluren was treated with in the liquid diet for 2 week. The mouse performed Rotarod, forelimb grip test, treadmill and open field activity tests. Furthermore, eccentric contraction was measured using Aurora system with extensor digitorum longus (EDL) muscle from each mice. Restored dysferlin was visualized with immunoblot and immunohistochemistry in muscle tissue.

**Conclusion:** Most of the functional markers successfully improved with ataluren administration. Our results suggested that the readthrough strategy can be applicable to nonsense mutation disease including dysferlinopathy.

Paper Number: 23

## 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) antibody-associated inflammatory myopathy's delayed presentation mimicking inherited myopathy

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HMGCR antibody-associated myopathy is a necrotizing autoimmune myopathy with active necrosis and regeneration of muscle fibers without inflammation. Its disease progression can be subacute as well as chronic. Here we discuss on a young lady with childhood onset myopathy which was initially diagnosed as inherited one but later found out to be HMGCR antibody-associated myopathy. A 17-year-old girl presented with slowly progressive proximal myopathy, with positive Gower's sign at 6 years of age and ankle contractures. Neck flexion was 3/5 and extension was 4/5. Upper and lower limbs strength was proximally 3 and distally 4. She has very high creatinine kinase (CK) of 11176 U/L (normal 30-135 U/L) and negative myositis antibodies panel. Nerve conduction study was normal but needle EMG revealed irritable myopathy. We proceeded with left biceps muscle biopsy which showed marked fiber size variation, scattered necrotic and regenerating fibers, some clustered regenerating fibers with no lymphocyte infiltration. Moderate to marked endomysial fibrosis was seen. Perimysial alkaline phosphatase activity was very minimal. Type 2C fibers were scattered. The above findings reflect long-standing active necrotic and regenerating process in myofibers. But, immunohistochemical (IHC) stains with dystrophin, sarcoglycan, dysferlin, caveolin 3, emerin, merosin, collagen VI,  $\alpha$ DG, p62, MxA, HLA-DR were negative and 1+ with HLA-ABC. She was initially diagnosed as inherited muscular dystrophy but after reviewing her muscle biopsy second time and inadvertently checking HMGCR antibody, finally she was fortunately diagnosed as treatable HMGCR antibody-associated inflammatory myopathy. There was no statin exposure history, extra-muscular involvement, associated connective tissue disease as well as no malignancy. This case highlights the importance of HMGCR antibody screening among undiagnosed chronic necrotizing myopathy and also prompts the essentiality of having facilities for muscle biopsy MHC staining and HMGCR antibody testing in all tertiary hospitals in order not to leave treatable disease untreated.

Paper Number: 43

## Follow-up study in Chinese patients with anti-SRP antibody myopathy

*Wei Zhang*

**Objective:** Anti-signal recognition particle (SRP) antibody myopathy is an immune-mediated necrotizing myopathy characterized by the presence of anti-SRP antibodies. We recruited a cohort of Chinese patients and followed up the immunosuppressive therapeutic effect and analyzed the risk factors related to refractory. **Materials and methods:** Forty-eight patients were recruited. Male: female was 14:34, including 6 teenagers and 42 adults. The mean onset age was  $40.9 \pm 17.2$  years and the time to admission was six (4, 18) months. We monitored the clinical symptoms, the fatty infiltration and edema of thigh MRI in 3, 6, 12, 18 and 24 months after treatment. Clinical follow-up indicators were MRC and mRS, imaging indicators were the change rates of thigh muscle fatty infiltration and edema. The patients were divided into non-refractory and refractory groups according to the clinical follow-up indicator in 12 months after treatment. We compared the clinical, thigh MRI changes and pathological features between two groups. **Results:** The follow-up study was complete in 40 out of 48 patients. Twenty-seven patients were non-refractory to the therapy and 13 were refractory. The mean onset age in non-refractory group and refractory group were  $37.26 \pm 18.06$  and  $50.77 \pm 15.77$  respectively, the proportion of weight loss after onset of disease was 40.7% for non-refractory group and 76.9% for refractory. Interstitial lung disease was 22.2% for non-refractory group and 69.2% for refractory. Binary logistic regression analysis verified the risk factors for refractory patients were male (OR=19.57, 95%CI=1.49-256.53), severe weakness (OR=7.51, 95%CI=41.03-54.88) and interstitial lung disease (OR=39.70, 95%CI=3.04-518.38). The mean fatty infiltration rate of thigh muscles in 3 months was higher in refractory group ( $P=0.022$ ). **Conclusion:** Male, severe muscle weakness and with interstitial lung disease were risk factors to refractory. Quick development of fatty infiltration in thigh MRI indicate poor prognosis for immunosuppressive therapy.

Paper Number: 45

## Clinical and histopathological features of Dermatomyositis with Anti-Nuclear Matrix Protein-2 antibodies in 5 Chinese patients

*Wei Zhang*

**Objective:** Myositis with anti-nuclear matrix protein-2 (NXP-2) is identified as myositis-specific antibodies related with dermatomyositis (DM). Anti-NXP-2 antibodies are often associated more severe phenotypes of myopathy in previous studies. We summarized the clinical and histopathological features of 5 Chinese patients diagnosed as DM with anti-NXP-2 antibodies. **Methods:** There were 4 females and 1 male with the onset age ranging in from 11 to 61 years old, with duration of disease ranging from 6 weeks to 2 years. Muscle biopsies and myositis-specific antibodies detection was performed in all 5 patients. **Results:** The initial symptoms were proximal limb weakness in 4/5 patients (neck weakness in 1/5 patient). Four patients had skin lesions and myalgia. One patient had only skin lesions devoid of myopathy at the initial stage. The main symptoms included dysphagia (2/5); subcutaneous edema in face (2/5), limbs (2/5) and abdomen (1/5), mild fever occasionally (2/5) and weight loss (2/5). Four patients had different degrees of proximal weakness and myalgia. None of the patients had calcification. Creatine kinase in 5 patients ranged from normal to 24 times. Only 1 patient had typical histopathological changes of DM. The muscle histology showed perifascicular atrophy in 1 patient, perimysium and endomysium edema in 4 patients. Muscle fiber necrosis and regeneration were rarely seen. Deep staining of capillaries under NSE was found in 4 patients. Inflammatory cells were mainly in perivascular regions. Deposition of membrane attack complex (MAC) was found in capillaries of 3 patients. MHC-1 was diffusely expressed in muscle fibers of 4 patients, two of whom showed the tendency of perifascicular upregulation. **Conclusion:** Our research broadened the clinical and histopathological spectrum of DM with anti-NXP-2 antibodies. We suggested deposits of MAC in capillaries might be a diagnostic clue or related to the pathogenesis of the disease.

Paper Number: 58

# Myositis-specific and Myositis-associated autoantibodies in Inflammatory myopathy with unusual tarry / greasy skin pigmentation in Mi2B cases: A first report from India with FDG PET-MR study

*Atchayaram Nalini, V Preethish-Kumar, Anita Mahadevan, Saraswati Nashi, Kiran Polavarapu, SeenaVengalil*

**Background:** Idiopathic inflammatory myopathies(IIM) include predominantly dermatomyositis(DM), polymyositis(PM) and necrotizing autoimmune myopathy (NAM). Latest studies show that myositis-specific autoantibodies(MSAs) and myositis-associated autoantibodies(MAAs) present distinct clinical phenotypes.

**Methods:** 41cases were recruited. Patients had involvement of muscle, skin and internal organs. Rheumatoid (RA) factor, anti neutrophilic cytoplasmic antibody (ANCA), antinuclear antibody (ANA) and myositis profile, CT/MRI of internal organs/muscle, paraneoplastic profile and whole body FDG PET-MR scan were performed.

**Results:** M:F=17:24. Mean age at onset=34.4±13.8 years(Range, 1-59), mean age at evaluation=37.1± 13.7 years(10-61), duration of illness=18.0 ± 8.4 months (12-24). Initial symptom were predominantly muscle pains, lower limb proximal weakness (PW), skin/cutaneous changes, joint pain. Prominent muscle pains in 38/41(92.7%); lower limb PW= 41/41,(100%), upper limb PW=19/24(79.2%); distal limb weakness=10/41 (24.3%), neck weakness=21/41(51.2%); dropped head syndrome=13/41(31.7%); truncal weakness=22/41(53.6%), bulbar symptoms=15/41(36.5%). Disease severity[mild=9/41; moderate=18/41; severe=14/41]. Loss of appetite=12/41(29.2%); loss of weight=24/41(58.5%). examination findings:[Muscle wasting=25/41(60.9%); facial weakness=15/41(36.6%); contractures=18/41(43.9%); exertional dyspnoea=20/41(48.7%); photosensitivity=18/41(43.9%); skin hyperpigmentation=26/41(63.4%); joint pains=22/41(53.6%); scleroderma features=23/41(56.0%);calcinosis=4/41(9.7%)].Skin lesions = 29/41 (70.7%). Tarry / greasy hyperpigmentation= 5 Mi2B cases). 11/41 were on wheel chair and 2 bed bound. Mean ESR=37.2±24.2 mm/hr; Creatine kinase=3817.8±4092.5 U/L; SGOT(22/24)=142.7±134.8 U/L; SGPT(22/24)=101.6±92.8 U/L. Thyroid function tests abnormal in four. Nerve conduction studies (40/41)=motor axonopathy. ANA positive =12/30 = 40.0%. ANA profile: MAAs positive in 21/35 cases. [Ro-52(strong = 5; weak = 4); PCNA (strong=1; weak=2); Sm-RNP (strong=6); PM-Scl100 (strong=2); SS-A (strong=3); SS-B (weak=2)]. MSAs positive in 15/23 [Mi2 (strong=3;weak=2); PM-Scl100/75 (strong=3;weak=2); Ro-52 (strong=4;weak=1); anti-SRP (strong=3;weak=1)]. Anti-synthetase (ASS) antibodies[OJ=1;Ku=1; PL-7=3;PL-12=4]. Paraneoplastic profile[anti-Yo strongly positive=1; weak=1].RA factor (2/41). ANCA was negative in all. Muscle biopsy (n=41) showed features of DM=22/41(53.6%); PM=7/41(17.0%); dystrophy/myopathy =4/41(9.7%); no diagnostic pathology = 8. FDG-PET-MR in 16 and CT thorax and abdomen in 15 in did not reveal evidence of malignancy. All showed good/excellent improvement with first line/second line immunomodulation/plasma exchange.

**Conclusion:** Comprehensive analysis of IIM's based on MSA and MAA. Systemic features were commonly associated with MAAs secondary to connective tissue disease and ASS. Mi2 was the commonest finding with unusual skin changes and anti-SRP the most difficult to treat. FDG PET-MR / CT chest and abdomen showed no evidence of malignancy.

Paper Number: 74

## Myositis Associated with Neuromyelitis Optica: a case report

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### Objectives:

Neuromyelitis optica (NMO) is an anti-aquaporin-4 antibody (AQP4 IgG) associated central nervous system inflammatory disorder that affects optic nerves and the spinal cord. There are reports of skeletal muscle involvement in NMO. We describe an illustrative case.

### Report of a case / Methods:

A 53 year-old-man, with a past history of treated pulmonary tuberculosis complicated by non-tuberculous mycobacterial infection, presented with acute-onset transverse myelitis at T4 segment and right painless retrobulbar optic neuritis. MRI showed increased T2 signal from thoracic spinal segments T2 to T12, most prominent T2 to T5. Leptomeningeal enhancement of the cord was also noted. Spinal fluid reveals marked pleocytosis of 346 nucleated cells (lymphocytes 55%), raised protein (2.89g/dL) and low glucose 2.1 mmol/L (capillary glucose 5.7 mmol/L). Brain MRI was remarkable for mild swelling and enhancement of the optic chiasm. Serum AQP4 IgG was raised. Abnormally high AST and ALT with no clinical or laboratory evidence of liver disease prompted a creatine kinase (CK) assay. It was raised, ranging between 9000 to 15000U/L. Patient confirmed that he has had no falls or intramuscular injections. The patient did not have proximal weakness of neck and upper limb. A needle electromyography examination revealed evidence of a mild irritable myopathy. Serum myositis panel consisting of 16 antibodies (Mi-2 $\alpha$ , Mi-2 $\beta$ , TIF1 $\gamma$ , MDA5, NXP2, SAE1, Ku, PM-Scl100, PM-Scl75, Jo-1, SRP, PL-7, PL-12, EJ, OJ and Ro-52) returned negative. There was also no clinical or serological evidence of a systemic autoimmune disease. Patient was started on intravenous pulse steroids and plasma exchange. Serum CK decreased to 3765, 861, and 464 U/ over 3 days.

### Conclusions:

Like our patient, other reported cases of NMO-AQP4 IgG associated myositis show minimal muscle weakness. There is good response to immunotherapy, at least as far as the decline in CK is concerned. The reports also warn of relapses accompanying optic neuritis and myelitis. AQP4 is anchored in the sarcolemma as a component of the dystrophin-associated protein complex. The significance of the AQP4 IgG in inducing muscle injury is yet to be clarified although in one case complement-activating IgG targeting sarcolemmal AQP4 was demonstrated.

Paper Number: 82

## Clinical features of patients with SRP and HMGCR antibody

Shuang Cai

**Objects** Necrotizing autoimmune myopathy (NAM) is a distinct subtype of inflammatory myopathy. signal-recognition particle (SRP) and 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) are the most commonly known autoantibodies in NAM. We aim to compare the clinical features of the two groups of NAM patients.

**Methods** Clinical records of 46 patients with SRP antibody and 21 patients with HMGCR antibody were reviewed. Therapies were followed up and clinical outcomes were recorded. Clinical information of the two groups of patients were compared using t-test, Fisher's exact (2-tailed) and Mann-Whitney Rank sum test.

**Results** Male to female ratio of the SRP group and HMGCR group were 19:27 and 7:14 respectively. The average onset age were 44.4 $\pm$ 13.6 yo and 35.3 $\pm$ 20.1 yo ( $p=0.07$ ). Time from disease onset to their first visit to physicians were 8.8 $\pm$ 10.0 months and 13.7 $\pm$ 20.3 months ( $p=0.195$ ). Mean maximum CK level were 6986.7 $\pm$ 4062.1 and 7973.4 $\pm$ 4410.6 ( $p=0.374$ ). The proportion of muscle strength less than grade 3 of proximal lower limbs were 13/42 and 7/19 ( $p=0.77$ ). The proportion of dysphagia were 22/45 and 4/21 (0.03). Seventeen of 45 patients with SRP antibody had interstitial lung disease, while none was found in HMGCR group. Coexisting myositis associated antibodies (MSAs) were found in 23/46 SRP patients and 3/20 HMGCR patients ( $p=0.012$ ). The proportion of combined therapy with immunotherapy other than corticosteroids were 22/26 and 13/21 ( $p=0.1$ ). The rate of relapse were 5/26 and 8/21, respectively ( $p=0.197$ ).

**Conclusions** Patients with HMGCR antibody tend to present with early onset, less likelihood of dysphagia, interstitial lung disease and coexisting MSAs. A high proportion of patients developed relapse during follow-up of the two groups of patients.

Paper Number: 96

# **Sporadic inclusion body myositis (sIBM): Clinico-pathological and magnetic resonance imaging case study**

*Yong Chuan Chee*

## **Objectives/Background:**

Inclusion body myositis (IBM), also called sporadic inclusion body myositis, is a slowly progressive muscle disease beginning in the middle or later life. Tremendous unmet medical need exists for patients with IBM resulting from its relentless progression coupled with lack of effective treatment. Its unique clinical, radiology and pathologic features and poor response to medical therapy are enigmatic, challenging the medical profession to better understand this disease.

## **Materials and methods:**

We report a case of biopsy proven sporadic inclusion body myositis showing classical differential patterns of muscle involvement in the upper and lower limbs using both quantitative manual muscle testing as well as magnetic resonance imaging (MRI).

The last few years have witnessed a remarkable advance in the role of MRI in the diagnosis and management of idiopathic inflammatory myopathies. MRI can be used to guide muscle biopsy site, to monitor disease progression and assist in the diagnosis of IBM and complements the clinical examination by demonstrating disease specific pattern of muscle involvement. This is particularly useful in patients who lack the cardinal muscle biopsy features or whom a muscle biopsy is not possible.

In our patient, MRI disclosed preferential patterns of muscle involvement within function groups such as the forearm muscles, with flexor digitorum profundus (FDP) being preferentially affected and the extensor muscles spared. While in the lower limbs, the quadriceps femoris are most severely affected. T1 weighted imaging demonstrated atrophy and hyperintensity in keeping with fatty infiltration of affected muscles and changes in STIR sequence also indicate muscle inflammation and edema.

Pathological features in inclusion body myositis such as endomysial inflammation and rimmed vacuoles are also showcased.

## **Conclusion**

This case study highlights the characteristic clinic-pathological features of sporadic inclusion body myositis with supportive imaging findings.

Paper Number: 118

## Delayed clinical presentation of inclusion body myositis preceded by asymptomatic hyperCKemia

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### Introduction

Patients with asymptomatic elevations of creatine kinase (CK) are frequently referred to the neurology outpatient clinics for further workup. We report one such case here of a patient with asymptomatic hyperCK-emia who was worked up extensively and found to have inclusion body myositis (IBM) on muscle biopsy. IBM is characterized by a steadily progressive, painless muscular weakness and modest atrophy, which is usually distal in the arms and both proximal and distal in the legs

### Objective

This case highlights the importance of considering the diagnosis of inclusion body myositis in patients with asymptomatic hyperCK-emia.

### Case presentation

A 58-year-old Malay man was referred to our Neurology Clinic for further work-up of raised CK. The high CK was detected during an admission for dengue fever, which he recovered from, uneventful. He had no myalgia, limb weakness or cramps. There was no history of strenuous work or exercise. He has no family history of neuromuscular disorders. Apart from hypertension and dyslipidemia he had no significant past medical history. His medications were Aspirin 150mg daily, Atenolol 100mg daily and lipid-lowering agents including statin and fibrate. Physical examination was unremarkable. Muscle power in both upper and lower limbs was 5 according to the MRC scale. There was no weakness of the finger flexors and thigh muscles. He was able to rise from a squatting position. Cerebellar and sensory examinations were intact. Gait was normal. His CK levels ranged between 840U/L to 1668 U/L over a 3-year period, and these remained elevated despite discontinuation of statin and fibrates. Other systemic causes of hyperCKemia, including drugs, hypothyroidism, connective tissue diseases and metabolic diseases such as Pompe disease were ruled out. His nerve conduction study and electromyography were normal. A Magnetic resonance imaging of both his upper limbs did not reveal any abnormalities. A muscle biopsy was eventually performed over the left vastus lateralis muscle. The results of the biopsy were in keeping with a diagnosis of inclusion body myositis (IBM).

### Conclusion

Asymptomatic hyperCK-emia is a rare but recognized manifestation of sporadic inclusion body myositis. The clinical manifestations may lag behind the biochemical results by years.

Paper Number: 123

## Proteomic study of sIBM patients and GNE myopathy patients

*Yutong Zhang*

**Background:** Proteomics are a frontier technique for studying the composition of proteins in cells, tissues or liquids, it has the characteristics of large scale, high throughput and so on. In the field of medicine, proteomics has shown attractive prospects in clinical diagnosis, disease pathogenesis and drug development. But the reports about proteomics of myopathy were still rare. The objective of the following study was to investigate the specific protein markers in patients with inclusion body myositis/myopathy through proteomics.

**Methods:** By using iTRAQ (isobaric tags for relative and absolute quantitation) technology and bioinformatics analysis, we identified the differentially expressed proteins in muscle tissues of three cases of sporadic inclusion body myositis sIBM and three cases of GNE myopathy to 3 cases of normal controls.

**Results:** Compared with the control group, there were 38 kinds of up-regulated proteins and 32 down-regulated ones in the sIBM group, 87 kinds of up-regulated proteins and 37 down-regulated ones in GNE group. There were 8 up-regulated proteins and 17 down-regulated proteins in patients with GNE myopathy compared with sIBM patients.

The results showed that the differential proteins from sIBM and GNE myopathy groups involved in the biological activity were as follows: proximal tubule bicarbonate reclamation, pancreatic secretion, glycolysis, bile secretion, fructose and mannose metabolism, enzyme activity, signal transduction pathway and so on.

**Conclusions:** The patients with sIBM and GNE myopathy have some related differential proteins that may be involved in a variety of physiological pathologies and provide a foundation for finding biomarkers of these diseases.

Paper Number: 73

# Caregiver Burden And Its Correlation To Quality Of Life In Caregivers Of Stroke Patients

*Bazli Bahar*

**Background:** After a stroke, patient care and rehabilitation largely continues at home by informal caregivers. Caregivers may suffer from high burden which is associated with certain patient or caregiver characteristics. Studies have shown that caregivers suffering from high burden may lead to negative consequences on their quality of life and further compromised the post stroke care.

**Aim:** To identify the correlation between caregiver burden and caregiver quality of life, and to look at patient and caregiver characteristics that contribute to caregiver burden.

**Methods:** A cross-sectional study was conducted involving stroke caregivers and their patients attending the neurology clinic or admitted to the medical ward in University Kebangsaan Malaysia Medical Centre from October 2017 to March 2018. Patient and caregiver characteristics were recorded. Caregiver burden was measured using Caregiver Strain Index and caregiver quality of life was assessed using WHOQOL-BREF.

**Results:** 121 pairs of patients and caregivers were recruited. Thirty-six percent of caregivers experienced high burden. Patients' poorer functional handicap (mRS 5) showed significant association with high caregiver burden (adjusted OR 4.51; 95% CI 1.023 – 19.94; p-value = 0.047). Chinese caregivers suffered more burden compared to their Malay counterparts (OR 2.64; CI 1.11 – 6.32, p-value 0.029). Pearson correlation showed significant inverse relationship between caregiver burden and all domains of caregiver quality of life.

**Conclusion:** Increased patient's functional handicap contributes to higher caregiver burden. Chinese caregivers are at higher risk of caregiver burden. High caregiver burden has significant correlation with poor caregiver quality of life. We recommend screening of caregiver burden on routine patient follow up to identify caregiver who at risk of high burden as a holistic management of post stroke patient.

Paper Number: 125

# Ciliary Muscle Focal Dystonia As A Hypothetical Causation Of Myopia

*Sng Kim Hock*

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This paper proposes that "Ciliary Muscle Focal Dystonia" is the cause of myopia.

"Focal dystonia" is an established neurological condition affecting task specific practitioners, regularly seen in the neurology clinic. The common focal dystonias are writer's cramp, typist cramps and musician's cramp e.g. piano, violinist, with over forty different reported task specific dystonias.

The pathology of myopia is described. The process of reading requires the total dependence on ciliary body and muscle function to produce accommodation, necessary for seeing near objects, whether a book, an iPad or an iPhone, as well as the computer screen.

Myopia reached astronomical figures of 38% among Singapore 12 year olds, and 29% & 12% among the similarly aged children of Australia and the United Kingdom in 2006. A proactive national myopia programme in Singapore has managed to reduce the incidence from 38% in 2004 to 33% in 2009.

Near vision requires the contraction of the ciliary muscle to pull the choroid, thus releasing tension on the lens, allowing it to thicken. Children begin reading as young as three years of age, and possibly even younger now with the iPad generation. Like all other focal dystonias, overuse, prolonged usage without intervals of rest has been the main factor in causation of Focal Dystonias.

It is thus hypothesised that the overuse of ciliary muscles in reading and viewing near objects at a young age results in many cases to "Ciliary Muscle Dystonia", and hence myopia. As in all focal dystonias, there may be an underlying predisposition to the task specific dystonia, as not everyone with repeated prolonged usage of a set of muscles, result in the disorder. Nevertheless, it is agreed that the repeated overuse of the same set of muscles can result in dystonia.

This paper also presents two simple principles to reduce if not prevent myopia for the next generation, through rest intervals between reading and the use of 'reading glasses' to reduce chronic strain on the ciliary muscles.

Paper Number: 126

# Levator Palpebrae Superioris Dehiscence – A Definite Cause For Muscular Tension Headaches

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Levator palpebrae superioris (levators) dehiscence results in ptosis, and “Tension Headache” from Occipitofrontalis muscle chronic contraction, both of which are corrected with surgical repair.

The levators are the main muscle for elevation of the eyelids, hence opening the eyes. Muller’s muscle, or superior tarsal muscle is innervated by the sympathetic third nerve, and has limited role in elevation of the eyelid.

While there are several causes of ptosis, levator palpebrae superioris dehiscence is a common cause, either hereditary or acquired. When the levators functions poorly, there is an immediate compensation by contraction of the occipitofrontalis muscle, correcting ptosis either completely or partially, taking place simultaneously with every act of eye opening, as a secondary action.

A simple bedside test is performed with the patient sitting up, with both eyes closed and relaxed. The clinician fixates the occipital frontalis muscle with both thumbs along the eyebrows and then asks the patient to open the eyes. Patients with levator palpebrae superioris dehiscence will be unable to do so effectively, with either complete ptosis or partial ptosis. On releasing the one or both frontalis muscles, there is immediate elevation of one or both eyelids.

This action by the occipitofrontalis muscle is seen as the furrows above the eyelid, an action called frowning of the forehead.

Chronic occipitofrontalis contraction due to moderate to severe levator palpebrae dehiscence results in severe muscular tension headaches in many cases, due to overactivity. This disorder has yet to be classified as a definite cause of headaches.

This abstract presents several cases of levator palebrae dehiscence causing headaches, with dramatic relief of headaches following surgical repair of the levator palpebrae superioris, assisted with brow lift and double eyelid construction.

Levator Palpebrae Superioris Dehiscence is a definite cause of Tension Headaches, due to chronic occipitofrontalis muscular strain. With surgical repair and associated minor reconstruction, headaches are literally cured.

Paper Number: 15

# Chronic Inflammatory Demyelinating Polyradiculoneuropathy: A Case Report with Positive Anti-Acetylcholine Receptor Antibody

*Yin Yin Tan*

## **Background:**

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a heterogeneous disease in which diverse autoantibodies have been described. Anti-acetylcholine receptor (AChR) antibody is commonly present in myasthenia gravis (MG) but co-existence in CIDP has not been reported.

## **Case Report:**

We report a 21 years old gentleman presented to us with bilateral lower and upper limb progressive ascending weakness over 10 months. He had dysphagia, dysphonia and dysarthria. There was no diplopia, drooping of eyelids, facial weakness or fatigability. There was no history of antecedent infection. He was initially investigated by another hospital for muscular dystrophy. MRI of his thigh was normal. He refused muscle biopsy.

At the time of first evaluation, he had tongue atrophy with fasciculations, generalised limb weakness with Medical Research Council (MRC) scale 3/5 and absent tendon reflexes. There was no sign to suggest upper motor neuron lesion. Nerve conduction study (NCS) revealed demyelinating neuropathies with secondary axonal motor predominant polyneuropathy and normal needle electromyography (EMG). His creatinine kinase was raised (929 U/L). His CSF analysis were normal. He was commenced on intravenous immunoglobulin (IVIG) for 5 days. Subsequently, his AChR antibody was positive (0.93 nmol/l). Trial of pyridostigmine failed to improve his symptom.

## **Discussion:**

This case illustrated the importance of clinical correlation with presence of autoantibodies. Our patient is less likely to have MG in view of simultaneous occurrence of MG and CIDP is rare and lack of clinical improvement after the trial of pyridostigmine. However, the coincidental occurrence of CIDP with MG cannot be totally excluded.

## **Conclusion:**

The interpretation of anti-AChR antibodies is rather complex and the presence in CIDP need to be further elucidated.

Paper Number: 16

# Feasibility Of Acute Stroke Thrombolysis Via Telemedicine For District Hospital: 2 Case Reports

*Yoke Fun Ho*

## **BACKGROUND**

The availability of in-house neurological expertise / acute stroke team is limited to major hospitals / tertiary centres in Malaysia. AHA/ASA 2018 Guidelines for Management of Acute Ischaemic Stroke made a new recommendation: Providing alteplase decision-making support via telephone consultation to community physician is feasible and safe (Class IIb; LOE C-LD)<sup>1</sup>. Is it applicable for district hospitals in Malaysia?

## **CASE 1**

A 58-year-old lady, with underlying hypertension, dyslipidemia and gastritis, presented to ED with facial asymmetry and left-sided weakness (MRC 2/5) onset about 3 hours ago. Initial assessment showed NIHSS 16 with no intracranial haemorrhage (ICH) in non-contrast CT. Decision for thrombolysis with alteplase was made after telephone consultation to neurologist. Post thrombolysis patient was complicated with occult bleeding not requiring blood transfusion. Otherwise she continued to improve neurologically and discharged at Day7 of admission with MRC 4+/5, NIHSS 6 and mRS 2.

## **CASE 2**

A 46-year-old lady, with underlying hypertension, was electively admitted to surgical ward for colonoscopy. She was noted unable to move all 4 limbs with aphasia during morning review. A diagnosis of brainstem stroke was made with NIHSS 18. Non-contrast CT showed no ICH. She was thrombolysed with alteplase after telephone consultation with neurologist. Post thrombolysis, she recovered completely with NIHSS 0 and was discharged at Day4 post thrombolysis.

## **CONCLUSION**

Both cases showed promising outcome for acute stroke thrombolysis in district hospital without in-house neurological expertise / acute stroke team.

## **DISCUSSION**

Telemedicine (phone consultation with neurologist) will enable more patients to be eligible and potentially benefited from acute stroke thrombolysis service before in-house neurological expertise / acute stroke team becomes widely available across various hospital settings in Malaysia.

Paper Number: 21

# Longitudinally Extensive transverse Myelitis (LETM) mimickers of Neuromyelitis Optica Spectrum Disorders (NMOSD): Clues to Diagnostic Recognition

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## Background:

Longitudinal extensive transverse myelitis (LETM) is a frequent manifestation of NMOSD. However, there are other causes of LETM which are important to recognize from a diagnostic and therapeutic point of view.

We report two cases of LETM

Case 1: Spinal cord infarct secondary to left vertebral artery dissection

Case 2: High cervical spinal dural arterio-venous fistula

## Case 1

A 14-year-old boy, presented with sudden onset of upper and lower limbs weakness preceded by short-lived chest pain, which occurred after two episodes of short distance running.

Neurological examination showed flaccid paraplegia with areflexia and sensory level at T2. Upper limbs power graded as MRC 4/5 with symmetrical reflexes. Plantar responses were equivocal.

Autoimmune screening including serum aquaporin 4 antibody were negative. Normal echocardiogram and coagulation profiles. CSF analysis was normal with absent oligoclonal bands.

MRI spine showed longitudinally extensive anterior spinal cord lesion with presence of 'Owl's eyes' signs. MRA showed irregularity and pseudo-dilatation of the V3 and V4 segment of left vertebral artery. Cerebral angiogram was normal (Figure 1 in poster).

## Case 2

A 50-year-old Chinese male presented with progressive lower limbs weakness for 3 months with painful paresthesia, urinary and bowel retention.

Neurological examination revealed spastic paraparesis with sensory level at T6. Serum NMO Ig G was negative. Normal CSF analysis. Initial MRI spine showed T2 intramedullary hyperintensities from medulla to C7. His weakness worsened even after completing immunotherapy. Repeat MRI/MRA spine revealed long segment hyperintense cervical cord lesion with cord expansion and anterior serpiginous T2 flow voids. CTA and spinal angiogram showed dural fistula at left C1 level with a likely feeding artery from meningeal branch of left vertebral artery (See Figure 2 in poster).

## Conclusion:

Presence of atypical clinical history such as age of onset with possible trigger, unusual temporal history of the disease and associated symptom onset, atypical presentations with flaccid lower limbs (e.g. case 1), lack of response to immune mediated therapies and persistently negative biomarkers (e.g. anti AQP4 antibodies) supported by neuroimaging interpreted by neuro-radiologist gives clues to alternative diagnoses of LETM other than NMOSD.

Paper Number: 22

# The Usefulness of Perfusion Imaging in Acute stroke with Low Non-Contrast CT ASPECTS for Reperfusion Therapy

*Chen Fei Ng, Syazarina Syaris Osman, Wan Asyraf Wan Zaidi, Ching Soong Khoo, Shahedah Koya Kutty, Rabani Remli, Norlinah Mohamed Ibrahim, Hui Jan Tan, Wan Nur Nafisah Wan Yahya*

## Objectives:

The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) has been widely used in the assessment of acute ischemic stroke to guide reperfusion therapy. Earlier studies showed that baseline non-contrast CT (NCCT) ASPECTS of  $\leq 7$  predicted functional dependence and symptomatic intracerebral haemorrhage in patients who underwent thrombolysis. Perfusion imaging such as CT perfusion may be more accurate to evaluate established infarct and salvageable penumbral tissue.

## Method:

We described a case of right middle cerebral artery (MCA) infarct with low baseline NCCT ASPECTS, who was successfully thrombolysed with intravenous alteplase based on significant penumbra on CT perfusion.

## Results:

A 66-year old man with no known medical illness presented with sudden onset of left-sided body weakness and slurred speech for 2 hours. He was a heavy smoker for 30 years. On examination, he had left hemiparesis, left lower facial palsy, left homonymous hemianopia, neglect and dysarthria. The initial National Institute Health Stroke Scale (NIHSS) was 15. NCCT ASPECTS was 3. CT angiogram and CT perfusion of the brain were done to stratify further for reperfusion therapy. CT angiogram showed chronic stenosis at M1 segment of the right MCA but no large vessel occlusion. However, CT perfusion revealed a significant penumbra of  $>50\%$  with small infarct core. He was given intravenous alteplase at 3 hours. On the second day, his NIHSS improved to 5 and the repeated CT brain did not show intracranial haemorrhage. He was discharged home 4 days later with modified Rankin scale of 2.

## Conclusion:

NCCT ASPECTS may overestimate infarct core as cortical swelling may represent penumbral tissue. Perfusion imaging, such as CT perfusion is more reliable in guiding patient selection for reperfusion therapy.

Paper Number: 28

# A Randomized Double-Blind Placebo-Controlled Trial Of Probiotics For Constipation In Parkinson's Disease

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**Background:** Constipation is the commonest gastrointestinal symptom in Parkinson's Disease (PD), affecting up to 70% of patients, and causes significant impairment in quality of life. However, there is a paucity of randomized clinical trials (RCT) to evaluate the efficacy of treatments for constipation in PD. This study aims to investigate the effects of probiotics on constipation in PD.

**Methods:** This is a randomized, double-blind, parallel-group, placebo-controlled RCT. PD patients fulfilling ROME-IV criteria for functional constipation were recruited consecutively and randomized to receive either 4 weeks of probiotic capsules containing strains of Bifidobacterium, Lactobacillus and Enterococcus; or identical-appearing capsules containing (inactive) maltodextrin. Data regarding patient demographics, clinical status (including MDS-UPDRS), body mass index, medications, dietary intake, and physical activity (SIMPAQ) were collected. The primary outcome was the change in the average number of spontaneous bowel movements during the last 2 weeks of the treatment phase, compared to the 2-week pretreatment phase, as recorded by stool diary. Secondary outcomes included changes in the constipation severity scale (adapted from ROME-IV criteria), stool consistency (Bristol stool scale), and quality of life scale related to constipation (PAC-QOL). Adverse effects were recorded. Sample size calculation revealed that 36 patients were required in each arm to achieve clinical superiority with alpha of 0.05 and power of 0.80.

**Results:** To date, 67 patients have been recruited. Interim intention-to-treat analyses were performed on 43 patients who have completed the study and 2 drop-outs. There were no significant between-group differences in age, gender, BMI, physical activity, PD duration, total MDS-UPDRS, and PD medications. Spontaneous bowel movements per week (the primary endpoint) increased significantly in the treatment group ( $1.10 \pm 1.70$ ) compared to placebo ( $-0.26 \pm 0.79$ ,  $P=0.005$ ). Total ROME-IV, PAC-QOL and stool consistency also improved significantly ( $-3.53 \pm 2.67$  vs.  $-0.77 \pm 2.73$ ,  $P=0.002$ ;  $-21.47 \pm 19.61$  vs.  $-2.58 \pm 13.22$ ,  $P=0.001$ ;  $-0.41 \pm 1.11$  vs.  $0.27 \pm 0.77$ ,  $P=0.021$ ), with higher rates of satisfaction with treatment in the treatment group (55.6% vs. 24%,  $P=0.031$ ).

**Conclusions:** This interim analysis showed significant improvements in bowel frequency, stool consistency, constipation severity scale, and quality of life in patients receiving probiotic treatment. To date, patient enrollment and retention have been satisfactory, with no significant adverse events reported.

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Paper Number: 30

# A Rare Case of Atypical Pantothenate Kinase-Associated Neurodegeneration(PKAN) Mimicking Young-Onset Parkinson's Disease: Case Report

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## Introduction:

Neurodegeneration with brain iron accumulation (NBIA) encompasses a group of neurodegenerative diseases characterized by abnormal accumulation of iron in the basal ganglia. Pantothenate kinase associated neurodegeneration (PKAN) accounts for 50% of NBIA cases. It is a rare autosomal recessive disorder associated with mutation in the PANK2 gene located on chromosome 20p13. We describe a case of atypical PKAN here.

## Objective:

Create awareness among clinicians that NBIA should be considered as differential diagnosis of atypical parkinsonism.

## Case Report:

56 years old previously healthy female presented with progressively worsening bilateral hand tremors, slowing of movements and clumsiness since age 40. Physical examination revealed cerebellar signs. Otherwise, tone, power, reflexes and speech were normal. There were no retinal abnormalities and MMSE was 29/30. Baseline blood investigations, 24 hour urine copper, serum caeruloplasmin and Computed Tomography (CT) brain scan were reported normal. She was diagnosed as young Parkinson's disease and started on pergolide and selegiline. However, she progressively declined with anxiety, failing memory, gait instability, worsening tremors and frequent falls. Magnetic Resonance Imaging (MRI) of the brain revealed 'eye-of-the-tiger' sign, bilateral symmetrical hyperintensities within the central part of the globus pallidus and substantia nigra. Genetic testing confirmed mutation in the pantothenate kinase 2 gene with exon 3 (p.D268G). Her diagnosis was revised to PKAN. She received regular physiotherapy and rehabilitation and able to carry out daily activities independently.

## Discussion:

Atypical PKAN is characterized by later onset (age >10 years), psychiatric disturbances and more gradual progression of disease. MRI brain reveals iron accumulation in the basal ganglia("eye of the tiger sign")and substantia nigra which is virtually pathognomonic for PKAN. Genetic testing revealed PKAN gene mutation, confirming the diagnosis for our patient. The management of PKAN is usually symptomatic. The use of anticholinergics and botulinum toxin for dystonia and Baclofen for spasticity had been widely practised. Benefits of iron chelation are questionable. Our patient has been compliant to rehabilitation program and was able to function independently. Prognosis of PKAN remains poor.

## Conclusion:

Although rare, recognition of NBIA is essential and multidisciplinary rehabilitation program can improve quality of life.

(343words)

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Paper Number: 35

# Myasthenic Crisis Precipitated by New Direct-Acting Antiviral Agents (DAAs) Treatment For Chronic Hepatitis C Virus(HCV) Infection: A Case Report

*Loo LK, Tan KC, Lee CK, Hoe CH, Eow GB, Tan Kenny*

## Background

Myasthenic crisis is a medical emergency precipitated by various factors including infection, electrolyte imbalance, and medications. Treatment of hepatitis C with Interferon and ribavirin has been implicated in myasthenic crisis but limited data regarding the new direct-acting antiviral agents(DAAs). We report a case of sofosbuvir and daclatasvir induced myasthenic crisis in a 68-year-old man who has generalized Myasthenic Gravis (MG).

## Case summary

A 68-year-old gentleman with underlying generalized MG in remission, was referred to gastroenterology team for chronic HCV infection. He was treated with Pegylated-Interferon and ribavirin. However, patient was partially responded as HCV viral load still detectable at week 24 of treatment. Pegylated-Interferon was terminated in January 2018 and retreated with DAAs (sofosbuvir and daclatasvir) and ribavirin in May 2018. Otherwise, there were no other new medications prescribed.

On day 5 of DAAs administration, patient complained of fever, cough, breathlessness, dysphagia and generalized weakness for 3 days. On assessment, his GCS was 15/15, normotensive, tachycardic and tachypnoeic with Oxygen saturation 70% under room air. Lungs were clear on auscultation. There was no ptosis and no fatiguability. Cranial nerves were intact and there was no proximal muscle weakness. His chest radiograph was normal but arterial blood gas showed type II respiratory failure. Other investigations did not show evidence of infection or electrolyte imbalance. He was treated as myasthenic crisis and electively intubated for impending respiratory failure. Pyridostigmine, intravenous hydrocortisone and intravenous Immunoglobulin were given. DAAs and ribavirin were withheld since admission. During hospitalization, patient remained afebrile and all cultures were negative. Patient was successfully extubated and discharge home with oral prednisolone and pyridostigmine on day 12 of admission.

## Conclusion

This case highlights the potential correlation of new direct-acting antiviral agents and myasthenia crisis. Physicians need to be vigilant in identifying this life-threatening condition when prescribing new medication to myasthenic patients.

Paper Number: 37

## Video narratives: Promoting medication understanding and use self-efficacy among stroke patients

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**Background:** Multimedia technology has helped health behavior interventionist in patient education and reduced the gap of communication between healthcare providers and patients. However, this technique has not been confirmed effective to promote self-efficacy in medication understanding and use among stroke patients. Therefore, this study aimed to develop video narratives for stroke patients.

**Methodology:** A proposed set of learning outcomes and lead questions according to Health Belief constructs were developed by a panel of ten experts via the Delphi method guided the interview scripts.

**Results:** Ten bilingual stroke patients provided open-comments about the video scripts based on their perspectives using a Likert-scale questionnaire and feedback form. The video scripts were revised and finally approved by the expert panel.

**Conclusion:** We successfully developed four (4) video scripts (Malay and English). The expert panel and stroke patients confirmed the face and content validity of our tool. An engagement feedback is warranted for the full confirmation of video scripts.

Paper Number: 44

## Diagnostic Challenges of Hashimoto Encephalopathy: A Case Report

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### Background:

Hashimoto encephalopathy (HE) is a rare, heterogeneous autoimmune disease with variable clinical manifestations. The pathophysiology remains unclear. The term HE is debatable and the nature of the relationship between HE and Hashimoto thyroiditis is argued.

### Case Report:

We report a case of a 35 year-old female who presented with acute behavioural changes. She appeared withdrawn, unkempt and responding inappropriately to questions. No fever or focal neurological deficits reported. She has an underlying hyperthyroidism since 2011 receiving carbimazole, 5mg every other day. Her thyroid-stimulating hormone (TSH) and thyroxine (T4) levels were 1.37 uIU/mL and T4 19.46 pmol/L respectively. Intravenous acyclovir and ceftriaxone were initiated empirically for central nervous system (CNS) infection. Magnetic Resonance Imaging (MRI) of the brain was unremarkable and her electroencephalogram (EEG) demonstrated loss of posterior dominant rhythm with a background of predominantly beta waves. Unfortunately, lumbar puncture was not performed due to strong refusal from the family. The other work outs for infection performed were unremarkable. The high suspicion of Hashimoto encephalopathy arose in view of her previous history of positive anti-microsomal antibody (1:1600). After 10 days, she then somehow improved clinically and discharged with the plan of starting corticosteroid therapy after assessing her clinical status during the clinic review later. The diagnosis was supported by the elevated level of anti-thyroglobulin (TG) antibody.

### Discussion:

The clinical manifestations of HE are variable and non-specific; typically acute to subacute onset of altered consciousness with confusion. The diagnosis is made from the clinical presentations, high thyroid antibodies and elimination of other causes of encephalopathy. Elevated anti-thyroid peroxidase (TPO) and/or anti-TG antibodies are the essential characteristic features. HE does not appear to be related to the thyroid status and high titre of antibody is not an indicator of a more severe disease. MRI brain and EEG findings are non-specific with CSF analysis may show elevated total protein (75%). Many studies have shown that steroid therapy is effective. Yet this is not necessarily the case and spontaneous recovery is possible.

### Conclusion:

HE is frequently underestimated and a high index of suspicion is recommended among young patients with unexplained encephalopathy with the other causes of encephalopathy rigorously excluded.

Paper Number: 59

# Bilateral medial medullary infarct – A rare but disabling stroke

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## Background

Medial medullary infarct is a rare (<1%) type of infarct, and we would like to present a case report on a bilateral medullary infarct.

## Methods: case report and results

A 59 years old lady presented with complaint of recurrent vomiting for two days followed by a sudden onset of bilateral upper and lower limb weakness. She had two days' history of speech and swallowing difficulty. She had a past history of diabetes with poor glycaemic control, hypertension and a previous ischaemic stroke with full recovery.

On examination, she was fully conscious. She had a weak voice, absent gag reflex and weak tongue movement. Her upper limb power bilaterally was 3/5 proximally and 4/5 distally while her lower limb power bilaterally was 1/5 proximally and 2/5 distally. She had generalised hypotonia with bilateral extensor plantar reflexes. She had no ophthalmoplegia or facial asymmetry. Her proprioception, fine touch and pin prick sensation was normal bilaterally.

Initial plain CT brain done on arrival showed chronic infarcts in the right thalamus, left external capsule and right frontal lobe. On day 8 of admission, MRI brain T2 image showed hyperintense lesion ('heart appearance' shape) at bilateral medial medullary area. There was restricted diffusion at bilateral medial medullary region. MRA showed Her left vertebral artery was dominant with the flow leading to basilar artery. The right vertebral artery was hypoplastic and beaded, with its termination as PICA. She was started on dual antiplatelet (aspirin and clopidogrel) and was referred for rehabilitation team for rehabilitation.

Bilateral medial medullary stroke is a rare but disabling stroke. Patients usually present with sudden onset quadriparesis/quadriplegia, bulbar palsy, hypoglossal palsy, loss of deep sensation with or without respiratory failure. Diagnosis of bilateral MMI is often delayed. With MRI, diagnosis is made easier with the characteristic 'heart appearance' sign in the ventral medulla.

## Conclusion

In conclusion, we are reporting a case of bilateral MMI presenting with quadriparesis with bulbar palsy. High index of suspicion and MRI should be performed in similar patients in future for accurate diagnosis and to prevent further complications.

Paper Number: 60

# A Rare Case of Pericallosal lipoma presenting with Status Epilepticus

*Yue Hui Lau*

**Introduction:** Lipomas are considered rare congenital tumors with incidence estimated at 0.06%-0.46% of all intracranial tumors caused by abnormal differentiation the persistent primitive meninges. About 45% of lipoma occurs in the pericallosal region followed by the quadrigeminal cistern and suprasellar cistern. Epilepsy is the most common symptom in supratentorial lipomas and occurs in approximately 50% of cases of callosal lipomas.

**Objective:** Create awareness of intracranial lipoma as a cause of seizure among clinicians

## Case Report:

A 42 year old previously healthy gentleman was admitted with complains of headache, behavioural changes, and generalised tonic-clonic seizures. He subsequently fell on a hard ground, hitting the back of his head. On examination, his Glasgow coma score was 14/15 with normal pupils, afebrile, with no neurological deficit. There were no signs of lacerations, bruises nor base of skull injuries. Blood investigations were normal.

He was treated as status epilepticus and started on intravenous sodium valproate. The computerised tomography of brain was highly suspicious for pneumocephalus with a large mass of air-like low density in the Sylvian fissure. Magnetic resonance imaging of brain however revealed curvilinear lesion in interhemispheric fissure closely related to the corpus callosum measuring approximately 4.8x1.7x1.3 centimetre suggestive of pericallosal lipoma. He was managed conservatively and was discharged well with tablet sodium valproate.

## Discussion:

Intracranial lipomas are generally asymptomatic and its association with epileptic seizures remains controversial. Lipomas in the sylvian fissure or cortex usually present with epileptic seizures, presumably due to irritation of the cortex. Surgery is not indicated as the risks of resection are high. Antiepileptic medications are usually successful in controlling seizures.

## Conclusion

In conclusion, intracranial lipomas are rare and mostly congenital due to an abnormal differentiation of the meninx primitiva. They are often managed conservatively as attempts at resection are associated with high mortality

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Paper Number: 61

## Occurrence of Multiple Sclerosis in a patient with Myasthenia Gravis post thymectomy; A Case Report

*Huey Tean Kok*

**Background:** Multiple Sclerosis (MS) and Myasthenia Gravis (MG) are distinct autoimmune diseases, some studies suggest a co-morbidity despite differences in pathologies. An autoimmune pathogenesis is implicated in both Myasthenia Gravis and Multiple Sclerosis, but the coexistence of the two disorders has rarely been documented, and for this reason we report this case.

**Case Presentation:** A 34 years old lady, presented with fatigability, double vision and ptosis was diagnosed as Myasthenia Gravis in 2003 with anti-Achetylcholine receptor antibody positive. She underwent thymectomy one year after the diagnosis and symptoms were controlled until 2010. She developed myasthenia crisis precipitated by infection and intravenous Immunglobulin was given. Thereafter, she was on azathioprine, pyridostigmine and prednisolone. During tapering dose of prednisolone, she developed left foot dropped with spastic gait. The power of left knee flexion was 2/5, left ankle dorsiflex and plantar flexion was 1/5 and proprioception impaired both lower limbs. She was diagnosed as Multiple Sclerosis fulfilled McDonald 2017 criteria with MRI finding showed multifocal small lesions seen at periventricular regions and patches of abnormal signal intensity changes at the spinal cord from C2-C6 level which showed hypointense on T1, hyperintense on T2 and not suppressed on FLAIR while spine lesion enhances post contrast. She was started on s/c interferon 3 times per week, however, she relapsed in 2014 when she developed right internuclear ophthalmoplegia, cerebellar signs and worsening of muscle strength over left lower limb with power 1/5. Hence, she was changed to fingolimod and the disease was controlled since 2014.

**Discussion:** Multiple Sclerosis and Myasthenia Gravis have relatively the same distribution for age. They also share some HLA typing characteristics. There are immunological similarities with largely T cell mediated and dysfunctionalities of T regulator cells. It has been suggested that immune dysregulation could be induced by thymectomy and a considerable number of patients showed different autoantibodies after thymectomy.

Paper Number: 65

## Phenytoin toxicity presenting with acute visual loss, acute delirium and abdominal pain, a case report

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Phenytoin is a widely prescribed antiepileptic agent for both focal and generalized seizure. We report a case of a 20-year-old man with focal epilepsy presented with acute bilateral visual loss, delirium and abdominal pain. His random phenytoin serum concentration on admission was 43.6 mg/L, well above the recommended therapeutic range of 10-20 mg/L. Extensive investigations had ruled out other vascular or demyelinating causes. His visual symptoms completely resolved after withholding phenytoin for 72 hours. This case illustrates that acute phenytoin toxicity should always be considered in any patient with epilepsy presenting with unexplained visual or neuropsychiatric symptoms.

Paper Number: 66

## Brain Abnormalities In Nmosd: A Case Encounter

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**BACKGROUND-**Neuromyelitis Optica Spectrum Disorder (NMOSD) is an inflammatory CNS syndrome associated with serum aquaporin-4 immunoglobulin G antibodies (AQP4-IgG). It primarily attacks the optic nerve and spinal cord leading to optic neuritis and transverse myelitis respectively. These are the classic initial presentation for most patients. However, we encountered a patient who presented with encephalitis and brainstem manifestation, as well as transverse myelitis as an initial presentation.

**CASE DESCRIPTION-**She was a 31year old lady, who had a week history of fever with unusual behaviour and visual hallucination which progressed into reduced consciousness, preceded by diplopia and spasm of her lower limbs a month earlier. On examination, she had complex ophthalmoplegia, RAPD was absent and power of her all 4 limbs were reduced. She required prolonged ventilation due to episodes of apnoea. She experienced two episodes of cardiorespiratory arrest which were successfully resuscitated on both occasions. Her serum AQP4-IgG subsequently came back positive. MRI showed multifocal non-enhancing hyperintense lesions on T2WI & FLAIR involving the whole spinal cord, whole brainstem, right cerebellar peduncle, both cerebral peduncles, periventricular white matter of the posterior horn of left lateral ventricle, subcortical white matter on both frontal-parietal-occipital regions and bilateral centrum semiovale.

**CONCLUSION-**Although NMOSD has long been regarded as a disease without fulminant brain involvement as compared to multiple sclerosis, more recent studies revealed that brain abnormalities are not rare in NMOSD. Wingerchuk 2015 Diagnostic Criteria for NMOSD recognizes brain abnormality as some of its core clinical characteristic, namely acute brainstem syndrome and symptomatic cerebral syndrome, which we believe were responsible for this particular patient's presentation.

Paper Number: 69

## Bilateral Medial Medullary Infarction: A Case Report

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**Introduction-** Bilateral infarction of the medial medullary is a rare condition which represents less than 1% of posterior circulation stroke. Here, we describe a patient who presented to us with rapidly progressive quadriplegia with severe dysarthria.

**Case description-**He was a 56 year old gentleman who smoked heavily and had been previously healthy. He presented with one day history of all four limbs weakness and inability to speak. It was preceded by dizziness for one month duration. On examination, he had normal comprehension but was mute. His tongue was immobile. The extraocular muscle movements were normal and no gaze abnormality observed. Power of his all four limbs were 2/5 on initial presentation, which rapidly progressed to 0/5 within hours. The limbs were hypotonic with preserved deep tendon reflexes and extensor plantar response observed bilaterally. He subsequently developed upper airway obstruction with prominent stridor and required intubation. Brain MRI revealed the typical 'heart shaped' appearance at the medulla at DWI and FLAIR suggestive of bilateral medial medullary infarct. It also showed acute infarction at inferior pons and bilateral cerebellum. MRA neck demonstrated total absence of flow in the right vertebral artery and a short segment high grade stenosis at the intradural left vertebral artery, with intraluminal filling defect suggestive of a thrombus. The basilar artery appeared to be reduced in calibre.

**Conclusion-**It is crucial for clinicians to have high index of suspicion for medullary infarct syndromes in patients with quadriplegia and lower cranial nerve palsies, as they carry catastrophic consequences. High resolution neuroimaging is vital in its early and prompt diagnosis.

Paper Number: 70

# Kuala Lumpur Regional Integrated Stroke Intervention System – Stroke Thrombolysis Registry (KRISIS - STR ) Audit 2009 – 2017 : Improvement of Door-to-needle time

*Wan Asyraf Wan Zaidi*

## **Introduction :**

Hyperacute stroke treatment with intravenous recombinant tissue plasminogen activator (r-tPA) is a very time-dependent therapy. Treatment delay must be avoided in order to achieve good therapeutic outcome. It is very important for a stroke capable centre to audit the timeliness of the thrombolytic treatment to deliver the treatment efficiently and lower the risk of adverse event.

## **Methodology:**

We conducted a retrospective study, the data was extracted from our KRISIS – STR from 2009-2017. The information collected including patient demographics, stroke severity, door-to-needle, onset-to-needle and treatment outcome measured by modified Rankin scale (mRS). We analysed the door-to-needle (DNT) and onset-to-needle to two group ( 2017 and before 2017).

## **Results :**

A total of 156 patients underwent reperfusion treatment from 2009-2017. Intravenous r-tPA were given to 146 ( 93.6%) patients and 10 (6.4%) patients underwent mechanical thrombectomy. In 2017, 33 (6.7 %) out of 491 patients were treated with intravenous thrombolysis. We treated higher National Institute of Health Stroke Scale (NIHSS) in 2017 with mean of 14 (4-31) in comparison with before 2017, mean of 12 (1-26), ( $p = 0.042$ ). The DNT in 2017 mean was 101 minutes ( SD = 40 ) and before 2017 was 127 minutes ( SD = 55 ), ( $p = 0.168$ ). Around 18.2% patients were treated within 60 minutes from arrival in 2017 as compared to 4.3% in 2016. Patients arrived faster in 2017 with onset-to-needle time mean of 200 minutes ( SD = 73 ) and before 2017 the mean was 214 minutes ( SD = 51 ), ( $p = 0.141$ ). The mRS upon discharge mean was the same with mean of 2 ( SD = 2 ), ( $p = 0.082$ ). From 2009-2017, 61.6% of patients treated achieved favorable outcome upon discharge and only 7.5% suffered intracerebral hemorrhages.

## **Conclusion :**

Although there is an improvement with the DNT in 2017, further work need to be done to identify factors contributing to treatment delay.

Paper Number: 79

# Case series of atypical Guillain-Barré Syndrome (GBS) and concomitant neurological illness: Clinical interpretation above diagnostic criteria

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## Background:

There are various clinical phenotypes and electrophysiological subtypes of Guillain-Barré Syndrome (GBS), making clinical diagnosis challenging and prognostication process uncertain. Currently available clinical diagnostic criteria and classification were based on clinical phenotypes, requiring clinician ruling out GBS mimics. However, this can be challenging in the context of concomitant presentation with another neurological illness or the lack of clinical suspicion.

## Methods:

We described 3 cases of GBS with either atypical presentation or with concomitant neurological pathology and their respective neurophysiological features from a secondary hospital in Sarawak, Malaysia.

## Results:

First subject was a 60-year-old lady with background uncompensated Hepatitis B-related liver cirrhosis and diabetes mellitus, presented with classical form of GBS with concomitant statin induced myopathy following recent antecedent gastroenteritis. She was started on atorvastatin 3 months prior. Clinically, she had predominant proximal weakness with generalised areflexia. Maximum creatinine kinase was 26470 U/L. Lumbar puncture (LP) did not reveal albuminocytological dissociation. However, nerve conduction study (NCS) showed axonal subtype polyneuropathy. Statin therapy was withheld, and a trial of 5 days course intravenous immunoglobulin (IVIg) showed remarkable recovery with ability to ambulate without support on discharge. Second subject was young gentleman in his 20s' with underlying Hepatitis C, presented with recent history of progressive areflexic lower limb paraparesis with sensory level at T10 dermatome. MRI whole spine and CSF study were unremarkable. NCS demonstrated axonal motor sensory subtype polyneuropathy. Similarly, he improved remarkably to full MRC score following a course of IVIg. Our third subject, 67-year-old lady with background hypertension, presented with 3 days history of acute asymmetrical generalised weakness, affecting predominantly the left. Examination showed left facial upper motor neuron weakness, generalised areflexia and diffused sensory deficits. CT brain demonstrated a recent right lacunar infarct. CSF study revealed albuminocytological dissociation and NCS confirmed demyelinating subtype polyneuropathy. Despite IVIg therapy, she developed respiratory muscles weakness, requiring prolonged mechanical ventilation. Multiple complications ensued, with her eventually succumbed to severe sepsis related to prolonged hospital stay.

## Conclusion:

GBS can have atypical presentation and complicated by other neurological pathology. High index of suspicion supported by specific diagnostic tests may improve diagnostic accuracy and treatment outcome.

Paper Number: 80

# Delayed Onset MELAS Presenting With Expressive Dysphasia

*Jian Qin Chia*

**Background:** Mitochondrial Encephalopathy and Lactic Acidosis with Stroke-like Syndrome (MELAS) is the most commonly inherited mitochondrial disease with multisystem involvement and a plethora of clinical manifestation – mainly seizures and stroke like symptoms. Onset of symptoms is usually between 2-15 years old. We report a case of MELAS first presenting with expressive dysphasia in an adult male.

**Case Report:** Patient is a 19-year-old male who presented with sudden onset of expressive dysphasia. Nine days later, he developed short lived episodes of generalized tonic clonic seizures. On further questioning, he had a younger brother who passed away at the age of 8 due to metabolic encephalopathy and a mother who has hearing impairment since young. Clinical examination reveals that the patient is of short stature. He had difficulty naming objects and displayed some misarticulations when asked questions. Comprehension was intact. He showed no cerebellar signs nor any pyramidal weaknesses. Blood work revealed raised serum lactate. Cerebrospinal fluid analysis was normal. MRI brain showed a right temporo-parieto-occipital area infarct with mass effect on the right lateral ventricle, no enhancement post contrast. Genetic study showed that patient had m3243 A>G mutation. A deltoid muscle biopsy demonstrated ragged red muscle fibers. He was started on oral arginine, Coenzyme Q10, riboflavin and phenytoin. After 2 months, patient exhibited near complete resolution of symptoms and was fit free.

**Conclusion:** Clinicians should be cautious in diagnosing young patients with stroke as they may have an unusual aetiology. Stroke in MELAS is postulated to be due to mitochondrial cytopathy or angiopathy. Nitric oxide deficiency is believed to play a role in development of MELAS complications. Treatment is mainly supportive care and nitric oxide precursors supplement such as arginine and citrulline. Aspirin and statin, which are mainstay treatment of ischemic stroke, may not be useful in patients with MELAS. Although this condition is not curable yet, a correct diagnosis is prudent for patient to receive correct treatment, prognostication and future planning.

Paper Number: 81

# Stroke Burden in Hospital Tengku Ampuan Rahimah (HTAR): A Hospital-based Prospective Study

*Yue Hui Lau*

## **Background:**

The incidence and prevalence rates of stroke are decreasing in developed countries but there are an increasing number of patients being diagnosed with acute stroke in Asia Pacific. The results of the present study on acute stroke will significantly contribute to the Malaysia National Stroke Registry and hence global stroke epidemiological data.

## **Objective:**

To present epidemiological data of stroke including incidence and prevalence rates as well as associated risk factors from a prospective hospital-based registry from 2nd February to 2nd May 2018.

## **Methods:**

All patients diagnosed with stroke upon admission to HTAR were prospectively enrolled into the study from 2nd February to 2nd May 2018. Descriptive analyses were performed based on the National Stroke Registry (NSR) in describing the demographic, risk factors and disease pattern of stroke patients in Malaysia.

## **Results:**

A total of 78 patients were available for analysis. In general, the strokes reported in our study were predominantly ischemic in nature (85.9%), followed by intracranial haemorrhage (10.3%) and finally Transient Ischemic Attack (3.9%). Based on our pooled data, strokes were reported more in females (51.3%) as compared to males (48.7%). The highest number of strokes was recorded among the group ages of 50-54 years old (16.7%) followed by ages between 75-79 years old (14.1%) and 60-64 years old (12.8%). In terms of ethnicity, strokes were most common among the Malays (47.4%), followed by Indians (30.8%), the Chinese (15.4%) and finally foreigners which made up (6.4%). The most common risk factor was hypertension (76.9%), followed by alcohol consumption, diabetes mellitus, hyperlipidaemia and ischemic heart disease: 52.6%, %, 44.9%, 18% and 12.8% respectively. 20% of the stroke patients admit to emergency department within three hours. Among the acute ischemic strokes, we recorded a case of thrombolysis.

## **Conclusion:**

Stroke remains a major health burden in this country. These findings highlight the importance of implementation of risk factor control strategies which is essential to prevent further increase of stroke mortality and morbidity.

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Paper Number: 95

# Benchmarking in-hospital stroke team for Acute Ischemic Stroke (AIS) Thrombolysis in a tertiary stroke capable hospital in Malaysia: From a developing country's perspectives

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## Background

In Kuala Lumpur Hospital, IV thrombolysis service was commenced in June 2013. As a relatively young stroke centre, it is essential to report the safety and efficacy of our stroke service. We also aimed to evaluate our in-hospital management performance, comparing with recommendation standard from the 2018 AHA/ASA acute ischemic stroke (AIS) guideline.

## Methods

This analysis was part of our on-going local AIS thrombolysis database report conducted between June 2013 to December 2017. We included patients receiving intravenous rt-PA within 4.5 hours of symptoms onset. Data collected includes baseline demographics, stroke characteristics, time of stroke onset to arrival in the emergency department (ED); CT scan and administration of rt-PA. Outcomes analysis included treatment efficacy with modified Rankin Scale (mRS) and safety parameters assessed by the occurrence of symptomatic intracranial haemorrhage (SICH).

## Results

Fifty-four patients received IV rt-PA and 5 (9%) patients had endovascular thrombectomy over 54 months period. Large majority (94%) had at least moderate stroke severity (NIHSS > 5). There was a substantial delay in all in-hospital stroke team key performance from arrival at A&E to start of thrombolysis. Only fourteen (26%) patients had door-to-needle time within 60 mins (Mean 87.8 mins). Less than one-third of the patients had brain imaging performed within 20 mins of arrival (Mean 38.3 mins). The mean CT to needle (CTTN) time, encompasses interpretation of imaging, decision to administer thrombolysis, patient consent and reconstitution of rt-PA infusion was close to an hour (53.5 mins). A total of 10 (18.5%) in-hospital death occurred following administration of IV rt-PA, in which a third, (3 patients) had symptomatic ICB. Overall good functional outcome (mRS ≤ 2) at 3-6 months was comparable with national and international standard.

## Conclusion

IV rt-PA given within 4.5 hours from symptom onset in a tertiary stroke capable hospital in Malaysia was safe and associated with improved clinical outcomes without higher rates of mortality. However, in-hospital stroke team performance was below the standard set by international guideline. There is an urgent need for a better streamlined thrombolysis model and reorganisation of support services since net benefit of IV rt-PA is very much time-dependent.

Paper Number: 97

# Determining Optimal Early Rehabilitation After Stroke (AVERT-DOSE): A Multi-Arm Covariate-Adjusted, Response-Adaptive Randomised Controlled Trial

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## Background and Aims

In 2015, we completed the landmark, international RCT of early rehabilitation (The Lancet, 2015). We determined that too much training early interferes with stroke recovery and that most patients may be responsive to therapy if the right dose can be found (Neurology 2016). The aim of this study is to define the optimal early intervention regimens for people with mild and moderate stroke severity.

## Method

We will use a multi-arm, dose-finding, Covariate-Adjusted, Response-Adaptive (CARA) Randomised Clinical Trial (Figure 1) in two specified mild and moderate stroke severity strata. We will test three separate rehabilitation intervention regimens in each strata against a pre-specified control to identify the intervention regimen that results in fewer disabled patients at 3 months post stroke (mRS 0-2). A sample size of 2,572 patients will allow us to independently observe pre-specified effects in these two strata with power 80% and significance threshold of  $p=0.025$ . All analyses will be intention-to-treat. Patients with mild to moderate stroke will be recruited using our global trials network in Australia, New Zealand, Singapore, Malaysia, India and United Kingdom.

## Results

The trial protocol is in final stages of development with site identification underway.

## Conclusion

AVERT-DOSE will establish clear, definitive, early intervention protocols, that will ensure that stroke patients receive best evidence care, both here and in developing health service systems.

**If you are describing a clinical trial or clinical trial results, including any ongoing trial, please indicate the trial registration number in the following box. If this does not apply to you please indicate: N/A**

Protocol under development

Keywords

acute stroke

rehabilitation

response-adaptive

dose

cost effectiveness

Paper Number: 100

## Rapid Sequences Intubation (RSI) on Status Epilepticus (SE) Patients

*Desin Pambudi Sejahtera*

### Background:

Status epilepticus is a medical emergency that requires prompt and aggressive therapy to prevent neuronal damage and systemic complications. The first major problem and that must be considered is the maintenance of airway patency. Knowledge and skills regarding the management of the airway is the most needed expertise in the handling of the gravity of the SE in the emergency department. Disruption of the airway will very quickly could potentially result in death.

### Aim:

The purpose is to ascertain the literature on RSI in SE patients, so the clinicians have an evidence and guidance to make an emergency rescue to protect airway patency in SE patients.

### Method:

Collecting literatures on RSI and incorporating them then making conclusions about the RSI method of maintaining airway patency during SE.

### Result:

Important step in maintaining the patency of the airway, perform simple maneuvers to free the airway and provide ventilation as soon as possible. Management begins assess airway patency of the airway, assess awareness and breath adequate effort, to see an increase in the chest, to hear and feel the blast of air from the mouth and nose of the patient. Patients with airway obstruction can't adequately effective gas exchange. Patients with airway obstruction total, will not be able to talk, hypoxic, and will very quickly decreased consciousness. Partial airway obstruction, more because of the functional, because of the soft palate, tongue and epiglottis fall back and meet with pharynx posterior part. Exemption airway maneuvers include head tilt, chin lift and jaw thrust maneuver. Sometimes these maneuvers didn't work so need tools like oropharyngeal or nasopharyngeal airway. If the tool doesn't reach the target oxygenation, it is necessary to install a definitive airway tools by installing rapid method sequences endotracheal intubation (RSI). Installation of endotracheal intubation, should pay attention the indication, stage, complications, and consider the risks of failure. Intubation failure can be identified by a variety of simple checks. Maximum tolerance of failure for each patient is different, with an estimated three attempts, or about ten minutes.

Paper Number: 101

## A case of reversible parkinsonism in central pontine and extrapontine myelinolysis

*Elaine Chew*

**Background.** Osmotic demyelinating syndrome is an acquired demyelinating disorder. Rapid correction of serum sodium results in non-inflammatory demyelination in pontine and extrapontine regions. Classically, this has been described to have a biphasic presentation. There is an initial encephalopathic phase and progression to paresis with or without accompanying bulbar symptoms. Movement disorders, in particular parkinsonism have rarely been reported, possibly underdiagnosed.

**Case report.** A 63 year old gentleman presented with acute parkinsonism and dysarthria 8 days after his discharge from surgical ward for ileus. During his surgical admission, hyponatremia and hypokalemia developed as a result of emesis and bowel edema. Rapid correction of hyponatremia was done at a rate of 24 mmol/L over 24 hours. The recommended rate of sodium correction is 4-6 mmol/L within a 24 hour period. Subsequent MRI showed pontine and extrapontine myelinolysis. We report a case of reversible, symmetrical parkinsonism in a patient who made a rapid and complete recovery without dopaminergic treatment.

**Conclusion.** Pontine and extrapontine myelinolysis could achieve complete resolution with symptomatic treatment alone. Recovery may be related to the duration of hyponatremia at outset and predisposing conditions rather than the rate of sodium correction. Nevertheless, in the event of severe hyponatremia, sodium correction should still be carried out judiciously to prevent life threatening and permanent sequelae of osmotic demyelination syndrome.

Paper Number: 106

# Arteriovenous Fistula After Cerebral Venous Sinus Thrombosis

*Qin Jian Low*

## Background

We report a case of likely arteriovenous fistula (AVF) following cerebral venous sinus thrombosis (CVST).

## Methods

A case report of an AVF following CVST which presents with meningoencephalitis.

## Results

The patient was a 51-year-old gentleman with no comorbid, on 20th May 2018 experienced fever and headache for 3 days' duration. He had been fasting for the last 10 days during Ramadan. On arrival, his GCS was E1 V2 M5. Neurological examination revealed an increase tone at bilateral upper and lower limbs and generalized brisk reflexes with bilateral down-going plantar response. Initial CT brain showed a right occipital vascular malformation with prominent venous sinuses. MRV brain showed the presence of filling defect within the deep cerebral venous sinus involving the internal cerebral vein, vein of Galen and straight sinus. There were multiple tubular structures seen in the medial right occipital lobe which are hyper-intense on T1 and T2 images with blooming artefact on GRE suggestive of a vascular malformation likely an arteriovenous fistula (AVF). CSF study showed an opening pressure of 25 cmH<sub>2</sub>O, turbid appearance, 50 cells/mm<sup>3</sup>, predominantly 60% neutrophils, CSF protein raised at 4.1g/L, borderline CSF glucose 2.6 mmol/L, CSF/serum glucose ratio of 46%. CSF gram stain, latex agglutination, TB PCR, AFB and Indian ink were all negative. Marais score was negative for TB meningitis. There was no evidence of malignancy, head trauma, polycythemia. His anti-phospholipid study was negative. He was treated for bacterial meningoencephalitis with CVST and AVF and completed 2 weeks of IV ceftriaxone 2g bd and subcutaneous enoxaparin 1mg/kg bd. Neurosurgical team decided for conservative management of the AVF. After 1 month of treatment and physiotherapy, his GCS improved to E4 V2 M6 and he was discharged with warfarin.

## Conclusions

We suggest that the vascular malformation is likely an arteriovenous fistula (AVF) due to venous hypertension following the venous sinus thrombosis. The venous hypertension develops after venous thrombosis opens up the microvascular connections within the dura and these channels become hypertrophied resulting in direct shunting between arteries and veins. This patient does not have a baseline CT brain done previously.

Paper Number: 107

# Diagnostic Dilemma Of A Patient With Susac's Syndrome: A Case Report

*Huey Tean Kok*

**Background:** Susac's syndrome consists of the triad of encephalopathy, branch retinal artery occlusions and hearing loss. The complete triad may not be present at the onset, which makes the diagnosis more challenging. We reported this case to discuss the newly appreciated branch retina artery occlusion (BRAO) subset of Susac's Syndrome.

**Case presentation:** A 31 years old man, presented with sudden onset left facial asymmetry, aphasia and right hand grip weakness with acute confusional stage. He had history of left eye visual defect few years prior to this event. On physical examination, he had left 7th cranial nerve palsy, right hand grip strength 4/5 and other limbs strength were 5/5. On ophthalmic examination the visual acuity in the left eye was 6/9 and 6/6 in the right eye. Humphrey visual field demonstrated left inferior field defect superimposed with right superior quadrantanopia. There was ischaemia at the superior half of left retina with inner 2/3 of limiting membrane edema. The diagnosis was made left superior hemi retinal artery occlusion with macula sparing. Mental state examinations showed moderate cognitive impaired and EEG revealed the present of intermittent bilateral frontal and left temporal slowing. MRI brain showed multiple T2 hyperintense lesions at the left lentiform nucleus, body and tail of left caudate nucleus, left centrum semiovale, patchy cortical hyperintensities over the left frontoparietal convexity and these lesions enhance post contrast. Whereas, auditory testing revealed normal hearing bilaterally. Given the full clinical picture, a diagnosis of Susac's syndrome with subset of BRAO was made. Although he had not received any treatment for Susac's syndrome, he recovered with little residual disease in the left eye.

**Discussion:** Susac's syndrome is a multisystemic microvascular occlusive endotheliopathy with suspected immune-mediated pathogenesis. Diagnosing Susac's syndrome can be challenging, especially in patients presenting without all features of the clinical triad of encephalopathy, BRAO and hearing loss. We believe that the diagnosis of Susac's Syndrome can be made when only the encephalopathy and pathognomonic MRI lesions are present; the branch retina artery occlusion and hearing loss need not be present.

Paper Number: 108

## Bacterial Meningitis Following Spinal Anaesthesia For Caesarean Section

*Qin Jian Low*

### Background

Meningitis after lumbar puncture and spinal anaesthesia is extremely rare with potentially serious complications. There is much discussion about the etiology and prognosis of this condition.

### Methods

A case report of a bacterial meningitis following spinal anesthesia for caesarean section.

### Results

A 33-year-old lady para 1 female was admitted at 40 weeks of gestation for reduced fetal movement. Her past medical history and antenatal history was unremarkable. She was afebrile and urinalysis was normal. She was counselled and agreed for induction of labour. However, after eight hours of induction of labour, her cardiotocography showed variable deceleration and an emergency lower segment caesarean section (LSCS) was performed. Skin disinfection was done using alcohol and chlorhexidine solutions. Subarachnoid block was done using intrathecal fentanyl 15 mcg, heavy bupivacaine 0.5% and morphine 0.1mg. The LSCS was uneventful. Twenty-eight hours post op, she developed fever of 39C, worsening headache and confusion. There was neck stiffness and positive Kernig's sign. An urgent plain CT brain done was normal. Diagnostic lumbar puncture showed an opening pressure of 25 cmH<sub>2</sub>O, turbid CSF appearance with a white blood cells of 1470 cells/mm<sup>3</sup> and predominantly neutrophils. CSF glucose was 4.5 mmol/L with a ratio of less than 0.6. CSF protein was raised at 2.4g/L. No bacteria were seen on gram stain or culture. Her blood culture was negative. A diagnosis of 'introduced' bacterial meningitis was made. She was treated with 2 weeks of intravenous ceftriaxone 2g bd. She made an uneventful and complete recovery. She was discharged home with no neurological deficits.

### Conclusions

Spinal anesthesia complicated by meningitis is rare. It is vital that physicians remain vigilant to detect meningitis when patient presents with headaches, pyrexia and meningism in the post-operative period.

Paper Number: 109

## Evaluation of Secondary Prevention in Older Survivors of Ischemic Stroke: Data from Malaysia Stroke Registry

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**Introduction:** The risk of recurrent stroke is known to be greatest in the first 6 months following an initial presentation. Hence, secondary prevention measures is essential part of stroke care. Despite this, older patients often receive less aggressive secondary prevention strategies contrary to the evidence that most of these strategies can be effective in the elderly.

**Objective:** to evaluate the impact of age on receiving the secondary prevention medications at the time of hospital discharge. Pre specified secondary prevention drug classes studied were antiplatelet, lipid lowering agent and antihypertensive.

**Method:** In this study, records of acute ischemic stroke patients from Malaysia National Stroke Registry were retrospectively examined. Patients were divided into 2 groups: those who were less than 80 years of age and those who were 80 years old and more.

**Result:** There were 8947 of < 80 years old and 755 of ≥80 years old patients registered in Malaysia National Stroke Registry from July 2009 to December 2017. Male represented 56.1% of patients in young group and 43.9% in older group. Compared to young age, older age were less likely to receive antiplatelet (87.9% vs 91.8%; p=0.001) and anti-hypertensive drugs (45.4% vs 50.4%; p=0.009). Factors associated with antiplatelet prescribing identified in older age were lacunar stroke (OR 3.06; 95% CI 1.35, 6.90), good Modified Rankin Scale upon discharge (OR 1.28; 95% CI 1.04, 1.57) and male (OR 1.64; 95% CI 1.04, 2.58) whereas underlying diabetes mellitus (OR 1.51; 95%CI 1.09, 2.09), atrial fibrillation (OR 2.30; 95% CI 1.31, 4.02) and unclassified stroke (2.09; 95%CI 1.12, 3.90) were the factors associated with antihypertensive prescribing.

**Conclusion:** After hospitalization for ischemic stroke, there was an age disparity in antiplatelet prescribing contributed by OCSF classification, MRS upon discharge and gender as well as antihypertensive drug prescribing which associated with underlying DM and AF and also OCSF classification.

Paper Number: 111

## Phenotypic Characteristic Of Families With Spinocerebellar Ataxia (SCA) 3 In Malaysia

Noorasyikin Mohamed Arifin

**Objective:** To describe phenotypic characteristics of genetically confirmed SCA 3 patients in neurology unit PPUKM

**Methods:** 15 patients from 7 families tested positive for ATXN 3 were recruited. Patients were assessed for onset and duration of illness. Clinical phenotypes i.e. cerebellar signs, ocular movement disorder, pyramidal and extrapyramidal signs, peripheral nerve dysfunction, cognitive dysfunction and other related disorder such as dysphagia and incontinence were also analyzed. Objective evaluation using scale for the assessment and rating of ataxia (SARA) and quality of life (QoL) score using EQ5D-3L were also performed.

**Results:** All 15 patients had at least 3 generations with family history of similar neurological abnormalities. Youngest patient registered was 16 years old and oldest was 59 years old with median age of 36.0 years (IQR 33.0-39.0). The shortest duration of disease was one year and longest was 11 years with median 4.0 years (IQR 2.0-6.0). First presentation in all patients was progressive gait instability and currently 7 (46%) were wheelchair dependent. Median time to wheelchair in 7 patients were 12 months (IQR 12-24). Total of 11 (73%) patients had appendicular ataxia and 14 (93%) patients had dysarthria. In terms of ocular movement abnormalities, 10 (67%) subjects presented with nystagmus whereas 7 (47%) had ophthalmoplegia and diplopia. The median of duration of illness to onset of ophthalmoplegia was 12 months (IQR 6-21). Nine (60%) patients had pyramidal signs. Only 3 (20%) patients had signs of parkinsonism, 2 (13%) had dystonia and one patient (6.7%) had cognitive dysfunction. There was a marked heterogeneity among siblings with SCA 3 manifested in variable neurological signs. Median SARA scale was 12.5 (IQR 8.5-19.0) and median QoL score was 60.0 (IQR 40.0-80.0).

**Conclusion:** SCA 3 phenotype is similar to that described in the literature with progressive ataxia plus pyramidal syndrome, parkinsonism and ataxia.

Paper Number: 112

## Overlap Syndrome in Demyelinating Diseases

Jie Ping Schee

### BACKGROUND :

Demyelinating diseases are a heterogeneous group of immune-mediated disorders which continue to evolve phenotypically from various clinical, neuroimmunological, radiological, and pathological points of view. In resource-limited settings, one is left with mainly the power of observation, neuroimaging with 1.5 Tesla MRI of the brain and spinal cord, and limited access to biomarkers for clinical interpretation of demyelinating diseases.

### METHODS :

A single Neurologist (S.V.) with the assistance of a Physician (S.J.P.) conducted comprehensive evaluation while retrospective reviewing medical records of 493 consecutive patients with central nervous system demyelination in the Demyelinating Disease Database at Kuala Lumpur General Hospital, Malaysia. We explored their demographics, detailed clinical and para-clinical features including neuroimaging.

### RESULTS :

We identified a group of 22 patients with a relapsing-remitting clinical course and optico-spinal or spinal cord involvement with or without brain lesions, i.e. two scenarios namely overlapping features of either (i) MRI of brain resembling 2017 McDonald neuroimaging criteria for Multiple Sclerosis (MS) and MRI of spinal cord resembling Neuromyelitis Optica Spectrum Disorder (NMOSD) according to International Panel for NMO Diagnosis (IPND) International Consensus Diagnostic Criteria For NMOSD 2015, or (ii) no typical MS-like brain lesions but with optical lesions resembling that of NMOSD and spinal cord involvement particularly short segment myelitis resembling MS-type myelitis. Despite sharing certain clinical and radiological features of both MS and NMOSD, these patients were tested negative for cerebrospinal fluid oligoclonal bands, serum anti-aquaporin 4 antibody, and serum anti-myelin oligodendrocyte glycoprotein antibody. They were steroid responsive during acute attacks / relapses and majority were treated with maintenance immunosuppressants or trial of MS disease modifying therapies that were considered unlikely to exacerbate NMOSD, such as Rituximab.

### CONCLUSIONS :

These patients might constitute a novel entity of MS / NMOSD overlap syndrome which necessitates careful elucidation and further research.

Paper Number: 116

# Reliable change index (RCI) in assessing mindfulness-based intervention for people with epilepsy (PWE)

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## Background

Mindfulness-based interventions (MBI) are proven to significantly reduce psychiatric symptoms and promote good mental health among the neurological population. The efficacy of MBI for epilepsy however, have yet to be thoroughly investigated.

## Objectives

The efficacy of MBI in PWE was examined in Studies 1 and 2. The primary aim is to investigate its clinical significance via the Reliable Change Index (RCI) and the magnitude of a treatment effect over a control using the number-needed to treat (NNT) approach.

## Method

Study 1 was conducted in Hong Kong. Total 60 drug-resistant epilepsy were randomly allocated to the mindfulness (MT) or social-support group (SS) to receive a four 2.5-hour biweekly sessions. The 2nd study was a preliminary study conducted in Malaysia, with 9 epilepsy patients participated in the mindfulness trial to receive a six 2.5-hour weekly sessions. Primary outcomes included depression and anxiety. Secondary outcome was on quality of life. Jacobson's methodology was used to determine the RCI in outcome measures. The calculation of NNT was based on patient's baseline risk and the average control patient in the trial.

## Results

In studies 1 and 2, post-treatment assessments showed that patients in the MT group experienced greater reduction in depressive and anxiety symptoms ( $p < .05$ ). Contrary to Study 1, the MT group in Study 2 found an improvement in quality of life (QOL) ( $p < .05$ ). RCI in studies 1 and 2 showed that the improvement in QOL was statistically reliable ( $40.0 \approx 66.7\%$ ). The extent of gains were reflected in levels of depression ( $43.3 \approx 55.6\%$ ) and anxiety ( $33.3 \approx 44.4\%$ ). NNT analysis showed 5 epilepsy patients would have to receive MBI over four 2.5-hour biweekly sessions.

## Discussion

Mindfulness therapy is effective in reducing psychological distress and improving quality of life in PWE. Our findings showed two important clinical significance that the: (i) amount of change that has occurred in the MT group was large enough to be meaningful and (ii) improvement of scores (RCI) were not due to imprecision of measuring tools. Implementation of a psychological therapy requires consideration on the length and success rate of the therapy, our NNT measure therefore offers psychobehavioural scientists to consider this intervention.

Paper Number: 120

# A Rare Complication of Intravenous Immunoglobulin (IVIg) – Type II Myocardial Infarction Post IVIG for Myasthenia Crisis

*Chu Grace***Introduction :**

Myasthenia Crisis, a complication of myasthenia gravis characterised by worsening muscle weakness involving respiratory failure requiring mechanical ventilation, often necessitates either intravenous immunoglobulin (IVIg) or plasma exchange (PE) as part of treatment. Intravenous immunoglobulin, although considered a relatively safe medication with mostly minor adverse effects, may have rare but serious complications from its hypercoagulable state. We describe a 43 year old gentleman who developed type II STEMI post IVIG.

**Case Report :**

A 43 year old gentleman, who defaulted follow up and medications for underlying myasthenia gravis, presented with progressive shortness of breath for two weeks, associated with diplopia, difficulty swallowing and progressive upper limbs weakness. He was treated with IVIG for myasthenia crisis. Upon 12 hours following the IVIG infusion, he developed severe central chest pain with electrocardiogram revealing dynamic changes of ST elevation over anterolateral leads. His initial electrocardiogram was sinus rhythm without ischemic changes. Before he could be thrombolysed, his symptoms resolved and the repeated electrocardiogram showed signs of reperfusion within 17 minutes. His echocardiogram done on the same day showed hypokinesia at anteroseptal region with reduced ejection fraction. Cardiac biomarker (CK-MB) subsequently was only modestly raised. Subsequently, plasma exchange was done for him on alternate days for 5 cycles. He had no more cardiac event during his remaining hospital stay otherwise. Coronary angiography was yet to be done for him as he was subsequently intubated for mechanical ventilation and was complicated with multiple episodes of nosocomial infections. Repeated echocardiogram however showed resolution of the ejection fraction and hypokinetic areas albeit minimal global pericardial effusion.

**Conclusion :**

There had been few case reports regarding myocardial infarct following IVIG infusion due to its hypercoagulopathy state causing arterial thrombosis, especially in patients with underlying cardiovascular risk factors. However, significant, though transient reactive coronary vasospasm due to the hyperviscosity state too, may lead to type II myocardial infarction secondary to mismatch in oxygen demand and supply.

Paper Number: 121

# A Case Report of Lafora Disease

*Tien Lee Ong***Background:**

Lafora body disease is a rare and fatal autosomal recessive disorder most commonly affecting adolescents with normal neurological function. The disease is characterised by progressive myoclonic seizure, visual hallucinations, dysarthria, and ataxia with progressive cognitive and behavioural deterioration. The condition is often fatal within 10 years of onset, usually from status epilepticus or from complications related to nervous system degeneration.

**Results:**

Herein we report a case of a 26-year-old Malay gentleman with epilepsy, progressive cognitive decline and unsteady gait for 7 years. The seizure semiology varied from generalised tonic-clonic seizure with post ictal aggressive behaviour to focal seizure with right eye deviation, ictal blinking, bilateral facial and mouth twitching to myoclonic jerk. The seizures occurred up to 20 times a day. His cognitive impairment and seizures progressively worsened and he eventually became bed bound in 2017. He had normal birth and developmental milestones and completed his secondary education. There is no history of febrile fit or brain infection. There is no family history of consanguinity, however he has two younger brothers with similar illness.

He was admitted in January 2018 for post ictal aggressive behaviour and was subsequently intubated for status epilepticus one month later. His seizures remain poorly controlled despite being on five antiepileptic agents. At present he has spontaneous eye opening but is unaware of his surroundings. There is no focal neurological deficit on examination. Serial EEGs showed an encephalopathic background with bilateral multifocal spike and polyspikes with frontocentral predominance. Skin punch biopsy of his left thigh showed Periodic acid-Schiff stain (PAS)-positive intracytoplasmic inclusion bodies at the eccrine duct, establishing the diagnosis of Lafora Disease.

**Conclusion:**

Lafora Disease is not well recognised in Malaysia. A high index of suspicion is important to identify the disease in patients with progressive myoclonic seizures and gradual cognitive decline. Early recognition may not alter the long-term outcome; however, it will assist in prognostication and providing genetic counselling to the family members. Although genetic studies are the gold standard in diagnosing Lafora Disease, skin biopsy is a useful tool in establishing the diagnosis in resource-limited settings.

Paper Number: 124

# Post spinal Meningitis With Subdural Collection – An Uncommon Complication After Spinal Anaesthesia for Caesarean Section

*Seng Wee Cheo*

## Introduction :

Post spinal meningitis is a rare but potentially life threatening complication following spinal anaesthesia. In most instances, its presentation is typically acute, 24-48 hours after procedure. The exact incidence is unknown. Here, we reported a case of post spinal meningitis with subdural collection following spinal anaesthesia.

## Method :

Case Report.

## Results :

A 31 year old lady, gravida 3 para 2 at 34 weeks of gestation with twin pregnancy initially presented with labour pain. Antenatally, this was an uneventful pregnancy. Cardiotocography (CTG) at presentation was reactive for twin 1. CTG for twin 2 showed poor beat to beat variation with no acceleration. She was then posted for emergency lower section caesarean section(LSCS) for fetal distress. Subarachnoid block was done at L3 level after 2 attempts. Intrathecal fentanyl and bupivacaine were given. 5 minutes post spinal anaesthesia, patient developed high spinal symptoms with sudden onset back pain and shoulder numbness. She was resuscitated with intravenous ephedrine, phenylephedrine and fluid and responded. She managed to go through the surgery. Post op day 2, patient complained of severe headache, associated with neck stiffness and fever. No cough, no diarrhoea, no vomiting or dysuria. Conscious level was normal. On examination, blood pressure was 108/60mmHg, pulse rate was 98bpm, temperature of 40C. Full blood count showed haemoglobin 8.6g/dl, white blood cell 12.9x10<sup>9</sup>/L, platelet 291x10<sup>9</sup>/L,. Renal profile was normal. Bicarbonate was 11.9mmol/L. She was then admitted to intensive care unit and intubated for respiratory distress. Subsequently, she undergone contrast enhanced computed tomography of brain which showed meningeal enhancement with left fronto-parietal subdural collection with maximum thickness of 5mm. We then performed a spinal tap on following day. CSF examination showed no cell seen, total protein of 0.21g/dl and normal glucose ratio. CSF cultures, latex agglutination were negative. She was then treated with 6 weeks of intravenous antibiotics. Interval CT scan showed marked improvement. Eventually, she recovered well.

## Conclusion :

Post spinal meningitis can be potentially life-threatening. Hence, it's an important differential to be considered in fever following procedure. Full aseptic technique is essential during procedure as well.

Paper Number: 119

## Aluminium chloride exposure changes learning and memory and SOD and CAT in Zebra fish (*Danio rerio*)

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**Background:** Aluminum (Al) is the third most common and abundant metal on earth after oxygen and silicon. Al is usually considered most toxic in its soluble ionic form.

**Methods:** To assess the toxicity of AlCl<sub>3</sub>, Zebra fish were exposed to AlCl<sub>3</sub> and its impact in learning and behavior and ROS enzymes namely SOD and CAT were analyzed.

**Results:** In a nutshell, behavioral analyses showed memory retention in control fishes and anxiety like behavior in Al treated fish. Further, the level of SOD increased in treated fish in comparison to the treated fish brain. The level of CAT decreased in Al treated fish brain in comparison to the control fish brain.

**Conclusions:** Such studies are helpful to understand the effect of heavy metals (Al) and their impacts in the brain including behavior and to molecules. These may be useful to understand metal toxicity and neurodegeneration in disease and aging studies.

Paper Number: 20

## Changes in electroencephalography (EEG) spectral power in frontal and parietal cortices in freely moving rats elicited by mitragynine from *Mitragyna speciosa*

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Kratom (*Mitragyna speciosa*) is a widely abused herbal drug preparation in Southeast Asia. It is often consumed as a substitute for heroin, but imposing itself unknown harms and addictive burdens. Mitragynine is the major indole alkaloid of kratom that has recently been reported to induce morphine-like behavioural and cognitive effects in rodents. The changes in brain activity of its user either acute or repetitively remained unreported. Here, we investigate the effects of mitragynine treatment in freely moving rats using electroencephalography (EEG) activity. Rats were administered with mitragynine (1 and 30 mg/kg) after 7 days of electrode implantation surgery. Morphine (5mg/kg) and Methamphetamine (1mg/kg) were used as positive control. Brain activity was recorded 1 hour after acute and repetitive exposure of mitragynine. We found that mitragynine triggered changes of brain activity in both low and high doses. Animal treated with mitragynine (1 mg/kg) produced EEG synchronization characterised by continuous large-amplitude synchronized activity, with no prominent changes in specific power density both in acute and repetitive studies in recorded regions. Mitragynine (30 mg/kg) produced an EEG desynchronization characterised by a general decrease in amplitude of all the frequency bands (0-50 Hz) with prominent upsurge of theta power (4.75-6.75 Hz) after acute administration, and decreased of delta power (1.25-4.5 Hz) after repeated administration only at frontal cortex. These results suggest that mitragynine elicited a biphasic (synchronization and desynchronization) changes of brain waves affecting specific frequency bands and region depending on the dose.

Paper Number: 47

## Anti-TRPM4 antibody improves hippocampal long-term potentiation deficit in chronic cerebral hypoperfused rats

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**Background:** Transient receptor potential melastatin 4 (TRPM4) is a calcium-activated, non-selective cation channel. Activation of TRPM4 following hypoxia/ischemia leads to oncotic cell death. As hippocampus is one of the brain regions most vulnerable to cerebral hypoperfusion, damage to the neurons can lead to the synaptic dysfunction. Therefore, the present study aims to evaluate the effect of single administration of anti-TRPM4 antibody on the long-term synaptic plasticity in chronic cerebral hypoperfusion (CCH) induced rats.

**Methods:** Male Sprague Dawley rats (200-250 g) were subjected to permanent bilateral occlusion of common carotid arteries (PBOCCA) or sham-operated surgery. Immediately after surgery, the rats were given single loading dose of anti-TRPM4 antibody (0.5 µg/g body weight each) intraperitoneally. Electrophysiological recordings were conducted under urethane anaesthesia 28 days after the surgery

**Results:** The results demonstrated that CCH resulted in inhibition of hippocampal LTP formation without affecting the basal synaptic transmission. Interestingly, treatment with anti-TRPM4 antibody significantly rescued the impairment of LTP in PBOCCA rats.

**Conclusions:** The present findings suggest a novel role for TRPM4 expressed in adult hippocampus in restricting synaptic plasticity after CCH. The potential of anti-TRPM4 antibody to improve neuronal plasticity represent a promising role of this antibody-based therapeutic in targeting ion channels to treat various neurological diseases which warrant further investigation.

Paper Number: 52

## Mitragynine (Ketum)-induced memory impairment of Swiss albino mice in the IntelliCage® system

Wan Ismail Nurul Iman

**Background:** Mitragyna speciosa (Ketum) is a traditional medicinal plant in the northern region of Malaysia and southern region of Thailand. Ketum leaves have been recreationally consumed as a substitute to opium due to their stimulant and euphoric effects, hence subject to addictive liabilities. Mitragynine, a major constituent of Ketum leaves, has recently been reported to impair cognitive performance in rodents, although mechanisms remain unclear. The present study aimed to identify the effect of mitragynine sensitisation on mice spatial learning and reversal learning, and the possible involvement of cannabinoid (CB1) receptor.

**Methods:** Male Swiss albino mice were subjected to a 28-day chronic regimen with mitragynine (5-25mg/kg, ip, n=6), or mitragynine + NIDA-41020 (CB1 receptor antagonist, 20mg/day, oral, n=6). Control group received Tween-20 vehicle (1ml/kg, ip, n=6). The automated home-cage IntelliCage® social learning system was used to observe the effect of mitragynine sensitisation on mice spatial learning (Day 15 to 21) and reversal learning (Day 22 to 28).

**Results:** Mitragynine-sensitised mice exhibited failure to perform operant learning task and to acquire the water-rewarded corner ( $p < 0.05$ ) and spatially-shifted corner ( $p < 0.05$ ) relative to the vehicle-control group. However, place learning and reversal learning deficiencies seen in mitragynine-sensitised mice were significantly ameliorated with the administration of NIDA-41020.

**Conclusions:** These findings implicate the role of brain CB1 receptors in the spatial learning deficit associated with chronic mitragynine use. Future studies to deliberate the underlying neuronal basis are warranted, particularly in relation to emerging Ketum use and misuse.

Paper Number: 68

## Evaluating the effect of mitragynine, the main indole alkaloid of ketum in relieving abdominal pain during menstruation

*Noorul Hamizah Mat*

**Background:** Several testimonials about the effectiveness of ketum in relieving premenstrual syndrome has been reported by ketum users in the United States. The opioid-like effects of ketum is the main reason for its consumption. Therefore, the study was aimed to evaluate the analgesic effects of mitragynine, the main indole alkaloid of ketum by evaluating its effectiveness in relieving menstrual symptoms, particularly the abdominal pain in rats mimicking human symptoms and to investigate the effective dose of mitragynine in relieving abdominal pain.

**Methods:** Female Sprague Dawley rats were pretreated intraperitoneally with either mitragynine (1, 5, 10, 12.5, 15 or 30 mg/kg) or vehicle (20% Tween 80) 30 minutes prior to 2% acetic acid administration (i.p.) and the writhing behaviour was recorded for 60 minutes. Writhing was presented as contraction of abdominal muscles which was accompanied by behaviour such as pronounced stretching of the hind and fore limbs, arching of the back as well as twisting and turning the dorsoabdominal muscles after induction with acetic acid. The number of writhing frequencies were averaged every 5 minutes interval and the total percentage of inhibition was evaluated by comparing with vehicle.

**Results:** All mitragynine doses were found to significantly reduced writhing behaviour ( $p < 0.0001$ ) except for 1 mg/kg. Mitragynine (15 and 30 mg/kg) demonstrated 100% inhibition in writhing behaviour compared to vehicle ( $p < 0.0001$ ), which indicated that no pain perception was experienced by the rats.

**Conclusions:** This study suggested that mitragynine has a potential as an anti-analgesic property with 15 mg/kg is the effective dose to develop this effect. Thus, mitragynine can be potentially developed as a new pain killer for relieving menstrual symptoms.

Paper Number: 75

## Effects of mitragynine on the brain activity of Sprague-Dawley rats

*Farah Wahida Suhaimi*

Mitragynine is the principal active alkaloid isolated from the leaves of kratom (*Mitragyna speciosa* Korth) and it exhibits a wide range of pharmacological activities. This plant has been traditionally used as a self-treatment for opiate addiction and to relieve pain. Despite the extensive use, the neural effects of kratom or mitragynine remains unclear. Therefore, the present study was performed to investigate the effects of mitragynine on brain activity in chronically-treated animals for 28 days. Adult male Sprague-Dawley rats were implanted with electrodes over the frontal cortex, neocortex and hippocampus. Electroencephalogram (EEG) was recorded at day 1, 7, 14, 21 and 28, throughout the treatment's regimen. On the day of EEG recording, drug was administered after 10 minutes of baseline EEG recording. EEG activity was recorded for 60 minutes post-injection of a particular drug. Mitragynine caused dissociative patterns in EEG of both cortical tissues (frontal and neocortex) and hippocampus. Repeated exposure to equal dose of mitragynine at 10 mg/kg caused an increase in delta power and a decrease in alpha power in both frontal cortex and neocortex. On the contrary, repeated exposure to mitragynine regardless of the doses decreased the delta power but only mitragynine at 5 and 10 mg/kg decreased the alpha power in the hippocampus. In conclusion, changes in EEG reflect that mitragynine is able to challenge the local network stability that ultimately lead to alteration in brain functions.

Paper Number: 98

## Neurocognitive Profiles And Selected Thrombogenic Inhibitors (TAFI, TFPI) In Apparently Asymptomatic Individuals With Cerebra L Small Vessel Disease

*Zakiyyah Munirah Mohd Zaki, Che Mohd Nasril Che Mohd Nasir, Mazira Mohamad Ghazali, Wan Zaidah Abdullah, Nur Suhaila Idris, Muzaimi Mustapha*

Cerebral small vessel disease (CSVD) has long been used to describe a group of pathological processes with various aetiologies that affect the small perforating arteries, venules, and capillaries of the brain. White matter hyperintensities (WMH) is one of the presentations for CSVD identifiable as silent lesions and the pathomechanism remains incompletely understood. This phenomenon is postulated to be a slow but progressive significant causal factor of cognitive decline, rising a concern on vascular dementia in old age. This study aims to address the temporal relationship between neurocognitive profiles and the thrombogenic biomarkers (TAFI, TFPI) in apparently asymptomatic individuals with cerebral small vessel disease. This study involved random sampling of subject from individuals whom attended Klinik Rawatan Keluarga Hospital USM. An online-based cardiovascular risk prediction QRISK2 was used to assess the cerebrovascular risk hold by each subject. Thirty three (N=33) subjects that met the inclusion and exclusion criteria were consented and underwent brain MRI scanning and the baseline presence of WMH (Fazekas Scale). The participants also completed Wechsler Adult Intelligence Scale (WAIS-IV)(2008) neurocognitive assessment and blood sampled for TAFI/TFPI assays. The blood plasma is stored in -800C until further assessment of TAFI and TFPI by using ELISA method. These procedures except MRI scanning were repeated after 1-year time window. There was significant correlation of all continuous variables tested (age, QRISK2 score, perceptual reasoning, working memory, processing speed) except TAFI, TFPI; and there was no significant association notable either between plasma TAFI, TFPI or cognitive function with presence of WMH. In conclusion, the association of blood biomarker (TAFI, TFPI) in relation to MRI findings of WMH is not significantly associated with the cognitive decline across the subjects.

Paper Number: 99

## Uncovering the Neural Correlate of Alpha Brainwaves Signals in Receptive Auditory Quranic and non-Quranic Stimulation

*Mohd Zaki Zakiyyah Munirah*

The routine recitation of Quranic verses among Muslims, customarily in rhythmic intonation from the ways of the Prophet Muhammad, is recognised to elicit the sense of inner serenity to both the reciters and the listeners. However, the underlying neural mechanism remains unclear with limited literature on alpha brainwaves from mostly electroencephalography (EEG) studies.

This study examined the alpha brainwaves from real-time recording using synchronised magnetoencephalography and electroencephalography (MEEG) on various auditory stimuli of different Quranic recitation styles for well-known Quranic verses (Ayatul Qursi). Data of alpha brainwaves were obtained from twenty consented healthy non-Arabic speaking adult subjects (aged 21-35 years old, 10 Muslims, 10 non-Muslims). Three different styles of Ayatul Qursi recitation stimuli were used (namely Murattal Asim Tartil, Asim Tadwir and Tarannum Asli). Non-Quranic auditory stimuli were Arabic News and Arabic Poem.

The frontal alpha power for EEG and MEG data showed that there were no significant changes in the production of frontal alpha waves by comparison, for each of the stimuli for both groups. However, the comparison of mean frontal alpha power among different groups based on stimuli showed some significant changes. The frontal alpha power for EEG data showed a significant difference in group for pre-test with Muslim group; mean(SD), 0.91(0.30) compared to non-Muslim group; 1.23(0.23),  $p=0.014$ . Muslim group also showed high significant increase of alpha power than non-Muslim in frontal MEG data in Murattal Asim Tartil recitation styles; 1.96(0.29) vs. 2.23(0.20),  $p=0.026$ . For Arabic poem stimuli, Muslim group showed significant increase compared to non-Muslim group; 2.00(0.18) vs. 2.33(0.26),  $p=0.005$ . Of note, the Muslim group also showed significant difference than non-Muslim for pre-test; 2.00(0.22) vs. 2.26(0.25),  $p=0.025$ . The results of this study suggest that rhythmic Quranic recitations elicit varied frontal alpha brainwaves power for the different styles of recitation. These data may reflect the variable degree of attention attained during receptive listening of both rhythmic Quranic recitations and non-Quranic stimuli used in the study.

Paper Number: 102

## Associating Gamma Brainwave as Neural Correlate of Melodic (Qiraat) Recitation of Holy Quran

*Mohd Waqiyuddin Abdullah*

Past research on human brainwaves suggest that music and certain meditative practices could help in achieving attentive tranquillity from the alpha and theta brainwaves, respectively. However, studies on gamma brainwaves remain scarce. Gamma wave is known to actively oscillate when high mental processes taking place, that include attention. The role of gamma wave to mediate attention among Muslims when they listen and/or read the Holy Quran, typically with specified melodic recitations however, remains unknown. Hence, this study aimed to determine the frontal gamma brainwave activity in response to the receptive listening of melodic (Qiraat) recitation of Ayatul Kursi from the Holy Quran.

A total of 20 healthy normal subjects (10 Muslims and 10 non-Muslims) were consented and recruited. Seven different stimuli of three Quranic recitations and two non-Quranic stimuli were presented during brain activity recording session using 64 channel electroencephalography (EEG). The Quranic recitation styles used were Murattal Asim Tadwir, Murattal Asim Tartil and Tarannum Asli, while non-Quranic stimuli consisted of Arabic news, Arabic poem as well as pre- and post-testing (no stimulus). Gamma brainwave was recorded and transformed into frequency domain by applying Fast Fourier Transform (FFT) technique using BESA Research 6.1 software. SPSS was used for statistical analysis, in which repeated measure ANOVA was run to find the significance of gamma activity between each stimulus as well as to compare between Muslim and non-Muslim groups. Our results indicated that there was no significant difference of gamma band power between each of Quranic and non-Quranic stimuli. However when comparing between Muslim and non-Muslim groups, higher significant gamma power ( $p=0.015$ ) found in Muslim group (mean $\pm$ sd,  $1.78\pm 0.76$ ) compared to non-Muslim group ( $1.43\pm 0.29$ ) for Murattal Asim Tadwir recitation. In addition, the cumulative gamma power of Muslim ( $1.85\pm 0.55$ ) compared with non-Muslim ( $1.44\pm 0.87$ ) also appeared significant ( $p=0.003$ ). Our data suggest that prior exposure to Quranic recitation may influence a more sustained attention, thus eliciting stronger gamma wave. Different recitation styles of the Holy Quran also infer variable gamma wave response that warrant further works.

Paper Number: 103

## Pipeline Image Processing in Cerebral Small Vessel Disease (CSVD) for White Matter Integrity Determination among asymptomatic individuals

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Cerebral small vessel disease (CSVD), in its asymptomatic or silent spectrum, is often found as incidental finding from magnetic resonance imaging (MRI) brain scanning. Diffusion tensor imaging (DTI) in combination with MRI brain scanning is an emerging neuroimaging method that can identify CSVD or white matter hyperintensities. Several methods exist for this purpose, with no specific gold standard in place to optimize the use of DTI in CSVD. This study aimed to compare their reproducibility and reliability in the assessment of white matter ischemic integrity in asymptomatic CSVD by using several combinations of pipelines processing. Upon consent, 48 subjects who met the study inclusion/exclusion criteria were recruited from the Clinic of Family Medicine at Hospital USM underwent MRI brain scanning. The images of the MRI brain scanning were further analyzed using several sets of DTI pipeline processing software involving different combinations of pipelines. The software used in variable combinations included DSI Studio, MRI converter, Fiber Tracking, MedInria 2.2, MedInria 1.9, Matlab, FSL, MRTrix, TrackVIs and Free Surfer. We found few parameters that can be used to compare the reproducibility and reliability between the combination of DTI software pipelines processing such as visualization, detection of white matter hyperintensities (WMH), tractography, the finding of WMH region of interest (ROI), tract statistic, and availability of WMH atlas. Later, such data can be used to optimize and develop a specific profile for CSVD disease spectrum for each of the tested DTI software pipelines processing.

Paper Number: 104

# Correlations Between Ischaemic Cerebral White Matter Changes And The Neurocognitive Profiles In Apparently Asymptomatic Individuals

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**Background:** White matter hyperintensities (WMHs), asymptomatic lacunar infarcts, brain microbleeds (BMBs), and enlarged perivascular spaces (EPVS) have been identified as silent lesions attributable to cerebral small vessel disease (CSVD). All these markers have been individually linked to predisposition of cognitive impairment. This study aimed to examine the relationship between CSVD from incidental MRI findings and neuropsychological performance among apparently healthy individuals.

**Methods :** This was a pilot study that involved random selection of subjects' population who attended Klinik Rawatan Keluarga, Hospital Universiti Sains Malaysia. The subjects, who met the inclusion and exclusion criteria, were recruited, had their QRISK2 scores estimated for cerebro-cardiovascular risk and underwent MRI brain scanning using Philips 3-Tesla Achieva MR scanner as well as completed neuropsychological assessment using Wechsler Adult Intelligence Scale (WAIS-IV) (2008). The WAIS-IV included there index scales such as Perceptual Reasoning (PRI), Working Memory (WMI) and Processing Speed (PSI). The baseline MRI images were used to determine the presence of WMHs and scored using Fazekas scale.

**Results :** Sixty subjects, aged between 25 to 62 years old were recruited. Approximately 30% of them had family history of heart attack, 10% on hypertension treatment and 60% without comorbidity. Among the subjects, 23 (38.3%) of them have WMHs on MRI, and the rest appeared normal. Among subjects with WMHs, 39.1% (n=9) were in younger age group (25-39) and 60.9% (n=14) were in the middle-age group (40-62). Data from the neuropsychological tests were variable from among WMHs subjects, as well the case for the brain region predilections. Age ( $r=0.3, p<0.05$ ) and QRISK scores ( $r=0.4, p<0.05$ ) appeared to be correlated to the presence of WMHs. There was also a significant association between subjects with and without WMHs in the WAIS-IV PSI performance,  $t(0.07,58)=0.07, p=0.02$ .

**Conclusions :** These results suggest that in older people, CSVD may contribute to cognitive decline by affecting information processing speed and executive function. Given that presence of WMHs may also indicate an increased risk of symptomatic cerebrovascular events, thus careful interpretation is required in order to determine its clinical relevance for the individual subjects.

Paper Number: 105

## Conditioned place preference (CPP) as a behavioural platform for rodent addiction model of Ketum alkaloid (mitragynine)

*Umami Nasrah Talib*

Ketum (*Mitragyna speciosa*) is a widely increasing abused herbal drug preparation in Southeast Asia with mitragynine (MG) as the major psychoactive alkaloid of ketum plant. While MG might have been known for its analgesic, muscle relaxant and anti-inflammatory effects, but research demonstrating its rewarding properties and effects on behaviour are limited. This study focused on determining the rewarding properties of low dose (1 mg/kg – 4 mg/kg) MG on male Swiss albino mice, using conditioned place preference (CPP). Present study has successfully modified a manually functioned CPP, a valuable tool in determining the rewarding properties of abused drug. Here, we investigated the effects of 1 mg/kg to 4 mg/kg of MG treatment on reward related behavior and locomotor activity in mice using CPP, and compared them with those of morphine and  $\Delta$ -9-tetrahydrocannabinol (THC).

The result of current study revealed that 4 mg/kg ( $t = -0.219$ ,  $P = 0.034$ ) of MG has its highest potential rewarding properties compared to other doses (1 mg/kg – 3 mg/kg) (1 mg/kg:  $t = -0.472$ ,  $P = 0.06$ , 2 mg/kg:  $t = -0.511$ ,  $P = 0.165$ , 3 mg/kg:  $t = -1.044$ ,  $P = 0.218$ ) where it enhanced the time spent in drug paired compartment after conditioning and significantly induced CPP. This effect resembles more to that of morphine ( $P = 0.982$ ). Unlike 2 mg/kg to 4 mg/kg (2 mg/kg:  $t = -1.810$ ,  $P = 0.130$ , 3 mg/kg:  $t = -6.618$ ,  $P = 0.112$ , 4 mg/kg:  $t = 2.094$ ,  $P = 0.09$ ), current study found that 1 mg/kg of MG ( $t = -3.265$ ,  $P = 0.028$ ) potentiated the locomotor activity of the mice in CPP. Again, this effect resembles more to that of morphine. However, daily MG exposure incrementally from 1 mg/kg, 2 mg/kg, 3 mg/kg and 4 mg/kg for 28 days did not induce CPP suggesting that treatment of low dose MG does not expose its rewarding properties as well as not affecting the locomotor activity. These findings promote a relatively safe profile of low dose MG treatment or exposure can be extended to explain the effects on human users.

Paper Number: 113

## Coxsackievirus A16 and Enterovirus A71 infections in a one-day old mouse model show similar neuronal involvement in the brainstem and spinal cord

*Kum Thong Wong*

Background: Coxsackievirus A16 (CV-A16) and Enterovirus A71 (EV-A71) are closely-related enteroviruses that cause the same hand-foot-mouth disease (HFMD), which may be complicated by encephalitis. Nonetheless, CV-A16 appears to be far less neurovirulent in human populations than EV-A71. We conducted a comparative study in a mouse model to better understand the infectious disease pathology of these two viruses.

Methods: Groups of 1-day old mice were subcutaneously inoculated with 50  $\mu$ l of clinically isolated CV-A16 and EV-A71 (dose:  $3.56 \times 10^5$ /ml). The tissues were harvested for light microscopy, immunohistochemistry and in situ hybridization to detect viral antigens and RNA, respectively. Tissues were also obtained for viral titration. To determine the lethal doses needed to kill 50% (or LD50) of the animals, another group of mice were subcutaneously inoculated with 50  $\mu$ l of 10-fold dilutions ( $10^{-1}$  to  $10^{-6}$ ) of CV-A16 or EV-A71.

Results: All infected mice developed signs of infection including reduced mobility, limb weakness or paralysis progressing to moribund stage and death between 3-7 days post-infection. Viral antigens/ RNA were detected in neuronal bodies in the brainstem and spinal cord of both CV-A16 and EV-A71 infected mice but not in the cerebral cortex, thalamus, hypothalamus, hippocampus or other brain regions. Viral antigens/RNA were also detected in brown fat and inflamed skeletal muscles. Similarly, there were no significant differences between CV-A16 and EV-A71 titers in the blood, skeletal muscles, brown fat and brain. The LD50 doses for CV-A16 and EV-A71 were  $1.78 \times 10^4$  CCID50/ml and 46.8 CCID50/ml, respectively.

Conclusions: The histopathological and virus titration findings in our mouse model confirmed that both CV-A16 and EV-A71 are neuronotropic, and that the infectious disease pathology may be similar. This suggests that with a suitably high viral dose, CV-A16 can cause the same infection in the central nervous system as EV-A71. However, the LD50 for CV-A16 is about 380 times higher than EV-A71, suggesting that CV-A16 infection/encephalitis only occurs at a higher viral dose. Thus, CV-A16 may be less neurovirulent than EV-A71, consistent with observations in human infections.

Paper Number: 114

## Japanese encephalitis virus can infect sensory and autonomic neurons: Evidence from in vitro and in vivo studies

*Kum Thong Wong*

Background: Japanese encephalitis virus (JEV) is well known to infect neurons in the central nervous system (CNS). We investigated if peripheral sensory and autonomic neurons could likewise be susceptible to JEV infection.

Methods: Murine organotypic culture systems for dorsal root ganglia (DRG) and intestinal autonomic ganglia (IAG) were developed by harvesting the appropriate tissues from 1-day-old ICR mice. After careful dissection, the approximately 1x3mm fragments were infected with JEV/Nakayama strain (106CCID50/ml, volume 4ml/Petri dish) and incubated over a 5-day period on membranes at the air-medium interfaces with Neurobasal medium. Tissue fragments were harvested at 1, 3 and 5 days-post infection (dpi) for histopathological analysis. The in vivo experiment was done using a 2-week-old ICR mouse model, which was infected via the left hindlimb footpad with the JEV/Nakayama strain (106CCID50/ml, volume 20µl). All mice (n=6) were observed over several days, humanely euthanized near the terminal stage of infection, and tissues collected for histopathological analysis. Viral antigens and viral RNA were detected in infected tissues using specific immunohistochemistry and in situ hybridization assays, respectively.

Results: The DRG and IAG organotypic cultures were viable and were able to support viral infection. Both viral antigens and RNA were localized in neuronal bodies as early as 3 dpi and were very prominent by 5 dpi. All the mice succumbed to infection, and predominantly neuronal viral antigens/RNA were found in the DRG, peripheral sensory nerves, intestinal autonomic ganglia, brain and spinal cord.

Conclusions: Apart from the CNS neurons, sensory and autonomic neurons could be infected by JEV, suggesting that infection of peripheral neurons could potentially contribute to the pathogenesis of JE.

Paper Number: 115

## Transcriptome analysis of Japanese encephalitis virus infection of neuronal cells

*Kum Thong Wong*

Background: Japanese encephalitis (JE) is an important cause of viral encephalitis and is characterized by neuronal injury and neuroinflammation. A clear understanding of neuronal cell responses to infection remains under investigated. In this study we aim to investigate the mRNA response of neuron cells during the active phase of JE virus infection.

Method: Neuronal cells (human neuroepithelioma or SK-N-MC cells) were infected with JE virus (Nakayama prototype) at a multiplicity of infection of 10. After viral replication was confirmed, total RNA were extracted at 48 and 60 hours post infection (hpi). RNA microarray profiling using the Affymetrix Human PrimeView gene chips was performed. Upregulation or downregulation of genes were defined as fold changes that were  $\geq 2$  or  $\leq -2$ , respectively, and P-values  $< 0.05$ . Biological functions and pathways associated with these genes were analyzed using the Ingenuity Pathway analysis. A few selected upregulated genes involved in innate immunity were validated by qPCR and immunofluorescence.

Results: At 48 hpi and 60 hpi, 1051 and 1532 genes were upregulated, respectively, while 237 and 1147 genes were downregulated, respectively. Functional analysis of the expressed genes showed distinctive dysregulation in the host cell machinery, including anti-microbial responses, cell signaling, cellular functions and maintenance, cell death and survival, protein synthesis, cell cycle, etc. Analysis of highly upregulated (10 folds or more) genes showed a broad initiation of innate immunity responses with high upregulation of proinflammatory cytokines/chemokines. Upregulation of chemokines IL8, CXCL10 and CXCL11, and pattern recognition receptors RIG-1 and MDA5 were confirmed by qPCR. CXCL11 was also detected in JEV infected cells by immunofluorescence.

Conclusion: This study provides an overview of the molecular pathophysiological responses in JE, and that innate immunity response is an important part of the neuronal response to infection. CXCL11, RIG-1 and MDA5 in particular may be important in JE neuropathogenesis.

Paper Number: 117

# Cerebral small vessel disease (CSVD) in apparently asymptomatic individuals: Multimodalities longitudinal study

*Che Mohd Nasril Che Mohd Nassir*

## Background:

The prevalence of cerebral small vessel disease (CSVD) for asymptomatic ('silent') manifestation is typically obtained from incidental findings of white matter hyperintensities (WMHs) on magnetic resonance imaging (MRI). This study aimed to explore novel surrogate markers for the assessment of white matter integrity in CSVD among apparently healthy asymptomatic individuals with neuropsychological, neuroimaging and microparticles (MPs) profiling.

## Methods:

The recruited subjects with low to moderate cardiovascular risk prediction score based on QWRISK2 underwent 3T MRI brain scan (image obtained were further processed for diffusion tractography analysis), followed by neuropsychological assessment to measure their perceptual reasoning, working memory and processing speed using Weschler Adult Intelligence Scale (WAIS-IV), and 18 ml of fasting peripheral blood was collected prior to flow cytometry analysis for microparticles enumerations. Similar procedure were carried out at baseline and after one-year.

## Results:

At baseline, 48 healthy individuals were recruited (mean age:  $38.81 \pm 10.9$ ); 24 were young adults, YA (mean age  $29.7 \pm 4.33$ ) and 24 mature adults, MA (mean age:  $47.92 \pm 7.01$ ). Fifteen (29.4%) had WMHs (WMH+) detected (YA, n=5; MA, n=10). However, after one-year, 40 (mean age:  $39.35 \pm 11.31$ ) were able to participate; eight (20%) subjects were lost to follow up fourteen (35%) subjects were WMH+. Age as a whole influenced the presence of WMHs and WMH+ subject as having higher risk of CSVD. WMH+ subjects showed higher mean percentage of MPs especially platelet derived MPs (CD41a and CD62P). In term of white matter integrity, QRISK2 score increased with reduced integrity (measured by fractional anisotropy, FA) of white matter tracts of superior corona radiata (SCR) and superior longitudinal fasciculus (SLF). The integrity of white matter tracts such as left SLF and left anterior corona radiata were correlated with CD235a ( $r = -0.313$ ,  $p = 0.030$ ) and CD62P ( $r = 0.289$ ,  $p = 0.047$ ), respectively. Reduced white matter integrity (in term of reduced FA) was found to correlated with reduced neuropsychological performance among subjects especially the one with WMH+.

## Conclusion:

Although with a relatively limited small sample size and one-year follow-up period, this study had established the correlations between cardio-cerebrovascular risk prediction by QRISK, neuropsychological performance, WMHs/white matter integrity from diffusion MRI and MPs profiling as potential surrogate markers for CSVD in apparently asymptomatic individuals.