Oculopharyngodistal Myopathy in a Thai Family

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There has been controversy whether oculopharyngodistal myopathy (OPDM) commonly seen in Japan is a distinct disease entity or a variant of oculopharyngeal muscular dystrophy (OPMD) initially described in French-Canadians and has since been reported in other ethnic groups. Both diseases have autosomal dominant inheritance and OPDM patients are clinically similar to OPMD with slowly progressive ptosis, ophthalmoplegia and dysphagia except that most of the former usually have distal as opposed to proximal weakness and most of them are genetically different from the latter. The authors report here 2 siblings with clinical features of OPDM. This entity is rare outside Japan and this is the first family to be reported from Thailand.

Keywords : *Oculopharyngodistal myopathy, Thai family*

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When a patient with slowly progressive ptosis and ophthalmoplegia is encountered, certain diseases come to mind. The relatively more common disorder is chronic progressive external ophthalmoplegia (CPEO), a mitochondrial disorder which is usually presented as a sporadic case and can be definitely diagnosed by mitochondrial DNA analysis. Hereditary CPEO is rare, being transmitted as autosomal dominance and is associated with nuclear DNA mutation[1-3]. If the patient also has dysphagia in addition to fixed ptosis and ophthalmoplegia, differential diagnosis would include oculopharyngeal muscular dystrophy (OPMD) and oculopharyngodistal myopathy (OPDM). Typically, both disorders are hereditary and the mode of transmission is autosomal dominance. However, they may be differentiated clinically by the distribution of limb weakness in that the weakness is more often proximal in OPMD and more often distal in OPDM. OPMD can be genetically diagnosed by the presence of short GCG expansions in the polyadenylate binding protein nuclear 1 gene (*PABPN1*) of chromosome 14q11.2-q13 in OPMD but not OPDM[4-7]. On the other hand, OPDM is a rare entity and most cases have been seen in and reported from Japan with no definite genetic defect being identified as yet. The authors report here 2 Thai patients who are siblings and presented with slowly progressive ptosis, ophthalmoplegia, mild dysphagia and distal wasting clinically consistent with OPDM.

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Case Report

Patient 1 (P1), a 43-year-old man and Patient 2 (P2), a 35-year-old man, brother of P1, presented with bilateral slowly progressive ptosis beginning at the age of 35 and 33 respectively. This was gradually followed by abnormal voice, slight difficulty in swallowing and wasting of muscles of forearms and hands bilaterally. Their parents are not related. According to the patients, there were no other members of the family affected. On examination, there were nasal voice, bilateral ptosis, limitation of extraocular muscle function in all directions, weakness of orbicularis oculi, wasting of masseter and temporalis muscles, wasting and weakness of forearm muscles and intrinsic

muscles of the hands (Fig. 1, 2). All of the signs were more severe in P1. There was also wasting and weakness of tibialis anterior muscles in P1. The deep tendon reflexes (DTR) were all absent and the sensation was normal. Edrophonium chloride (Tensilon) test was negative in both patients. Physical examination of their father, aged 88, revealed slight wasting and weakness of intrinsic muscles of both hands with normal DTR and sensation. Their mother, aged 73, had wasting and weakness of forearm muscles and intrinsic muscles of both hands with normal reflexes. She also admitted to having distal numbness with mild glove and stocking pin prick sensory loss. Both parents had no ptosis or ophthalmoplegia. Their mother's sister, aged 69, had bilateral ptosis and also slight wasting and weakness of forearm muscles and intrinsic muscles of both hands with normal DTR and sensation. No other members of the family were affected.

The serum creatinine kinase of P1 and P2 were 1868 and 169 U/L respectively (N 0-169). Other serum biochemical tests including glucose were normal in both patients and their mother and aunt. Electrocardiogram was normal. Repetitive nerve stimulation test showed normal response. Nerve conduction study was consistent with mild sensorimotor axonal polyneuropathy in both patients and their mother. EMG showed increased short to normal duration small amplitude polyphasic units with normal interference pattern compatible with myopathic change in deltoid and vastus lateralis in both patients In addition, there were fibrillation potentials and positive sharp waves with increased short to normal duration small amplitude polyphasic units consistent with mixed myopathic and neurogenic pattern in tibialis anterior in P1. Mitochondrial DNA study showed no deletion and was negative for base substitution at position 3243, 8344, 8356 and 8993. Muscle biopsy from the left quadriceps of both patients showed only a few atrophic muscle fibers with all the enzymes of the respiratory chain including cytochrome oxidase (COX) being present. No ragged-red fibers were detected. Rimmed vacuoles were observed in a few muscle fibers with a frequency of 5% in P1 and 1% in P2. Electron microscopy revealed electron dense whorls of membranes.The mitochondria were normal. No intranuclear nor cytoplasmic filaments were demonstrated. Molecular genetic analysis was performed with DNA extracted from the blood undergoing polymerase chain reaction by the method of Brais'[5]. The amplified fragments were loaded onto polyacrylamide gel examined with a fluorescent image scanner and also sequenced. Result of the analysis showed that the number of GCG repeats in the *PABPN1* gene was normal in both patients and their mother and aunt.

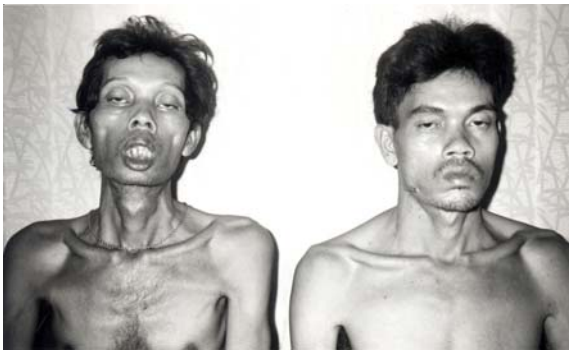

Fig. 1 Photograph of P1 (left) and P2 (right). Note the unique feature of the face with marked ptosis and wasting of the temporalis and masseter muscles in P1. The signs are less severe in P2

Fig. 2 Photograph of the arms and hands of P1. Note wasting of the forearm muscles and intrinsic muscles of the hands

Discussion

Clinically, these two patients looked very much like oculopharyngodistal myopathy (OPDM) in view of the distal wasting and weakness. However, there have been several reports of patients with typical oculopharyngeal muscular dystrophy (OPMD) with distal involvement[7-9]. Therefore, it is rather difficult to differentiate OPDM from OPMD by the phenotype and there has been controversy about the entity of these two disorders. The clinical presentation of this family is more like that of OPDM. Most clinical features are similar to OPMD except that the distal muscles were more severely affected. Both disorders are dominantly inherited and characterized by late-onset progressive ptosis and dysphagia although autosomal recessive and sporadic cases have been reported in

OPDM[6,7]. It is interesting that in this Thai family, the patients' mother and aunt had only distal muscle wasting with mild ptosis in the latter. The mode of inheritance is considered to be autosomal dominant with variable expression in the mother and aunt. Minami et al studied 5 patients with clinically typical OPDM but one of them had GCG trinucleotide expansion in the *PABPN1* (previously called polyadenylate binding protein 2, *PABP2*) gene. They thought that OPDM is genetically heterogeneous and most cases are distinct from OPMD[7]. The present study of a Thai family confirms that OPDM is genetically distinct from OPMD even though they may be clinically similar to OPMD patients except for distal muscle involvement. Minami et al also studied the entire coding sequence and the exon-intron boundaries of this gene but no mutation was found.

Another interesting finding is the mild sensorimotor axonal polyneuropathy which has been less well recognized. Neuropathic findings have been reported in a case series of OPMD with a review of the literature by Hardiman et al[10]. However, some of their cases were not typical of OPMD clinically and they were before the time of molecular genetic analysis to confirm the diagnosis. On the other hand, this issue has seldom been associated with OPDM. Nevertheless, it is noteworthy that this may be another aspect that these two disorders have in common. It seems likely that either of them is not a single nosological entity and that these two disorders are genetically linked. Further study is needed to elucidate the molecular genetic etiology of OPDM.

OPMD was initially reported in French-Canadians and has subsequently been reported in other ethnic groups including Japan, Taiwan and Malaysia. This has also been confirmed in a family in Thailand (Taweechue K et al, personal communication). On the other hand, OPDM is common in Japan and, to our knowledge, has never been reported from elsewhere. This is the first family to be reported from Thailand.

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โรค Oculopharyngodistal myopathy ในครอบครัวผู้ป่วยไทย

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Oculopharyngodistal myopathy (OPDM) เป็นโรคซึ่งพบบ่อยในประเทศญี่ปุ่น ยังเป็นที่ถกเถียงกันว่าโรคนี้เป็นโรคเดียวกับ oculopharyngeal muscular dystrophy (OPMD) ซึ่งรายงานครั้งแรกในคนแคนาดาที่มีเชื้อสายฝรั่งเศสและต่อมาก็พบในคนกลุ่มอื่น ๆ ด้วย หรือว่าเป็นคนละโรคกัน ทั้งสองโรคเป็นโรคซึ่งถ่ายทอดทางพันธุกรรมแบบ autosomal dominant และมีลักษณะทางคลินิกคล้ายคลึงกันมาก คือมีหนังตาตกซึ่งเป็นมากขึ้นเรื่อย ๆ กลอกตาไม่ได้และกลืนลำบาก ผิดกันตรงที่ OPMD มีกล้ามเนื้อแขนขาส่วนโคนลีบและอ่อนแรง ส่วน OPDM เป็นกล้ามเนื้อส่วนปลายที่ลีบและอ่อนแรงและผู้ป่วยส่วนใหญ่มีความผิดปกติทางพันธุกรรมที่แตกต่างจาก OPMD ผู้ป่วย OPDM พบน้อยนอกประเทศญี่ปุ่น ผู้ป่วยสองรายนี้นับเป็นการรายงาน OPDM ครอบครัวแรกในประเทศไทย