CASE REPORT

Oculopharyngeal muscular dystrophy: underdiagnosed disease in Hong Kong

CME

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Despite the advances in the understanding of the molecular basis for oculopharyngeal muscular dystrophy in the last decade, it remains an underdiagnosed disease, especially among the Chinese. In the presence of a positive family history and late-onset ptosis, dysphagia, and proximal muscle weakness (its cardinal features), we suggest that *PABPN1* gene analysis should be the first-line investigation to rule out this condition. Muscle biopsy can be reserved for atypical cases. Non-specific mitochondrial changes in the muscle specimens of these patients should be appreciated, so as to avoid diagnostic confusion. It is hoped that greater awareness among medical professionals and judicious use of *PABPN1* gene analysis will lead to earlier diagnosis, better management, and avoidance of unnecessary invasive investigations of affected patients.

Introduction

Oculopharyngeal muscular dystrophy (OPMD) is a late-onset progressive muscle disease characterised by a number of cardinal features, namely ptosis, dysphagia, and proximal muscle weakness. It was first described in a French-Canadian family by Taylor in 1915,[1] and the term OPMD was first used by Victor et al in 1962.[2] Since then, OPMD has been reported among different ethnicities; the highest prevalence being in Bukhara Jews (1:600)[3] and French-Canadians (1:1000).[4] It has rarely been encountered in Chinese populations, with only few case reports in the literature. Herein we report on two OPMD Hong Kong Chinese patients with molecular confirmation. Both were initially suspected to have mitochondrial disease. The molecular genetics and diagnostic pitfalls of muscle biopsy in OPMD should be appreciated.

Case reports

Case 1

A 57-year-old Chinese man was referred to the Clinical Genetic Service (CGS) for suspected mitochondrial disease in March 2010. He enjoyed good past health until he was 50 years old, when he developed bilateral ptosis and dysphagia. The symptoms were so mild that he could cope with his daily activities. Apart from ptosis, there were no other visual symptoms. He could tolerate solid food but choked easily when swallowing liquids. He had had nasal speech for years but denied other neurological complaints and there was no diurnal variation in his symptoms. His family history was significant, in that his mother and younger brother also had similar ptosis and dysphagia since the age of 50 years, but had never undergone formal medical assessment.

On examination, he had bilateral ptosis (Fig 1a) and dysphonia. There was no facial weakness, external ophthalmoplegia, or pigmentary retinopathy. Proximal muscle weakness (MRC grade 4/5) and mild winging of scapula (Fig 1b) were noted. No fatigability or myotonia was demonstrated. The rest of the neurological examination and other systems were normal.

Neuroimaging and upper endoscopy yielded nil abnormal. Videofluoroscopic swallow study showed mild aspiration for thin liquids, but normal tolerance of solid food. His plasma creatine kinase and lactate levels were mildly elevated to 380 U/L (reference level, <190 U/L) and 4.2 mmol/L (reference level, <2.2 mmol/L), respectively. Serum anti-acetylcholine receptor (anti-AChR) antibody and electromyopathy yielded no abnormality. Results of routine biochemistry, haematology, urinalysis, and determination of autoimmune markers were unremarkable.

Muscle biopsy was then performed (Fig 2). Light microscopic examination with histological stains and enzyme histochemistry showed only mild non-specific changes.

Key words
Hong Kong; Muscular dystrophy, oculopharyngeal; Neural conduction; Poly(A)-binding protein 1

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Specific abnormalities like ragged red fibres, intrasarcoplasmic and nuclear inclusions, and rimmed vacuoles were not demonstrated. Electron microscopy (EM) showed small aggregates of mitochondria; some of which had structural abnormalities suggestive of mitochondrial disease. These mitochondria were almost entirely filled and stretched lengthwise by the long rectangular paracrystalline inclusions.

Case 2

A 56-year-old Chinese man was referred from a neurologist to the CGS, also for suspected mitochondrial disease in September 2009. He had good past health till he was 45 years old, when he developed bilateral ptosis and dysphagia. The symptoms were slowly progressive and did not affect his daily function. He denied other neurological complaints, and there was no diurnal variation of symptoms. Systematic review of other systems yielded nil abnormal. Initial investigations showed normal plasma lactate, creatine kinase levels, and serum anti-AChR antibody levels. Neurophysiological studies were uninformative. Neuroimaging and upper endoscopy showed no pathology. However, his family history was positive; his younger brother and mother also have had similar symptoms (dysphagia and ptosis since the age of 50 years) though without a definitive diagnosis.

Physical examination showed bilateral ptosis and dysarthria. There was no facial weakness or ophthalmoplegia. Fundal examination was normal. Proximal muscle weakness (MRC grade 4+/5) of the upper limbs was noted. The distal muscles of the upper and lower limbs were normal. There was no fatigability or myotonia. The rest of neurological examination and other systems were normal. Light microscopic examination of a muscle biopsy specimen was normal, but EM study showed swollen mitochondria with paracrystalline inclusions suggestive of mitochondrial disease.

眼咽型肌營養不良症：香港一種被忽略的疾病

過去十年，在分子生物學上的進步令我們認識眼咽型肌營養不良症（OPMD）。可惜的是此症在醫學界中，尤其是在華籍人口中仍然被忽略。我們建議有陽性家族史、遲發性眼瞼下垂、吞嚥困難和近端肌肉無力等徵狀的病人接受*PABPN1*基因測試以排除OPMD，而在非典型病例才進行肌肉活檢。同時要注意OPMD的肌肉活檢會有非特異性的粒線體病變，以避免診斷混亂。我們希望本病例報告能提高醫護人員對OPMD的警覺性及明智使用*PABPN1*基因測試，使患者得到及時診斷和醫治，以及避免不必要的侵入性檢查。

Overview

Despite the non-specific mitochondrial changes in the muscle biopsies of the above two patients, the constellation of late-onset ptosis, dysphagia, and proximal muscle weakness together with a positive family history led to the suspicion of autosomally

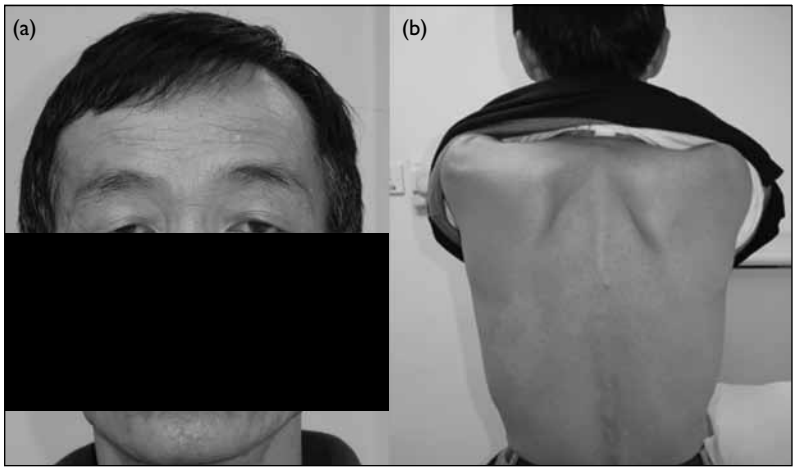

FIG 1. Clinical photos for patient 1
(a) Forehead wrinkling and bilateral ptosis
(b) Mild proximal upper limb wasting and scapular winging

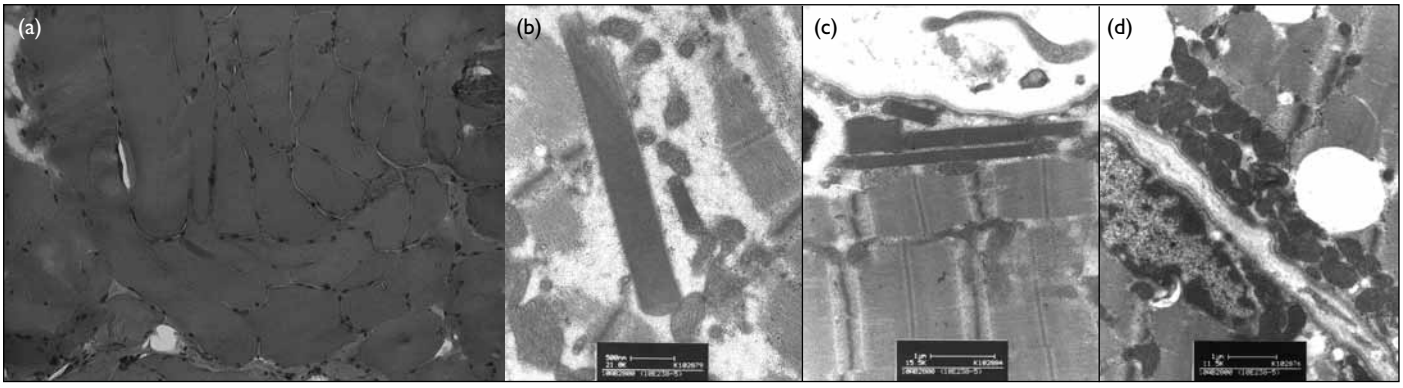

FIG 2. Histology and electron microscopy of the muscle biopsy
(a) Non-specific slight variation of fibre size and few angulated atrophic fibres (H&E stain, x 20), (b) and (c) illustrate rectangular paracrystalline inclusions in the mitochondria spanning almost their entire length and width, and (d) a slight increase of mitochondria in subsarcolemmal aggregates

dominant OPMD. Therefore, *PABPN1* gene analyses were performed. A heterozygous c.21_22ins $(GCG)_4$ insertion mutation and a heterozygous c.24_25ins$(GCG)_3$(GCA) insertion mutation in exon 1 of the *PABPN1* gene were detected in patients 1 and 2, respectively. Both mutations resulted in abnormal expansion of a polyalanine tract from the normal 10 alanine residues to 14. Thus, the diagnosis of autosomal dominant OPMD was confirmed in both cases.

Discussion

There are two allelic forms of OPMD: autosomal dominant (OMIM#164300) and rarely autosomal recessive (OMIM#257950). Both are caused by triplet repeat expansions of a $(GCN)_{10}$ tract or rarely a point mutation[5,6] in the first exon of the polyadenylate-binding protein nuclear 1 (*PABPN1*) gene located at chromosome 14q11.2. The expansions result in lengthening of the N-terminal polyalanine domain in the protein product. The *PABPN1* gene normally contains $(GCG)_6$ repeats followed by $(GCA)_3(GCG)$ in the first exon. The stretch is translated into 10 consecutive alanine residues. Regarding the autosomal recessive type, the polyalanine tract is expanded to 11 alanine residues; whereas in autosomal dominant type, the expanded polyalanine tract consists of 12 to 17 alanine residues. The $(GCN)_{11}$ recessive mutation is also a reported polymorphism, with a prevalence of 1 to 2% in Caucasian and Japanese populations. Two mechanisms have been proposed for the triplet repeat expansions, namely unequal crossover and slippage during recombinations.[5,7] However, there is still no experimental evidence that fully supports either mechanism.

The understanding of the molecular basis of OPMD has progressed significantly in the last decade, although the pathogenesis has not been established. The PABPN1 protein is an essential polyadenylation factor for the extension of poly(A) tails of all eukaryotic mRNAs, which is shuttled between the cytoplasm and nucleus.[8] It was hypothesised the polyalanine expansion leads to toxic gain-of-function that results in protein misfolding and aggregation,[9] thus causing dysfunction of the PABPN1 protein. However, others dispute this hypothesis.[10]

In the pre-molecular era, the diagnosis of OPMD was based on the following three clinical criteria[11]: (1) a positive family history with involvement of two or more generations; (2) presence of ptosis (defined as either vertical separation of at least one palpebral fissure that measures <8 mm at rest), or previous corrective surgery for ptosis; and (3) presence of dysphagia (defined as swallowing time of longer than 7 seconds when drinking 80 mL of ice-cold water).

However, with the availability of a highly specific and sensitive molecular test, *PABPN1* gene testing is now recommended as the first-line investigation for all clinically suspected OPMD. Muscle biopsy is only indicated for atypical cases. The pathognomonic histological changes for OPMD are tubulofilamentous intranuclear inclusions,[12] but these are only present in 3 to 6% of cases for which special attention is necessary during EM study. Abnormal mitochondrial changes like paracrystalline inclusions are well-known secondary non-specific phenomena in OPMD[13] that can cause confusion, like our cases.

Although OPMD is a disease due to triplet repeat expansions, the mutations are mitotically and meiotically stable. Therefore, the genetic phenomenon of anticipation does not occur. The age of onset, however, is variable among patients with the same mutation. In the OPMD cohort of French-Canadian autosomal dominant $(GCN)_{13}$ carriers, the decade-specific penetrances are 99% (>69 years old), 63% (60-69 years old), 31% (50-59 years old), 6% (40-49 years old), and 1% (<40 years old).[14]

Concerning genotype-phenotype correlations, no study has demonstrated a statistically significant relationship between the size of (GCN) expansions and disease severity. However, clinical observation suggests that gene dosage has a definite influence on the age of onset and the clinical severity,[5] as the most severe phenotypes occurred in individuals who were homozygous for the (GCN) expansion. These individuals usually develop symptoms before the age of 45 years, and become wheelchair bound before reaching the age of 60 years. In the cohort of French-Canadian $(GCN)_{13}$ carriers, 5 to 10% had the severe phenotype,[15] of whom 20% had the compound heterozygous form of the $(GCN)_{13}$-dominant mutation and the $(GCN)_{11}$-recessive mutation/polymorphism of the *PABPN1* gene.[5] However, the cause of increased severity among the remaining 80% of affected persons is still unknown.

Genetic counselling for autosomal dominant OPMD is straightforward; the recurrence risk in offspring is 50%. Presymptomatic counselling and predictive testing can be provided to other at-risk family members. As OPMD is a late-onset disease causing relatively mild physical impairment, prenatal genetic testing has never been requested.

Currently, there is no available curative treatment for OPMD. Prevention of fatal aspiration is the paramount target. All measures are supportive with an emphasis on oromotor dysphagia, nutritional support, and eyelid ptosis. Ptosis surgery should be performed when there is impairment of vision or neck pain due to constant retroflexion. In selected OPMD patients, cricopharyngeal myotomy, dilation by bougies, or even botulinum toxin might be useful for dysphagic symptom.

Conclusions

With better understanding of the molecular genetics and supportive measures, the quality of life for OPMD patients has been significantly improved over last decade. However, it is still an underdiagnosed disease entity among the Chinese. We suggest that for patients with positive family history and cardinal clinical features of OPMD, *PABPN1* gene testing should be the first-line investigation. Muscle biopsy should be reserved only for atypical cases. One should be aware of non-specific mitochondrial changes in the muscle specimen of OPMD patients, so as to avoid diagnostic confusion.

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