

## SHORT REPORT

## Autosomal recessive oculopharyngodistal myopathy: a distinct phenotypical, histological, and genetic entity

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*J Neurol Neurosurg Psychiatry* 2004;75:1499–1501. doi: 10.1136/jnnp.2003.025072

We present a 25 year follow up of two siblings with autosomal recessive (AR) oculopharyngodistal myopathy. Remarkable in these patients, in comparison with patients with oculopharyngeal muscular dystrophy (OPMD), are the earlier age of onset, severe facial weakness, external ophthalmoplegia early in the course of the disease, and distal weakness in the limbs. Histological features included basophilic-rimmed vacuoles, but the typical OPMD intranuclear filaments were absent. These clinical and histological characteristics are comparable with those of two Japanese patients with AR oculopharyngodistal myopathy. This myopathy has usually been described as an autosomal dominant (AD) muscle disorder. It shares some clinical and histological characteristics with OPMD, but most patients with AD oculopharyngodistal myopathy are genetically different. Here we exclude an expansion of the GCG repeat or any other mutation in the coding region of the *PABPN1* gene (responsible for OPMD) in patients with AR oculopharyngodistal myopathy. From this we conclude that AR oculopharyngodistal myopathy is a distinct phenotypical, histological, and genetic entity.

Oculopharyngodistal myopathy was first described as an autosomal dominant (AD) muscle disorder with onset in late adulthood, characterised by ptosis as initial symptom followed by slowly progressive dysphagia and muscle weakness in the hands and lower legs.<sup>1</sup> Autosomal recessive (AR) inheritance of oculopharyngodistal myopathy has only been reported once in two Japanese brothers.<sup>2</sup>

Oculopharyngodistal myopathy shares some clinical and histological characteristics with oculopharyngeal muscular dystrophy (OPMD).<sup>3</sup> The clinical features of OPMD include late onset, slowly progressive bilateral ptosis, dysphagia, and limb girdle weakness. Histologically, there are unique intranuclear inclusions in the skeletal muscle fibres. Muscle biopsies show basophilic-rimmed vacuoles in the sarcoplasm, and other non-specific dystrophic alterations. OPMD is genetically characterised by a mutation in the polyadenylate binding protein nuclear 1 (*PABPN1*) gene. The first exon of the *PABPN1* gene normally contains a (GCG)<sub>6</sub> trinucleotide repeat, which is expanded to 7–13 triplets in patients with OPMD. The mode of inheritance is AD in most families, but AR cases have been documented.<sup>4,5</sup>

Two siblings with oculopharyngodistal myopathy with presumably AR inheritance were followed for 25 years in our neuromuscular centre allowing us to study its natural history. Here we describe the phenotypical, histological, and genetic features of AR oculopharyngodistal myopathy and compare these with the features of AD oculopharyngodistal myopathy and OPMD.

## PATIENTS

The brother and sister described below are part of a kindred of four of non-consanguineous Dutch parents. No other individuals in the family are known to be affected.

During the follow up of both patients standardised neurological examination, blood analysis, electromyography (EMG), and muscle biopsies were performed at regular intervals. *PABPN1* mutation screening was performed on DNA from peripheral blood lymphocytes.

## Patient 1

This patient, a woman, came to our clinic at the age of 27.<sup>6</sup> Her medical history was unremarkable. At the age of 25 she began walking on her toes and had tired legs, followed by loss of strength in her arms, drooping of the upper eyelids and difficulty swallowing. Later, she developed difficulties in pronunciation.

On examination at the age of 27 she had a myopathic face and bilateral ptosis (fig 1A). The eye movements were limited in all directions. The optic fundi were normal. She had symmetrical atrophy of intrinsic hand muscles and distal leg muscles. Muscle weakness was noticed in the dorsiflexors of her feet and toes (Medical Research Council (MRC) 4/5). The muscle strength of her arms and proximally in the legs was normal. She had bilateral contractures of the Achilles' tendon. Sensation and coordination were normal. Deep tendon reflexes were absent.

Laboratory measurements revealed normal levels of serum glucose, pyruvate, and lactate but creatine kinase (CK) was raised (629 U/l; normal for women <170 U/l). EMG revealed normal nerve conduction velocities. Needle examination of several muscles revealed myopathic characteristics and poor pattern on maximum voluntary contraction. The results of the muscle biopsies are summarised in table 1.

At the age of 37 she reported loss of strength in her legs and arms, which was more pronounced in her legs than in her arms. The drooping of upper eyelids was more severe and she had increasing problems with speaking and swallowing. She needed to use her hand to keep her mouth closed.

At the age of 46, she used a rolling walker indoors, but needed a wheelchair outside. On examination we found facial diplegia with bilateral ptosis and complete ophthalmoplegia (fig 1B). She had dysarthria with nasal speech. The muscle strength of the arms was MRC 4/5 both proximally and distally; that of the legs was MRC 3/5 proximally and MRC 2/5 distally. Sensation was still normal. Serum CK level was 332 U/l. An EMG showed myopathic characteristics and electrically silent areas. An electrocardiogram (ECG) was normal. Investigation of respiratory function revealed normal volumes, decreased inspiratory flow (58% of inspiratory vital

**Abbreviations:** AD, autosomal dominant; AR, autosomal recessive; MRC, Medical Research Council; OPMD, oculopharyngeal muscular dystrophy; *PABPN1*, polyadenylate binding protein nuclear 1



**Figure 1** Patient 1: (A) at the age of 27 (reprinted from Jaspard HH *et al.* Oculopharyngodistal myopathy with early onset of neurogenic features. *Clinical Neurology and Neurosurgery*, 1977;80:272–82, © 1977, with permission from Elsevier Science<sup>6</sup>) and (B) at the age of 46.

capacity instead of 91%) and decreased respiratory mouth pressures.

No mutations were found in the open reading frame of the *PABPN1* gene. The GCG repeat, splice donor and acceptor sites were normal.

### Patient 2

This patient, a man, came to our clinic at the age of 28. He complained of tired upper eyelids for about 10 years. He had bilateral ptosis, a myopathic face, and external ophthalmoparesis. The optic fundi were normal. There was loss of muscle strength distally in the legs (MRC 4+/5) but it was normal in the arms and proximally in the legs. Sensation and coordination were normal, and deep tendon reflexes were absent. His serum CK level was 1000 U/l (normal in men <200 U/l). The EMG was identical to that of patient 1.

At the age of 40, bilateral ptosis, external ophthalmoplegia, and facial diplegia were observed. He had dysarthria with nasal speech. There was muscle weakness and atrophy of the legs, more pronounced distally (MRC 3/5) than proximally (MRC 4–/5); this was less severe in the arms. Sensation was normal. His serum CK level was 742 U/l and an ECG was normal. As in patient 1, no mutations were found in the *PABPN1* gene.

At the age of 55 he was hospitalised because of severe pneumonia. He had a myopathic face, bilateral ptosis,

**Table 1** Histological characteristics of the muscle biopsies of both patients

	Patient 1		Patient 2	
	Biopsy 1 (27 years)	Biopsy 2 (46 years)	Biopsy 1 (28 years)	Biopsy 2 (39 years)
Light microscopy				
Type I fibres, NV = 35–50%	53%	40%	29%	17%
Type II fibres, NV = 50–65%	47%	60%	71%	83%
Abnormal variation in fibre size	++	+++	+++	+++
Rimmed vacuoles	+	–	+	++
Ragged red fibres	–	–	–	–
Signs of inflammation	–	–	–	+
Intrafascicular fat	+	+++	+	+
Internal nuclei, N = 0–3%	0%	50%	3%	47%
Fibre splitting	–	++	–	–
Atrophic fibres with pyknotic nuclear clumps	–	++	+	+
Checkerboard pattern	NV	NV	NV	NV
Electron microscopy				
Myelin figures	+	–	+	+
Thick filaments (14–18 nm)	+	–	+	+
Intranuclear inclusions	–	–	–	–

+, ++, +++: present, moderate, increased; –: absent. NV, normal value.

complete external ophthalmoplegia, and severe dysarthria. He had hypotonic paralysis of both legs and paresis of both arms, MRC 2 proximally and MRC 1 distally. Sensation was still normal. Some days later, he died from respiratory insufficiency.

### DISCUSSION

The 25 year follow up of these two Dutch siblings enabled us to define the natural history, and the histological and genetic features of AR oculopharyngodistal myopathy, and to compare these with the features of AD oculopharyngodistal myopathy and OPMD. We found important differences between the clinical presentation of our patients and that of patients with OPMD. First, the onset of disease was earlier (15–20 years) with the initial symptom being bilateral weakness of the tibialis anterior muscles or bilateral ptosis. Secondly, the pattern of muscle involvement was different. Remarkable in our patients were the severe facial weakness and the weakness of the external ocular muscles, which caused ptosis and limited the eye movements—these were more severe and occurred earlier compared with patients with OPMD. The muscle weakness in the extremities began distally in the legs instead of proximally and extended to the hands, and later to the proximal leg and arm muscles. Twenty five years after the first symptom, both patients became wheelchair dependent. Involvement of the pharyngeal muscles and gradual progression of disease were comparable with OPMD.

Muscle biopsies revealed basophilic-rimmed vacuoles in the sarcoplasm as described in OPMD, whereas on electron microscopy the typical OPMD intranuclear filaments were not seen. The genetic investigation excluded the OPMD mutation and any other mutation in the *PABPN1* gene affecting the open reading frame or the splice sites.

The phenotype and histological findings of our patients are comparable with those described by Uyama *et al.*,<sup>2</sup> including early onset, severe weakness of facial muscles, severe ophthalmoplegia, and weakness of the muscles of the extremities. Muscle biopsies of the Japanese patients had revealed basophilic-rimmed vacuoles in the sarcoplasm, and absence of intranuclear inclusions typical of OPMD on

electron microscopy. A mutation in the *PABPN1* gene was not excluded. Similar to the Japanese patients, our patients showed earlier onset of symptoms and more severe weakness, especially in facial muscles, but the distribution of muscle weakness was comparable with patients with AD oculopharyngodistal myopathy.<sup>1,7</sup> Likewise, Brais *et al* have reported more severe OPMD phenotypes including early onset of symptoms and more severe ophthalmoplegia caused by homozygosity for the (GCG)<sub>7</sub> allele, compound heterozygosity for the (GCG)<sub>9</sub> mutation, and (GCG)<sub>7</sub> polymorphism, and homozygosity for the (GCG)<sub>9</sub> mutation. Homozygosity for the (GCG)<sub>7</sub> allele leads to the AR form of OPMD.<sup>4,5</sup> Thus, similar to OPMD, oculopharyngodistal myopathy seems to have two modes of inheritance: AD and AR. Although we cannot formally exclude germ line mosaicism for AD oculopharyngodistal myopathy in one of the parents of our patients, the early onset and severity of symptoms suggest an AR inheritance.

In contrast with OPMD, oculopharyngodistal myopathy has not been characterised genetically. Schober *et al* described a family with AD oculopharyngodistal myopathy and an expansion of GCG repeat to 13.<sup>8</sup> Minami *et al* examined patients with clinically AD oculopharyngodistal myopathy for OPMD mutation.<sup>9</sup> Only one patient had an OPMD associated GCG expansion to 13, suggesting genetic heterogeneity for AD oculopharyngodistal myopathy. We excluded GCG repeat expansion in the first exon of *PABPN1* gene in our patients with AR oculopharyngodistal myopathy.

This is the second publication on AR oculopharyngodistal myopathy. We have shown that AR oculopharyngodistal myopathy is more severe than the AD variant. The pattern of muscle involvement and histological characteristics of both variants are comparable. Patients with AR oculopharyngodistal myopathy and AR OPMD have similar age at onset and severity of weakness, but different patterns of muscle involvement and different histological and genetic features. Therefore, AR oculopharyngodistal myopathy is a distinct phenotypic, histological, and genetic entity.

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Competing interests: none declared

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Received 1 August 2003

In revised form 5 December 2003

Accepted 23 December 2003

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