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The spectrum of elderly myopathies in an Asian population

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Abstract

Myopathies, although presenting more commonly in the younger age group, can occur and contribute significantly to disability in the elderly. To describe the spectrum of elderly myopathies, we reviewed 52 elderly patients (≥ 65 years) from the University of Malaya Medical Centre muscle biopsy databank, constituting 6.8% of 759 adult patients (≥ 18 years) who underwent muscle biopsy between 1992 and 2012. Commonest were the inflammatory myopathies (41/52, 78.8%), of which 43.9% had dermatomyositis; 23.9% polymyositis; 14.6% sporadic inclusion body myositis; 9.8% undifferentiated myositis and 2.4% overlap myositis. Seven patients (13.4%) had genetic myopathy; 2 muscular dystrophy and 5 chronic progressive external ophthalmoplegia, while 4 patients (7.7%) had drug-associated myopathy, 3 with statins. Malignancies were seen in 9.8% of inflammatory myopathies at diagnosis. Both acquired and genetic myopathies are seen in elderly Malaysians of all ethnicities and should not be misdiagnosed as some are potentially treatable and/or associated with malignancy.

INTRODUCTION

Myopathies encompass all age groups, although they commonly present in childhood, adolescence and young adulthood.[1,2] The process of aging results in gradual loss of muscle mass, quality and strength, a condition termed as sarcopaenia.[3] By the 65 years of age, about a third of muscle strength would have been lost.[4] Therefore, muscle diseases occurring in the geriatric population compound an already ongoing process of neuromuscular degeneration resulting in significant disability to the patient. It is therefore important to have an awareness and understanding of the types of myopathies seen in the older patients so as not to miss the diagnosis especially of those conditions which are amenable to therapy.

The spectrum of elderly myopathies has rarely been reported. Two reports, both from Caucasian populations, showed that acquired inflammatory myopathies were commonest while toxic and genetically determined myopathies were also seen.[5,6] Based on WHO estimates, the proportion of elderly in Asia will increase from 414 million (10%) in 2010 to 1.2 billion (24%) in 2050 with a likely corresponding increase in the occurrence of diseases of the elderly.[7] As with other diseases, myopathies will therefore be increasingly more common in this population group.

Malaysia, with an ethnically diverse population consisting of Malays and other indigenous races (67.4%), Chinese (24.6%), Indians (7.3%) and other races (0.7%), provides a unique opportunity to study disease prevalence in an Asian setting.[8] The aim of this study was to look at the spectrum of myopathies in Malaysian patients aged 65 years and above. We report their clinical presentations, histopathological findings and any differences in terms of age, gender and ethnicity.

METHODS

Clinical and histopathological data of patients, aged 65 years and above, from the University of Malaya Medical Centre (UMMC), Kuala Lumpur muscle biopsy databank were reviewed. The databank contains all patients who underwent muscle biopsy as a part of the investigation of their suspected neuromuscular disease (either in UMMC or done elsewhere and then referred for histopathological diagnosis) between 1992 and 2011. The UMMC being a major tertiary neurology centre in Malaysia receives the majority of muscle biopsy referrals from Kuala Lumpur as well as other parts of the country.

All patients gave their informed consent for muscle biopsy and muscle histopathological findings were investigated using standard

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histology and histochemistry as well as specialised immunohistochemical staining if required and reported by a trained muscle pathologist. Patients whose clinical findings and muscle pathology were consistent with myopathy were included while those whose biopsies suggested neurogenic and other disorders were excluded. Patients' medical records were then reviewed for clinical history (including family history), history of associated medical disorders (including connective tissue disorders and malignancies) and medications, and physical examination findings as well as laboratory investigations such as serum creatine kinase (CK) levels and electromyography (EMG) results carried out at the time of muscle biopsy.

Diagnosis of inflammatory myopathy was based on the traditional Bohan and Peter criteria with elements adapted from other published clinical and histopathological diagnostic criteria.[9-12] Inflammatory myopathy was classified into the various subtypes viz. polymyositis, dermatomyositis, sporadic inclusion body myositis (s-IBM) and overlap myositis. Specifically, as muscle immunohistochemistry for inflammatory cells was not carried out in all patients, inflammatory myopathy diagnosis required, in addition, perifascicular atrophy for dermatomyositis and rimmed vacuoles with or without COX-negative fibres for s-IBM. In cases of non-specific biopsy findings, patients were classified as clinical dermatomyositis if they had the typical skin rash and clinical s-IBM if they had slowly progressive weakness and wasting of quadriceps and forearm flexor muscles. Otherwise, they were classified as undifferentiated inflammatory myopathy. Overlap myositis was diagnosed if there was an associated connective tissue disease.

As molecular genetic tests for genetically determined myopathies were not readily available for some of the suspected myopathies, their diagnosis was based on characteristic clinical features, exclusion of other possible differential diagnosis and their muscle biopsy findings. Diagnosis of limb-girdle muscular dystrophy was based on clinical findings, with or without a positive family history, and dystrophic changes on histopathology, while diagnosis of chronic progressive external ophthalmoplegia (CPEO), a mitochondrial myopathy, was based on the presence of typical clinical features, exclusion of other conditions such as myasthenia gravis and oculopharyngeal muscular dystrophy (OPMD), and/or the presence of ragged-red fibres and reduced cytochrome oxidase (COX) staining in muscle fibres. Drug-associated myopathy was diagnosed in patients in whom the use of the drug was temporally related to the onset of myopathy.

Statistical analysis was carried out using SPSS version 20. Descriptive statistics and univariate analyses were carried out to compare differences between gender and ethnicities.

RESULTS

Between 1992 and 2011, there were a total of 1588 muscle biopsies reported at UMMC. Of the 759 biopsies from patients aged 18 years and above, 67 (8.2%) were from patients aged 65 years or older at the time of biopsy. Fifteen biopsies were diagnosed as non-myopathic and were excluded. The remaining 52 elderly myopathy patients constituted 6.8% of the adult patients who underwent muscle biopsy. Of these, 29 (55.8%) were women. Their mean age at the time of myopathy diagnosis was 70 years (range from 65 - 79 years). The majority of our patients, 31 (59.6%), were ethnic Chinese, followed by 11 Indians (21.2%), 9 Malays (17.3%) and 1 Kadazan (1.9%). The main presenting clinical features included proximal limb weakness in 44 patients (84.6%), myalgia in 12 (23.1%), skin rash in 8 (15.4%), ptosis and ophthalmoparesis in 5 (9.6%), dysphagia in 5 (9.6%) and respiratory insufficiency in 1 (1.9%), (Table 1). Serum CK level was available in 34 patients and raised in 27 (79.4%).

The types of myopathies seen in our elderly patients were as follows – inflammatory myopathy, genetic myopathy and drug-associated myopathy. Of these, inflammatory myopathy was the commonest diagnosis, seen in 41 patients (78.8%), followed by genetic myopathy in 7(13.4%) and drug-associated myopathy in 4 patients (7.7%). Of the 41 patients with inflammatory myopathy, there were 18 dermatomyositis (43.9%), 12 polymyositis (29.3%), 6 s-IBM (14.6%), 4 undifferentiated inflammatory myopathy (9.8%) and 1 overlap myositis (2.4%), with the last patient having associated systemic lupus erythematosus and scleroderma. Five of the 18 dermatomyositis and 2 of the 6 s-IBM patients did not have the typical muscle histopathology and were diagnosed on clinical grounds.

Among the 7 patients with genetic myopathy, 2 were diagnosed as having muscular dystrophy - 1 with facioscapulohumeral dystrophy (FSHD) based on typical clinical features and a positive autosomal dominant family history and the other

Table 1: Demographic features and symptoms of elderly myopathies (age ≥ 65 years) in Malaysians

	Patients with myopathy aged ≥ 65 years, n=52
Mean age at diagnosis	70 years (range 65-79)
Female	29 (55.8%)
Ethnic group	
• Chinese	• 31 (59.6%)
• Indian	• 11 (21.2%)
• Malay	• 9 (17.3%)
• Kadazan	• 1 (1.9%)
Symptoms	
• Proximal limb weakness	• 44 (84.6%)
• Muscle pain	• 12 (23.1%)
• Skin rash	• 8 (15.4%)
• Ptosis/ophthalmoparesis	• 5 (9.6%)
• Dysphagia	• 5 (9.6%)
• Respiratory insufficiency	• 1 (1.9%)
Elevated creatine kinase level	27/34 (79.4%)
Associated malignancy	4 of 41 inflammatory myopathy patients (9.8%)

being a limb-girdle muscular dystrophy type 1 (LGMD1) based on an autosomal dominant family history, limb-girdle pattern of involvement and muscle histopathological findings of dystrophy. Surprisingly, they were the oldest at the time of diagnosis (mean age, 76.5 years) but had the earliest age of onset of symptoms, one at 10 years and the other at 30 years. The other 5 patients were diagnosed as having CPEO and had a slightly younger age of diagnosis (mean 69.6 years, range 65-82). The time interval from onset of symptoms to diagnosis for other forms of myopathy was much shorter with 80% of the patients being diagnosed within a few months to a year after the onset. This was not significantly influenced by sex, ethnicity or clinical presentation.

Of the 4 patients with drug-associated myopathy, 3 had statin-associated myopathy (with a history of simvastatin use) while another patient had a history of corticosteroid use. Two patients with statin myopathy presented with muscle pain and weakness while the other had progressive muscle weakness and necrotizing features on muscle histopathology.

In elderly myopathy patients, while there was a slight overall female preponderance (female to male ratio = 1.3:1), this was primarily observed in patients with dermatomyositis which had a female to male ratio of 3.5:1 and to a lesser extent in polymyositis (female to male =1.4:1). On the other hand, gender distributions were equal in s-IBM (female to male = 1:1) and there was a male preponderance in the undifferentiated inflammatory myopathy patients (female to male = 1:3) as well as in the non-inflammatory myopathies (female to male = 1:2.7).

Malignancy was present in 4 (9.8%) of patients with inflammatory myopathy at the time of diagnosis, of whom 2 had dermatomyositis (2/18, 11.1%) and the other 2 had undifferentiated inflammatory myopathy (2/4, 50%). Two patients had lung carcinoma while 1 of the other 2 had nasopharyngeal and the other had laryngeal carcinoma. Unfortunately, we were unable to follow up all our patients to determine any subsequent malignancies.

DISCUSSION

Inflammatory myopathy was the commonest group of myopathies seen in elderly Malaysian patients. This is unsurprising as inflammatory myopathy was also the commonest diagnosis in the previous series of elderly myopathies from France and the US respectively although its proportion in our patients was higher at 79% (5,6). In a cohort of adult polymyositis and dermatomyositis patients from Singapore, the mean age at diagnosis was 50.3 years with a range of 19.2 to 83.1 years.[13] Our commonest subtype of inflammatory myopathy was dermatomyositis (43.9%) followed by polymyositis (29.3%) while the proportion of s-IBM was lower at 14.6%. This differs from the Caucasian population in which s-IBM appears to

be the commonest form of inflammatory myopathy in the elderly.[14,15] The lower proportion of s-IBM in our cohort was unlikely to be due to undiagnosed cases from non-specific muscle pathology as we had included cases of clinical s-IBM in whom muscle pathology was not diagnostic. Our findings are consistent with the impression that the incidence of s-IBM in Asian and other non-Caucasian populations is low.[16] The cause for the difference between ethnic groups is unknown. However, a recent study from Japan reported a gradually increasing incidence of s-IBM, in which the authors speculated that this could be due to changes in dietary habits and an increase in the western lifestyle.[17] If true, this would well be seen in other developing Asian countries, including Malaysia in the near future. The frequency of malignancy preceding diagnosis of 9.8% of our elderly patients with inflammatory myopathy was probably an underestimate as more patients were likely to develop cancer subsequently. Frequencies of malignancies in other Asian studies not specifically looking at older patients were 10.5% and 12.6% (Taiwan), and 22.7% and 22% (Singapore)[13,18-20] which is similar to or double our reported frequency respectively. However, it is likely that our cohort would have shown a greater proportion of malignancies subsequently, possibly greater than that in younger patients. The series of elderly myopathy patients from France reported a higher frequency with nine of 25 elderly inflammatory myopathy patients (36%) with malignancies.[5]

The late diagnosis of genetic myopathies reflects the relatively slow progression of some of these conditions. Our patients with FSHD and LGMD type 1 had developed symptoms when young but presented at an older age. In part, this is not unusual in Malaysia (and likely in other developing Asian countries) where trust in modern medicine is still lacking and many patients with chronic diseases seek help from traditional healers instead. The lower proportion of genetic myopathy compared to inflammatory myopathy may be because a number of these patients in the population are not brought to medical attention.

In our 5 CPEO patients, the mean age at diagnosis was 69.6 years. This late presentation is not unusual and late-onset mitochondrial myopathy with a mean age of presentation of 67.1 years has been previously reported.[21] In another study from Finland which 2 of their 10 CPEO patients were 67 and 86 years of age respectively at the time of examination while in another series of late-onset CPEO patients from Canada, the age ranged between 27 and 74 years.[22,23] Interestingly, in the latter study, the symptom duration prior to diagnosis varied from 1 to 50 years (mean 11.6 years). Other causes of ptosis and ophthalmoplegia such as myasthenia gravis and OPMD were clinically excluded in our patients, the latter in view of the absence of any prominent pharyngeal involvement.[24] A relationship between the use of statins and ptosis/ophthalmoparesis has been suggested and this could be a consideration in older patients, many of whom would be on the medication.[25] However, none of our CPEO patients were on statins.

The 3 patients (5.8%) with statin-associated myopathy had elevated CK and necrotizing myopathy, 2 of whom had significant muscle pain while the third had progressive limb muscle weakness while on statins. Despite its widespread use, the frequency of statin myopathy does not appear to be high. The series of elderly myopathies from France reported only 1 patient (2%), while a recent review of the literature yielded only 4 articles reporting 63 cases of necrotizing myopathy and 14 articles with 24 cases of inflammatory myopathy which were thought to be associated with statins.[5,26] These patients were mostly middle-aged and elderly.[26]

Although the majority of our elderly myopathy patients were ethnic Chinese Malaysians, this is likely to reflect the predominance of Chinese in urban areas such as Kuala Lumpur. The numbers of patients were too few to demonstrate any ethnic differences in the spectrum of myopathies, if any. The main limitations in the study were the lack of confirmatory molecular genetic diagnosis in suspected genetic myopathy patients and the classification of some inflammatory myopathy patients based on clinical features despite non-confirmatory muscle pathology. However, the inclusion of these patients was based on their probable diagnosis, because it was felt that this would give a better representation of the spectrum of our elderly myopathies.

In conclusion, elderly myopathies consist of 6.8% of patients undergoing muscle biopsy. They were predominantly acquired inflammatory myopathies but there were also genetic myopathies, especially CPEO, which could present at the geriatric age group and drug-associated myopathies. While muscle weakness may occur as a part of aging, this study demonstrates that myopathies do occur significantly in elderly patients and should not be missed. This is especially important in inflammatory myopathies as they may be treatable and associated with malignancy.

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