UNIVERSITI MALAYA
Faculty of Medicine

INAUGURAL LECTURE

TREATABLE MYOPATHIES

21 SEPTEMBER 2021

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BIOGRAPHY

Professor Goh Khean Jin graduated from the National University of Singapore in 1988. He continued to do his housemanship and first years as a medical officer in Singapore working at various hospitals including Singapore General Hospital and Tan Tock Seng Hospital. After training in Internal Medicine, he obtained his MRCP (UK) in 1993. He then decided to subspecialise in Neurology and was specialist registrar at the Department of Neurology, Tan Tock Seng Hospital (now part of the National Neuroscience Institute, Singapore) under the supervision of the then Head of Department, Dr Helen Tjia and Dr Tan Chai Beng, who was the senior consultant in Clinical Neurophysiology. He then returned home to join the Department of Medicine, University of Malaya (UM) as a lecturer in Neurology under Emeritus Professor Dato' Dr Tan Chong Tin at the end of 1995. He was awarded the Commonwealth Fellowship at the University Department of Clinical Neurology, University of Oxford from October 1999 to September 2000 and had the opportunity to work under the supervision of Dr Michael Donaghy, Reader in Clinical Neurology and an expert on peripheral nerve diseases and Dr Robin Kennett, consultant in Clinical Neurophysiology. In 2005, under the auspices of the Japan Society for the Promotion of Science (JSPS) he spent a month while on sabbatical at the Department of Neuromuscular Research, National Institute of Neuroscience, National Center for Neurology and Psychiatry, Tokyo, Japan where he worked with Dr Ichizo Nishino and Dr Ikuya Nonaka, both internationally well-known experts in the field of muscle disease.

Professor Goh was Head of the Department of Medicine from 2009 to 2014 and after that was Head of Division of Neurology, Department of Medicine and Head of the Neurology Laboratory, University of Malaya Medical Centre, from 2014 till the present, posts which he took over after the retirement of Professor CT Tan. The Division of Neurology is an important clinical department not just in UM but is a major tertiary neurology referral and training centre with 11 consultants who are experts in various neurology subspecialties including stroke, epilepsy, movement disorders, neuro-inflammatory diseases, neuromuscular disorders and clinical neurophysiology. The neurology laboratory provides clinical neurophysiology and neurosonology services to the UMMC.

Professor Goh has also been active in Neurology outside the University and was President of the Malaysian Society of Neuroscience (MSN) from 2002 to 2006 and President of the ASEAN Neurological Association (ASNA) from 2007 to 2011. He was the first chairperson of the Clinical Neurophysiology Section (now Clinical Neurophysiology and Neuromuscular Section) of the MSN which is affiliated to the International Federation of Clinical Neurophysiology (IFCN). He is also executive board member of the Asian and Oceania Myology Center (AOMC). As chairperson he has organised several international conferences in

Malaysia i.e. ASNA Biennial Convention, Kuala Lumpur 2009, AOMC Scientific Meetings, Penang 2007 and Kuala Lumpur 2018. He is currently Education chair for Neurology under the Malaysian Medical Council (MMC).

Professor Goh's clinical and research interests have been in the field of clinical neurophysiology and neuromuscular diseases. In that, he was privileged to work under the guidance of Prof CT Tan, who supported him in the pursuit of this subspecialty and to work with Prof Wong Kum Thong, neuropathologist at the Department of Pathology, whom among his varied research interests is muscle pathology. Prof Goh has published on all aspects of neuromuscular disease but has more recently concentrated on muscle disorders. Together with Prof Nortina Shahrizaila and Dr Tan Cheng Yin, well known consultants in neuromuscular disorders themselves, the neurology unit has a strong expertise in clinical neuromuscular diseases and clinical neurophysiology.

Professor Goh received the Excellent Service Award by UM in 2007, 2010 and 2017. As part of the Nipah Virus research team, he was co-recipient of the Mahathir Science Award (from the Academy of Science, Malaysia) in 2006 and The Merdeka Award for Health, Science and Technology in 2008. He was also awarded the 7th Royal College of Physicians, London and Academy of Medicine of Malaysia Award for Research in Malaysia in 2001 and the Malaysia Research Star Awards (MRSA) from the Ministry of Higher Education for number of citations in 2017 and 2019.

He is married to Professor Dr Ng Chiu Wan, a public health physician at the Department of Social and Preventive Medicine, UM and they have 2 children, Li Ying, a junior doctor in London, UK and Jun Xuan, a final year Integrated Design engineering student in the University of Bath, UK.

TREATABLE MYOPATHIES

Introduction

Neuromuscular disorders are a relatively uncommon and heterogeneous group of disorders involving the peripheral nervous system and consist of diseases of the anterior horn cell, peripheral nerve, neuromuscular junction and muscle. Of these, diseases of the muscle, myopathies are probably the least common compared the other neuromuscular disorders; many of which are genetic in aetiology, and often presenting in infancy or childhood. Until recently, apart from the inflammatory myopathies, it was a common misconception among general physicians that these disorders are rare and untreatable; and management is essentially supportive only.

In this lecture, I shall highlight several muscle disorders which present not in the paediatric but in the adult Malaysian population and for which specific treatments are now available.

Muscular dystrophy

Muscular dystrophies are genetic myopathies resulting in loss of proteins responsible for the integrity of muscle cell, resulting in progressive muscle weakness and degeneration. Muscular dystrophies are heterogeneous and encompass various disorders for e.g. the limb-girdle muscular dystrophies (LGMD), facioscapulohumeral dystrophy (FSHD) and the myotonic dystrophies. The commonest muscular dystrophy is Dystrophinopathy which result from mutations in the X-linked *DMD* gene with phenotypes ranging from the severe Duchenne MD (childhood onset), milder Becker MD (later onset) through an asymptomatic hyperCKemia (1). The estimated pooled prevalence of DMD and BMD was 4.78 and 1.53 per 100,000 males respectively (2).

The mainstay of treatment for DMD has been the routine use of oral corticosteroids (prednisolone at 0.75mg/kg BW) in addition to supportive management. This is usually started before significant worsening of limb weakness and has been shown to prolong ambulation and improve long-term cardiorespiratory function (3). However, in the Asian and Oceanian region, use of corticosteroids is not universal although many clinicians are aware of its benefits (4).

Emerging realistic therapies include the conversion of DMD to BMD phenotype by converting an "out-of -frame" into an "in-frame" mutation with the use of anti-sense oligonucleotides (ASO) for exon-skipping (e.g. eterplisen), inducingd read-through of a premature stop codon (ataluren) and gene replacement therapy with a virus vector (3).

Lipid Storage Myopathy

Lipid storage myopathies (LSM) result from disorders of lipid metabolism and present with progressive proximal muscle weakness, myalgia, exercise intolerance with or without metabolic crises, which can be triggered by intercurrent illness (5). Review of LSM cases in the muscle biopsy database of the Department of Pathology, University of Malaya, showed that the majority (75%) were Multiple Acyl Co-A Dehydrogenase Deficiency (MADD) (8). This was confirmed by the presence of mutations in the electron transfer dehydrogenase (ETFDH) gene leading to the dysfunction of the enzymes electron transfer flavoprotein (ETF) or ETFDH (also known as ETF-ubiquinone oxidoreductase (ETF-QO) which are mitochondrial enzymes involved in the electron transfer system in fatty acid oxidation (5). These enzymes are flavoproteins containing flavin adenine dinucleotide (FAD) prosthetic groups and supplementation with riboflavin improves muscle weakness and prevents acute exacerbations (5,7).

An initial report from Taiwan reported 4 cases (from 3 families) of MADD with a missense c.250G>A (pA84T) mutation on Chromosome 1q21.3 and this was subsequently shown to have a high allelic frequency among the Southern Chinese population in studies from China and Hong Kong (8,9). A review of the 9 Malaysian MADD patients, with a mean age of onset of 25.8 years, showed 6 (66.7%) ethnic Chinese, 2 (22.2%) Malay and 1 patient mixed Malay-Chinese. The c.250G>A (pA84T) mutation was found in 7 patients (4 homozygous and 3 heterozygous) including the 2 Malay patients (6). All except 1 patient improved with riboflavin supplementation at 100 mg/day and have remained well on follow up. The deceased patient presented acutely to another hospital and unfortunately the diagnosis was only made post-mortem (6).

Late-onset Pompe Disease (LOPD)

Pompe disease (glycogen storage disease Type II) is an autosomal recessive disease due to deficiency of the lysosomal enzyme acid-alpha-glucosidase (GAA) leading to accumulation of glycogen in the lysosomes of various organs, notably in skeletal muscles. It is generally classified according to the age of onset and the most severe form, infantile-onset Pompe Disease (IOPD), is characterised by a floppy infant with severe hypotonia and muscle weakness, hepatomegaly and cardiomegaly. Without enzyme replacement therapy (ERT), most infants die within the first year (10).

Late-onset Pompe disease (LOPD) can present after the first year of life until late adulthood with a slower and has a more varied clinical presentation and course. Most LOPD patients present with progressive proximal limb girdle muscle weakness and prominent diaphragmatic and truncal muscle weakness while cardiomyopathy is rare (10,11). Rare presentations include skeletal deformities

such as rigid spine and scoliosis as well as cardio-cerebral involvement (11,12). The prevalence of Pompe Disease (PD) ranges between 1 in 40,000 to 1 in 200,000 worldwide but has been reported to be 1 in 17,000 in the Taiwan which has carried out newborn screening for PD since 2006 (10).

Enzyme replacement therapy (ERT) for PD with algucosidase alfa (myozyme) has been shown to improve motor function, cardiomegaly and survival in IOPD and while ERT has improved motor and respiratory function and survival in LOPD (13). With the availability of ERT, active screening for LOPD in patients who present with limb-girdle muscle weakness and/or hyperCKemia has been carried out in several populations. LOPD has been reported in 1.6 to 2.4% of these patients (14). Since mid-2020 UMMC/UKMMC has begun a project to screen all patients with limb-girdle weakness/hyperCKemia and to date have found 2 (6.9%) LOPD cases of 29 screened, suggesting that LOPD may be not be uncommon in our population. Our 2 patients, both young ethnic Chinese men presenting with spinal deformities, rigid spine syndrome and scoliosis respectively, carry a mutation reported to be common in ethnic Chinese patients, c.2238G>C (p. Trp746Cys) (15,16). In addition, both also carried pseudodeficiency alleles, also common in Chinese, viz. c.1726 G>E (p. Gly576Ser) and c.2065G>A (p. Glu689Lys), a combination of which may predict a worse progression of symptoms and need for ERT (16).

Immune-mediated necrotising myopathy

Idiopathic inflammatory myopathies (IIM) are the usual group of disorders when we think of treatable myopathies. Since the Bohan and Peter criteria was introduced in 1975, which classified IIM into polymyositis (PM, no rash) and dermatomyositis (DM, associated with skin rash), numerous iterations of IIM classification have been published (17-19). Of these, the ones of most significance has been the European Neuromuscular Center (ENMC) clinic-pathological classifications of IIM and sporadic inclusion body myositis (s-IBM) and the incorporation of myositis specific antibodies (MSA) in the classification especially for DM and anti-synthetase syndrome (20). The ENMC IIM classification introduced necrotising myositis as an IIM subtype, now called immune-mediated necrotising myopathy (IMNM) and is characterised clinically by subacute severe progressive limb-girdle weakness and pathologically by multifocal myofibres necrosis which are more common than inflammatory cells (18,21). IMNM was more specifically defined with the discovery of two MSAs viz. anti-signal recognition particle (SRP) antibody and anti-3-hydroxy-3-methylglutaryl-coA reductase (HMGCR) antibody leading to the identification of 3 distinct IMNM subgroups, the third being the double seronegative group. Underlying cancer is seen in the anti HMGCR and double seronegative subgroups (21).

Using a combination of clinic-pathological and serological criteria In a Malaysian IIM cohort, IMNM makes up 29% of patients and together with DM

(23%) are most common IIM subtypes seen in our population (22). Previously, IMNM patients would have been diagnosed as PM but in fact, strictly defined PM is uncommon and in the new classification, would make up only about 7% of cases (22). In our IMNM cohort, 45.7% were anti-SRP positive, 20% anti-HMGCR positive, and 28.6% seronegative. Two (5.7%) patients had dual positivity The IMNM clinical course is typically severe progressive with incomplete response to corticosteroid treatment. Most of our patients required a combination of at least two immunosuppressive medications and at follow up, only 50% showed good recovery with minimal weakness while a third had at least moderately severe disability (21). However, they may be responsive intravenous immunoglobulin (IVIG) (23).

Hereditary Transthyretin Amyloidosis

Although not a myopathy, hereditary transthyretin amyloidosis (ATTRv) is another rare genetic neuromuscular disorder, in which ethnic Chinese-Malaysians share common mutations with other Southern Chinese populations and hence I have included in this lecture. Hereditary transthyretin amyloidosis (ATTRv) is an autosomal dominant progressive systemic disease with variable penetrance caused by mutations in the transthyretin (*TTR*) gene. These mutations result in dissociation of TTR tetramers, misfolding and aggregation of TTR monomers, and deposition of amyloid fibrils in numerous tissues, including peripheral nerves, heart and eyes (24).

ATTRv in Malaysians presents in seen predominantly in ethnic Chinese (86.7%) but there were also a Malay and Sri Lankan Tamil family in our cohort (25). ATTRv in Malaysians presents in late adulthood with progressive sensorimotor axonal polyneuropathy (with or without autonomic neuropathy) and most also had asymptomatic or mildly symptomatic cardiac involvement (25). The commonest mutation in Chinese-Malaysian patients was the Ala97Ser which is also common in Taiwanese patients (25,26). This is in contradistinction to populations with large kindreds of ATTRv viz. Portugal, Sweden and Japan where the commonest mutation is the Val30Met (24).

Treatment for ATTRv is divided into stabilisation variant TTR protein (diflunisal and tafamidis), suppression variant TTR synthesis (orthotopic liver transplantation and gene silencing with antisense oligonucleotides and small-interfering RNAs) and clearance of established tissue amyloid deposits (27). The use of Patisiran, a liposomal si-RNA has been shown to be effective in reducing TTR accumulation in tissues and has been approved for use in several countries.

Conclusions

This lecture highlights a few of neuromuscular disorders, considered rare but are seen in the adult Malaysian population. Several of these show that local Chinese

Malaysians share common mutations with other Southern Chinese populations with possibility of a founder effect. Therefore, it is important these patients be referred to a specialised neuromuscular unit for evaluation and for an accurate diagnosis be made, as there are now established and emerging therapies which clearly improve their outcome and prognosis.

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CURRICULUM VITAE

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Professional Qualifications

1988: Bachelor of Medicine and Surgery (MBBS), National University of Singapore

1993: Member of the Royal College of Physicians (MRCP, UK)

2002: Fellow of the Royal College of Physicians (Glasgow) (FRCP (Glasg)

2004: Fellow of the Academy of Medicine, Malaysia (FAMM)

Positions (post MRCP)

1993 – 1995: Specialist Registrar, Department of Neurology, Tan Tock Seng Hospital, Singapore

1995 – 1999: Lecturer, Division of Neurology, Department of Medicine, University of Malaya

(1999 – 2000: Commonwealth Fellow, University Department of Clinical Neurology, University of Oxford, United Kingdom)

1999 – 2005: Associate Professor, Division of Neurology, Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia

2005 – present: Professor, Division of Neurology, Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia

(2009-2014: Head, Department of Medicine, University of Malaya, Kuala Lumpur, Malaysia)

2014 – present: Head, Division of Neurology, Department of Medicine, University of Malaya and Neurology Laboratory, University of Malaya Medical Centre

Other positions (current)

1. Executive Board Member: Asian and Oceania Myology Centre (AOMC)
2. Chairperson: National Education Committee for Neurology Subspecialty, Malaysian Medical Council (MMC)
3. Council Member: ASEAN Neurological Association

4. Section Editor and Editorial Board Member, Neurology Asia
5. Member, World Muscle Society (WMS)
6. Member, Malaysian Society of Neurosciences (MSN)
7. Committee Member – National Neurology and Neurosurgery Drugs Subcommittee, Ministry of Health, Malaysia

Other positions (previous)

1. President – ASEAN Neurological Association (ASNA), 2007 – 2011
2. Hon. Secretary – ASEAN Neurological Association (ASNA) 2003 to 2007
3. President – Malaysian Society of Neurosciences (MSN), 2002 to 2006
4. Hon. Secretary – Malaysian Society of Neurosciences (MSN), 2000 to 2002
5. Chairperson, Clinical Neurophysiology and Neuromuscular Section, Malaysian Society of Neurosciences (MSN) – 2008 to 2017

Awards

1. 1999: Certificate of Merit for the Nipah Virus Outbreak, 1999. University of Malaya
2. 2007, 2010 and 2017: UM Excellence Service Award. University of Malaya
3. 1998, 2006 and 2012: UM Excellence Service certificate. University of Malaya
4. 2001: Royal College of Physicians, London and Academy of Medicine of Malaysia Award for Research in Malaysia
5. 2006: The Mahathir Science Award (as member of the UM Faculty of Medicine Nipah Virus Research team). Academy of Science, Malaysia
6. 2008: The Merdeka Award for Health, Science and Technology (as member of the Nipah Virus Encephalitis Investigation Team. The Merdeka Award Trust
7. 2017 and 2019: Malaysia Research Star Award (MRSA) 2017 – Citation Classic Award. Ministry of Higher Education, Malaysia

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