A South African family with oculopharyngeal muscular dystrophy: Clinical and molecular genetic characteristics

C M Schutte, C M Dorfling, R van Coller, E M Honey, E J van Rensburg

Clara Schutte is Head of the Department of Neurology in the Faculty of Health Sciences, University of Pretoria, South Africa. She has a special interest in genetic neurological conditions. Lizette van Rensburg, Associate Professor of Human Genetics in the Department of Genetics, Faculty of Health Sciences, University of Pretoria, has been involved in molecular genetic research for the past 20 years, with a special interest in genetic susceptibility to cancer. Celmari Dorfling is a Research Officer in Lizette van Rensburg’s Cancer Genetics Research Group. Riaan van Coller is a neurologist in private practice who is affiliated to the Department of Neurology at the University of Pretoria, and Engela Honey, a paediatrician with a special interest in human genetics, has been working in the Department of Genetics for the past 15 years.

Corresponding authors: clinical data – C M Schutte (cschutte@medic.up.ac.za); genetic data – E J van Rensburg (lizette.janssenvanrensburg@up.ac.za)


Oculopharyngeal muscular dystrophy (OPMD) (OMIM #164300) is a late-onset (>45 years) myopathy characterised by progressive ptosis, dysphagia and varying degrees of proximal muscle weakness. The ptosis is mostly restricted to the levator palpebrae and later involves other extraocular muscles. Complete external ophthalmoplegia is rare. The dysphagia is initially for solids only, but steadily progresses to an extent that patients may become malnourished. In later life these patients may suffer from bouts of aspiration pneumonia. Although proximal muscle weakness, facial weakness and dysarthria may occur, smooth and cardiac muscles appear to be spared. Pathologically, intranuclear inclusions are observed in the muscle fibres.\[1\]

Early descriptions of families with ptosis and dysphagia drew attention to the hereditary basis of the disorder, and after the 1962 publication by Victor et al.\[2\] the condition was recognised as a form of muscular dystrophy and given the name OPMD. The condition is mainly inherited in an autosomal dominant manner, although uncommon recessive forms have been described.\[3\]

OPMD has been recognised as a trinucleotide repeat expansion disorder.\[4\] The PABN1 gene, also known as PABP2, encoding the polyadenylate binding protein nuclear 1 (PABPN1) gene on chromosome 14q, is involved in the pathogenesis of OPMD. The PABPN1 protein is a nuclear protein that is involved in the polyadenylation of messenger RNA.\[5\] It associates with RNA polymerase II during transcription and facilitates movement of the released transcript through the nuclear pore, thus acting as a molecular chaperone for the proper export of poly(A) RNA from the nucleus.\[6\] Additionally, PABN1 was found to bind to SKIP (ski-interacting protein), and together they directly control the expression of muscle-specific genes. Following on from this, Apponi et al.\[7\] demonstrated that the normal protein plays an important role in myoblast proliferation and differentiation, whereas the extended polyalanine tract causes clumping or the PABN1 protein and accumulation in the nuclei of the skeletal muscle fibres.\[8\]

Recently Davies and Rubinstein\[9\] reported that apoptosis is directly involved in the pathology of OPMD, and that it is a major contributor to the muscle dysfunction in the disease.

The incidence of OPMD varies widely, ranging from 1/200 000 in France to 1/600 in Israel (Bukhara Jewish population). The disease has been described in more than 35 countries worldwide, with some variations in clinical presentation.

To our knowledge, this is the first South African (SA) OPMD family to be described. We report on the clinical and molecular genetic characteristics of this family.

The proband was a 64-year-old woman who presented with ptosis, progressive dysphagia and some proximal weakness to the neurology outpatient department at Steve Biko Academic Hospital in Pretoria, SA. With the assistance of the patient, a family pedigree was drawn up and contact details of as many family members as possible were obtained. All were then contacted and invited to take part in this study. After informed consent had been obtained,
four individuals were subsequently interviewed and examined clinically, and had electromyographic (EMG) studies performed. In addition, blood samples were taken from three individuals. Genomic DNA was extracted from peripheral blood using standard protocols. Exon 1 of PABN1, containing the region where the GCN repeat is located, was amplified using primers previously described\cite{9} with the Failsafe PCR Enzyme mix with buffer J (Epicentre Biotechnologies, USA). Cycle sequencing of the amplicons was performed with BigDyeV3.1 (Applied Biosystems, USA) and analysed on an ABI 3130 (Applied Biosystems).

The study was approved by the Ethics Committee of the Faculty of Health Sciences, University of Pretoria.

**Family pedigree**

An abbreviated pedigree of this Afrikaner family is depicted in Fig. 1. The index patient (III:17) was one of a sibship of 18, eight of whom are affected with OPMD. Their mother (II:2) was affected from the age of approximately 40 years. Noteworthy is the offspring of III:2, an unaffected daughter, who happened to marry her maternal cousin (III:3) who had OPMD. Their children (IV:1 and IV:2) inherited the disorder from their father.

**Patient III:17**

This 64-year-old woman reported that her first symptoms of ptosis had started at the age of about 40 years, but really interfered with her vision only 10 years later, when she needed eyelid surgery to correct the ptosis. Dysphagia was also present from age 40 years and progressed slowly up to a point where she now has to be very selective about the food she eats. On examination, she had normal higher functions (Mini Mental State Examination (MMSE) 27/30). She had dysarthria with somewhat nasal speech and dysphagia. She had a clearly myopathic ptosis, more marked on the left. There was weakness of the soft palate and tongue, and her speech was hoarse and dysarthric. Mild proximal and distal weakness was present, but this was difficult to interpret owing to her weak general condition. Findings on EMG conduction studies of the median and ulnar motor and sensory nerves were normal. Myopathic units were found in the deltoid muscle, and needle examination of the tongue revealed normal insertional activity and normal motor unit potentials.

The findings on repetitive stimulation studies of the accessory nerve were also normal. The patient underwent insertion of a gastrostomy tube to facilitate feeding.

**Patient III:9**

This woman was 75 years old when examined. Her data were retrieved retrospectively from her neurologist’s patient record files because she lived far away. She had severe dysphagia and had lost 15 kg over the past few months. On examination, she had almost total external ophthalmoplegia and ptosis, more marked on the left. There was weakness of the soft palate and tongue, and her speech was hoarse and dysarthric. Mild proximal and distal weakness was present. On EMG conduction studies of the median and ulnar motor and sensory nerves were normal. Myopathic units were found in the deltoid muscle, and needle examination of the tongue revealed normal insertional activity and normal motor unit potentials.

The findings on repetitive stimulation studies of the accessory nerve were also normal. The patient underwent insertion of a gastrostomy tube to facilitate feeding.

**Patient III:14**

As with III:17, this 70-year-old woman’s ptosis had started at approximately 40 years of age. She had experienced the first symptoms of dysphagia at around 50 years, after which it progressively worsened. Eyelid repair surgery had been performed twice in the past 20 years. On examination, higher mental functions were normal (MMSE 28/30), but the patient had marked dysarthria with prominent nasal speech and lip weakness; the eye movements were full except for some mild restriction of lateral gaze to both sides. There was asymmetry on elevation of the soft palate and severe dysphagia. She had a clearly myopathic face with weakness of the frontalis, levator palpebrae superioris and orbicularis oculi muscles and severe weakness of the upper lip levators and levator anguli oris. Limb weakness was very mild: the deltoids, pectorals, biceps, triceps and hip flexors and extensors were grade 4+/5 and, interestingly,
foot dorsiflexion and finger extension was also weak at grade 4/5. The deep tendon reflexes of the upper limbs were only present as a flicker with augmentation manoeuvres, the patella reflex was 2+/4, and the ankle reflexes were absent. The findings on sensory examination were normal. The patient also had high-arched feet.

EMG showed normal responses of the peroneal, tibial and radial motor nerves, the medial and lateral plantar responses showed low amplitudes, and the sural responses were normal. The PASPs were present and the response to repetitive stimulation of the ulnar nerve was normal. A needle examination of the left deltoid muscle showed some small myopathic units but no fibrillation potentials.

**Patient III:18**

Consistent with her sisters, this 63-year-old woman had noted ptosis at the age of 40 years and started complaining of dysphagia approximately 10 years later. She had had eyelid repair operations at least 15 years previously, and had also had oesophageal sphincter botulinum toxin injections and myotomy for severe dysphagia at the age of 56. She did not complain of limb muscle weakness. However, she noted that she had felt tired after bypass surgery following a myocardial infarction 2 months prior to her visit to neurology. On examination, her higher mental functions were normal (MMSE 30/30). She had very mild limitation of upward and lateral gaze, and a mild dysarthria was noticeable. Orbicularis oculi muscle power was slightly decreased and mild ptosis was present. Power of the latissimus dorsi and hip extensors was mildly reduced (4+/5), deep tendon reflexes in the upper limbs were a flicker with augmentation, the patella reflex was 2+/4, and the ankle reflexes were absent bilaterally. Findings on sensory examination and the co-ordination and gait were normal.

On EMG, the peroneal, tibial and radial motor responses as well as the response to repetitive stimulation of the ulnar nerve were normal, and PASPs were present. The amplitude of the medial and lateral plantar responses was somewhat decreased, but conduction velocities were normal. The amplitude of the sural response was also slightly decreased at point A. A needle examination showed normal muscle unit potentials in the deltoid muscle.

**Molecular analysis**

As shown in Fig. 2, cycle sequencing of exon 1 of the **PABPN1** gene of the three patients (III:14, III:17 and III:18) from whom blood samples were available revealed that they were heterozygous for a (GCG)$_n$(GCA)$_m$GCG or (GCN)$_m$ mutation. This expansion therefore increases the total number of alanine residues (GCNs) from the normal ten to 15.

**Discussion**

We describe the first SA Afrikaner family with genetically proven OPMD. The Afrikaners are mainly descended from Dutch, German and some French immigrants to the Cape during the 17th century. It is estimated that the founding Afrikaner population consisted of approximately 90 families by 1687. We therefore expected to find that our family would share a mutation with one of these founding populations. Many individuals with OPMD from North America and Europe carry a mutant (GCG)$_n$ or (GCN)$_m$ allele.[7] Studies from the UK showed an equal distribution of (GCG)$_n$ and (GCN)$_m$ (or (GCN)$_m$) and (GCG)$_n$) mutations.[8] and in Hispanic New Mexicans, the (GCG)$_n$ mutation was also commonly identified.[9]

Additionally, all patients had dysarthria, which ranged from very mild to moderate. Dysarthria is a finding that has been reported in patients with OPMD, but is rarely emphasised. A study by Young and Durant-Jones[10] evaluated voice intensity, resonance and pitch range in five patients with OPMD, showing changes in voice, articulation and resonance in all individuals, which was worse in those older than 70 years. Hyper-nasality, as a finding of the dysarthria, was reported in three of their patients. Of our four patients, the older two, at 70 and 75 years, also had the worst dysarthria. Mild proximal weakness, often described in OPMD, was noted in all our patients and neck flexion weakness in two. Interestingly, two of our patients also showed mild weakness of the tibialis anterior muscles, and one of the older patients also had clear weakness of finger extension, uncommonly seen in OPMD. The high foot arches in two patients and the absent ankle reflexes raised the clinical possibility of a peripheral neuropathy.

On electrophysiological studies, clear myopathic units were seen in two of our patients, and findings on all motor nerve conduction studies were normal. Low amplitudes of the medial and lateral plantar responses were noted in the three patients in whom these were tested, but the abnormalities were mild; in two, the amplitudes of the sural nerve responses were also minimally reduced. Involvement of the peripheral nerves in OPMD has been debated in the past decade. Finsterer[11] concluded in a recent editorial that involvement of peripheral nerves in OPMD should be evaluated further by studying only patients with genetically confirmed OPMD, since many of the patients with electrophysiological abnormalities were reported in the pre-genetic era. The significance of our electrophysiological findings is unclear; motor nerves and autonomic responses were not involved electrophysiologically, and if anything the lower amplitudes of the plantar responses may indicate a mild sensory neuropathy. However, all our patients were older than 60 years, age perhaps influencing the amplitude of sensory nerve responses, although the medial plantar responses should not be absent before the age of 70 years.

**Conclusion**

In conclusion, we have described the clinical and genetic features of the first SA family with OPMD.
**Author contributions.** CMS initiated the project, interviewed the patients, examined them and wrote up the clinical part of the paper; CMD and EJvR did the genetic analysis and wrote the genetic part of the article; and EMH and RvC helped with the clinical management of patients and reviewing of the manuscript.


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