Oculopharyngeal Muscular Dystrophy in Singapore: Not So Rare

Dear Editor,

Oculopharyngeal muscular dystrophy (OPMD) is a late onset, inherited muscle disease, characterised by ptosis, dysphagia, variable proximal limb weakness and slow progression.[1-3] The highest reported prevalence is amongst Bukhara Jews (Israel; 1:600) and French Canadians (1:1000). Amongst East Asians, OPMD is thought to be rare.[4,5] The risk of misdiagnosis remains high, particularly when family history is not available, or symptoms are mild or isolated. Typically, diagnosis may be delayed for 3 to 20 years, with most patients undergoing extensive investigations and treatment for other suspected neurological conditions.[6,7]

There have been a few reports from China, Taiwan, Hong Kong and Japan, with a small number of genetically confirmed OPMD cases from Southeast Asia (Thailand, Malaysia).[8-14] A previous case report from Singapore (1993) described a single patient, in whom OPMD was diagnosed clinically, with no genetic confirmation.[15] Under-recognition of OPMD may be one of the causes of the assumed rarity of OPMD in East Asia. Here, we describe 4 unrelated patients from Singapore diagnosed with OPMD over the past 4 years.

Case 1: A 67-year-old Chinese gentleman presented with progressive ptosis since his 30s (Fig. 1), as well as progressive dysphagia and dysphonia for 5 years. Investigations are summarised in Table 1. Family history, which was not apparent prior to diagnosis, was notable for similar symptoms in approximately 20 family members living overseas, including his father and paternal grandfather. Mitochondrial cytopathy was initially considered, and muscle biopsy was performed (left biceps brachii muscle); needle electromyography of the contralateral biceps brachii muscle showed subpopulations of myopathic motor units. Subtle mitochondrial abnormalities were evident, with no rimmed vacuoles observed (Fig. 2). Genetic screening for OPMD showed heterozygous expansion of (GCN) in *PABPN1* (13 repeats).

Case 2: A 52-year-old Chinese gentleman presented with progressive, bilateral, asymmetrical ptosis for at least 10 years, and progressive dysphagia and dysphonia for 5 years. Ocular movements were slightly impaired bilaterally. The initial diagnosis was myasthenia gravis (MG), based on positive single fibre electromyography (SFEMG) study. He did not improve with treatment for MG. Family history was notable for diagnosis of MG (based on SFEMG alone) in his late father, who presented at age 75, with progressive ptosis and bulbar symptoms for a few years. Genetic screening for *PABPN1* gene was performed for the index patient, which showed 13 repeats.

Case 3: A 68-year-old Malay lady presented with bilateral, progressive ptosis since her 50s and mild dysphagia for 10 years. Investigations are summarised in Table 1. A similar history of ptosis and dysphagia was reported in the patient's mother and 4 siblings, with onset of symptoms in the sixth decade. No ptosis or dysphagia was reported in her children (aged 25-43 years). Genetic screening for OPMD was positive with 13 repeats.

Case 4: A 58-year-old Chinese gentleman presented with history of choking for 3 to 4 years. Mild facial and limb-girdle weakness (Medical Council Research grade 4 to 4+) was noted on examination. Initial diagnosis included MG and facioscapulohumeral muscular dystrophy. Serum creatine kinase (CK) was mildly elevated, and mild muscle membrane irritability was noted on electromyography (EMG). A detailed review was notable for mild, symmetrical ptosis (not reported by patient), and similar complaint in

Fig. 1. Top panel: Case 1- Serial photographs over 50 years showing progressive, bilateral, and symmetric ptosis. Bottom panel: Cases 2 and 3, at index presentation.

Table 1. Clinical Features, Investigations and Clinical Course of Described Cases

Variable	Case 1	Case 2	Case 3	Case 4
Age at onset of symptoms	30s	40s	68	55
Gender	Male	Male	Female	Male
Ethnicity	Chinese	Chinese	Malay	Chinese
First symptom	Ptosis	Ptosis	Ptosis	Dysphagia*
Onset to final diagnosis	≥30 years	≥10 years	≥15 years	3 – 4 years
Ptosis	Yes	Yes	Yes	Yes
Dysphagia	Yes	Yes	Yes	Yes
Limb weakness	No	No	No	Yes
Predominant symptom	Ptosis	Dysphagia and ptosis	Ptosis	Dysphagia
Suspected neurological conditions (prior to diagnosis of OPMD)	MG, Mitochondrial cytopathy	MG	MG, Mitochondrial cytopathy	FSHD, MG
Treatment for myasthenia	No	Yes	No	No
Family history of similar symptoms	Yes	Yes	Yes	Yes
Investigations				
Serum CK (IU/L; 50 – 250)	155	99	147	402
Serum lactate (fasting)	Normal	Normal	Normal	Normal
Serum anti-acetylcholine receptor antibody	Negative	Negative	Negative	Negative
Electrophysiology				
Nerve conduction study	Normal	Normal	Normal	Normal
EMG	Myopathic units in biceps	Normal	Myopathic units in frontalis	Increased insertional activity in deltoid
RNS/SFEMG	ND/ND	Negative/ positive	Negative/ND	Negative/ND
Muscle biopsy	Subtle mitochondrial abnormalities ; no rimmed vacuoles	ND	ND	ND
Genetic test *(PABPN1)*	13 repeats	13 repeats	13 repeats	ND
Other investigations prior to diagnosis	Barium swallow; CT thorax; MRI brain	video fluoroscopy, MRI orbits	MRI brain	Anti MUSK antibody, Barium swallow, video fluoroscopy
Clinical Course				
Follow-up duration	4 years	4 years	3 months	2 years
Mobility	Independent	Independent	Independent	Independent
Nasogastric tube placement	No (Modified diet)	No (Modified diet)	No	No (Modified diet)
Ocular surgery	No	No	No	No

CK: Creatine kinase; CT: Computed tomography; EMG: Electromyography; FSHD: Facioscapulohumeral dystrophy; MG: Myasthenia gravis; MRI : Magnetic resonance imaging; MUSK: Muscle-specific kinase; ND: Not done; OPMD: Oculopharyngeal muscular dystrophy; RNS: Repetitive nerve stimulation; SFEMG: Single fibre electromyography

*Ptosis not noted by patient.

patient's 2 sisters and mother. Patient declined genetic testing; however, based on the clinical evidence, final diagnosis was that of OPMD.

Discussion

We have reported 4 patients of OPMD, from 4 different families in Singapore, diagnosed over a period of 4 years. Considering that each patient reported symptomatic relatives residing in Singapore, the total number of affected individuals in Singapore is significantly higher.

OPMD is caused by an abnormal GCN expansion within the *PABPN1* gene on chromosome 14 (14q11.2-q13), with the mutated gene containing 11-17 repeats.[2,3] Mean age at diagnosis and severity of clinical symptoms correlates to the number of GCN repeats.[16] No anticipation is noted, as the expansion tends to be stable. Most cases have an autosomal dominant (AD) inheritance, and cumulative penetrance is 99% at age >69 years.[17] Autosomal recessive OPMD is rare, and tends to be later in onset (>60 years), with fewer GCN repeats (11 repeats, as compared to 12-17 repeats in AD OPMD).[18]

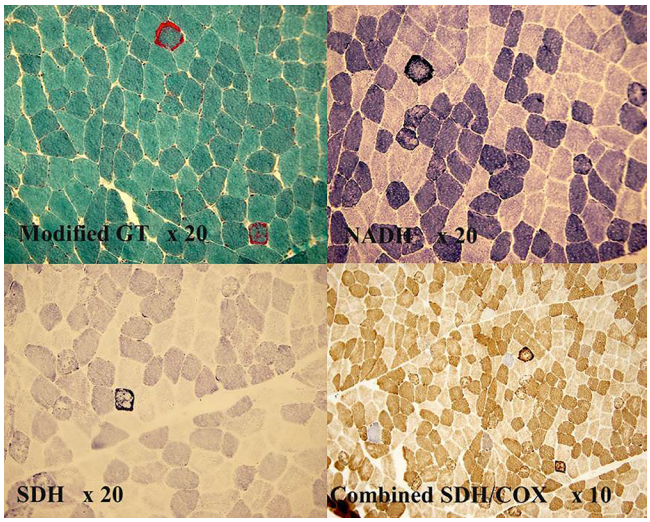

Fig. 2. Muscle biopsy (case 1); subtle mitochondrial abnormalities are noted, including (i) few ragged red fibres seen on modified GT stain, (ii) two fibres with increased subsarcolemmal densities seen on the NADH-TR and SDH stains, and (iii) few COX negative fibres. COX: Cytochrome oxidase; GT: Gomori trichrome; NADH: Nicotinamide adenine dinucleotide hydrogenase; SDH: Succinic dehydrogenase

Dysphagia precedes or is simultaneous with ptosis.[1,6,14] Proximal limb weakness tends to occur later in the course of disease, and may correlate with the size of the mutation (number of repeats). Recently, early involvement of pelvic girdle and proximal leg muscles—specifically the hip adductors and hamstrings—has been reported in a cohort of 14 Dutch patients with OPMD.[19] Extraocular muscle weakness may be noted, but complete external ophthalmoplaegia is rare. Occasional atypical or monosymptomatic presentations have been reported, especially in heterozygotes.[16,20] In this study, ptosis was the initial symptom in 3 of 4 patients, with dysphagia occuring 5 to more than 20 years thereafter. However, ptosis may initially go unnoticed by patients, as noted in Case 4. Thus, actual duration of ptosis may be much longer. Examination of serial facial photographs may be useful in such cases.

Serum CK may be elevated in patients with higher number of repeats, in homozygotes and patients with severe disease.[6,14,16] EMG examination may be normal in the early stages and in patients with only ocular and pharyngeal symptoms. In patients with limb weakness, myopathic changes and abnormal spontaneous activity may be seen. Notably, 1 of our patients had abnormal SFEMG. Increased jitter is not specific for MG, and caution must be exercised in interpretation.[21]

Common clinical misdiagnoses in OPMD include MG, mitochondrial myopathy, amyotrophic lateral sclerosis, and myotonic dystrophy. In the muscle biopsy, non-specific mitochondrial abnormalities, including large mitochondria , abnormal cristae, paracrystalline mitochondrial inclusions, on electron microscopy, are noted. Detection of filamentous intranuclear inclusions in skeletal muscle fibres (mutated *PABPN1*) by electron microscopy or immunostaining is helpful in confirming the diagnosis on biopsy.[22] Molecular genetic testing of *PABPN1* is confirmatory.

There is currently no cure for OPMD. The disease does not appear to affect life span; however, it significantly affects quality of life. Symptomatic management may include surgical procedures on the eyelids and pharyngeal muscles. Genetic counselling is a core part of management, and carrier testing may be offered to asymptomatic at-risk young adults, especially for purpose of family planning.

This study aimed to highlight that OPMD is not rare in Southeast Asia, though we acknowledge a possible tertiary centre bias. OPMD should be considered in any patient who presents with late onset, progressive ptosis, with or without dysphagia, as well as in patients who do not respond to MG treatment (Case 2); a detailed family history for similar symptoms is a useful pointer. Molecular genetic testing of *PABPN1* is recommended for suspected cases of OPMD. As shown in this study, some OPMD patients can have positive SFEMG or mitochondrial abnormalities on muscle biopsy, thus leading to wrong diagnoses. An increase in awareness of OPMD may help prevent unnecessary investigations, ineffective or potentially harmful treatment in affected individuals.

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