

## Oculopharyngeal Muscular Dystrophy Case Report

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### Abstract

**Background:** Oculopharyngeal muscular dystrophy (OPMD) is an aptly named disease characterized by ptosis and swallowing difficulties with possible subsequent involvement of proximal skeletal muscles. Diagnosis is based on history and clinical exam and confirmed with genetic testing, with muscle biopsy being reserved for negative DNA results.

**Case Summary:** A 59 year old right-handed woman presented for evaluation of weakness in bilateral lower extremities as well as difficulty swallowing. The patient states that she started with her symptoms in the last 6 months, when she noticed she had difficulty walking and maintaining balance, especially on uneven surfaces. She does complain of difficulty swallowing and right eye drooping more than left, both have been progressive over many years. She denies any shortness of breath, history of stroke or any sensory symptoms. Her mother has recently been diagnosed with confirmed oculopharyngeal muscular dystrophy. Therefore, she wanted to get established in the neuromuscular clinic for further evaluation.

On physical exam, cognitive exam was normal. Right eye ptosis greater than left was noted. No facial wasting noted. Strength exam was noted to be equal and normal throughout with exception of bilateral hip flexors at 4+. Sensation and reflexes were preserved. On EMG, myopathic units were observed. In her workup prior to presentation, her PCP had ordered a myasthenia gravis panel and MRI which were negative. Her PABPN1 testing came back consistent with OPMD and the diagnosis was given to the patient.

**Conclusion:** Oculopharyngeal muscular dystrophy (OPMD) is an aptly named disease characterized by ptosis and swallowing difficulties with possible subsequent involvement of other proximal skeletal muscles. It is primarily autosomal dominant involving PABPN1 GCN trinucleotide repeats with rare instances of recessive genotypes. Diagnosis is based on history and clinical exam and confirmed with genetic testing, with muscle biopsy being reserved for negative DNA results. Symptom management is the crux of treatment and often involves blepharoplasty and/or cricopharyngeal myotomy.

**Keywords:** Oculopharyngeal muscular dystrophy; OPMD; Case report

### Introduction

Oculopharyngeal muscular dystrophy (OPMD) is a rare autosomal dominant myopathic disorder that is characterized by ptosis, dysphagia, and proximal muscle weakness with an onset in the 5th-6th decade<sup>[1]</sup>. It has been shown that OPMD is frequently under diagnosed, resulting in the failure to provide proper advice on planning and preparation and perhaps slowing disease progression<sup>[2,3]</sup>. Here we present a case of a patient diagnosed with OPMD who presented with bilateral lower ex-

tremity weakness with a longstanding history of eyelid drooping and difficulty swallowing. This case highlights the importance of recognizing oculopharyngeal muscular dystrophy, a unique subtype of muscular dystrophy, as well as the underlying genetics. We aim to increase awareness of this rare disease with hopes of earlier diagnoses leading to better management.



## Case Description

### Patient Information

A 59 year old right-handed woman presented for evaluation of weakness in bilateral lower extremities as well as difficulty swallowing. The patient states that she started with her symptoms in the last 6 months, when she noticed she had difficulty walking and maintaining balance, especially on uneven surfaces. She does complain of difficulty swallowing and right eye drooping more than left, both have been progressive over many years. She denies any shortness of breath, history of stroke or any sensory symptoms. Her mother has recently been diagnosed with confirmed oculopharyngeal muscular dystrophy. Therefore, she wanted to get established in the neuromuscular clinic for further evaluation.

### Physical Exam

On physical exam, cognitive exam was normal. Right eye ptosis greater than left was noted. No facial wasting not-

ed. Strength exam was noted to be equal and normal throughout with exception of bilateral hip flexors at 4+. Sensation and reflexes were preserved.

### Diagnostic and Assessment

On EMG, myopathic units were observed. In her work-up prior to presentation, her PCP had ordered a myasthenia gravis panel and MRI which were negative. Modified barium swallow testing was performed and confirmed mild to moderate pharyngeal dysphagia. Given the EMG and physical exam findings consistent with OPMD, genetic testing was obtained. Her PABPN1 testing came back consistent with OPMD and the diagnosis was given to the patient. She was referred to speech therapy who recommended a diet consisting of moist, soft solids with thin liquids, taking single bites and sips, and alternating solids with sips of liquid.

Muscle	Insert Activity	Spontaneous Activity				Voluntary Activity				Max Vol Activity
	Insert	Fibs	+Waves	Fasc's	Other	Amp	Dur	Recruit	Polys	Activation
Tibialis anterior.R	Normal	None	None	None	None	Decr 1+	Decr 1+	Incr 1+	None	Max.
Gastrocnemius (Medial head).R	Normal	None	None	None	None	Normal	Normal	Normal	None	Max.
Vastus medialis.R	Normal	None	None	None	None	Decr 1+	Decr 1+	Incr 1+	None	Max.
Iliopsoas.R	Normal	None	None	None	None	Normal	Normal	Normal	None	Max.
Gluteus medius.R	Normal	None	None	None	None	Decr 1+	Decr 1+	Incr 1+	None	Max.
1st dorsal interosseous.R	Normal	None	None	None	None	Normal	Normal	Normal	None	Max.
Abductor pollicisbrevis.R	Normal	None	None	None	None	Normal	Normal	Normal	None	Max.
Flexor carpi radialis.R	Normal	None	None	None	None	Decr 1+	Decr 1+	Incr 1+	None	Max.
Triceps brachii.R	Normal	None	None	None	None	Normal	Normal	Normal	None	Max.
Deltoid.R	Normal	None	None	None	None	Decr 1+	Decr 1+	Incr 1+	None	Max.
Orbicularis oculi.R	Normal	None	None	None	None	Decr 2+	Decr 2+	Incr 2+	None	Max.
Orbicularis oris.R	Normal	None	None	None	None	Decr 2+	Decr 2+	Incr 2+	None	Max.

An EMG was performed with results as above. Neuroconductive studies were normal. Needle examination revealed chronic changes in proximal and bulbar muscles, consistent with OPMD.

## Discussion

### Epidemiology and Genetics

Oculopharyngeal muscular dystrophy (OPMD) is a late-onset disorder characterized by ptosis, dysphagia, and proximal limb weakness inherited in an autosomal dominant manner<sup>[1]</sup>. The prevalence of OPMD is estimated at one in 100,000 individuals in France<sup>[4]</sup>, while it is estimated to have a higher prevalence in Quebec at one in 1,000 individuals<sup>[5]</sup> and in the Bukhara population living in Israel at one in 600 individuals<sup>[6]</sup> due to founder mutations.

OPMD is caused by a GCN tri nucleotide expansion at the N-terminus of the first exon of poly (A) binding protein nuclear 1 gene (PABPN1, previously called PABP2) on chromosome 14q11.2-q13<sup>[7]</sup>. PABPN1 serves as a regulator of mRNA stability by controlling the poly (A) tail length of RNA transcripts<sup>[8]</sup>. The GCN expansion results in accumulation of mutant PABPN1 in the cell nucleus and subsequent formation of insol-

uble aggregates<sup>[9]</sup>. In normal individuals, there are 6 GCG repeats which increases to 8 - 13 in individuals with OPMD<sup>[7]</sup>. Brais et al. also found that an autosomal recessive form, with milder symptoms with a later onset, was associated with a (GCG) 7 expansion. The nomenclature for mutations has recently changed after a broader spectrum of mutations has been reported and is now referred to as GCN expansions which always code for alanine. The wild-type allele is (GCN) 10/Ala10, the autosomal recessive form is (GCN) 11/Ala11, and the autosomal dominant form is (GCN) 12-17/Ala12-17<sup>[10]</sup>. The number of trinucleotide repeats is correlated to the mean age at diagnosis and disease severity<sup>[11]</sup>. OPMD was found to have complete penetrance past age 70, as well as the following decade-specific penetrances for a single (GCG)n mutation: 1% (< 40), 6% (40 - 49), 31% (50 - 59), 63% (60 - 69), and 99% (> 69)<sup>[12]</sup>.

Over expression of expanded PABPN1 in animal and cellular models leads to cell death, which suggests that these insoluble aggregates are toxic<sup>[13]</sup>. PABPN1 is expressed in all cells,

however, PABPN1 levels have been found to be lower in skeletal muscles of both humans and mice compared with a variety of tissues. PABPN1 levels were also found to be lower in mice pharyngeal muscle as compared with other skeletal muscles<sup>[14]</sup>. In addition, it has been shown that myogenic defects occur after PABPN1 falls below a certain level, manifesting as skeletal muscle weakness in OPMD<sup>[15]</sup>. The depletion of functional PABPN1 is accelerated in OPMD as aggregates of expanded PABPN1 form, furthering this hypothesis<sup>[16]</sup>.

### Clinical Presentation

Onset of OPMD usually occurs in the 5<sup>th</sup> - 6<sup>th</sup> decade of life with slowly progressive ptosis and dysphagia, and possible subsequent development of proximal limb girdle muscle weakness<sup>[17]</sup>. In several large-scale studies, ptosis due to asymmetric weakness of the levator palpebrae muscles was the most common presenting symptom<sup>[18-20]</sup>. Dysphagia has been reported to be the most common presenting symptom in a cohort of Chinese individuals<sup>[21]</sup>. A study of 72 French Canadian individuals with OPMD who were carriers of a (GCN)<sub>13</sub> mutation showed a mean age of onset of ptosis at 48.1 years (range 26 - 65) and of dysphagia at 50.7 (range 40 - 63)<sup>[22]</sup>. Extraocular muscle weakness has also been found to be a frequent symptom<sup>[19]</sup>, but complete external ophthalmoplegia is uncommon<sup>[17,23]</sup>. As the disease progresses, the following clinical findings have been reported: loss of tendon reflexes without clear polyneuropathy, proximal arm and leg weakness, facial muscle weakness, dysphonia, and tongue atrophy and weakness<sup>[17]</sup>. With late progression of the disease, dysphagia often causes malnutrition and predisposes to aspiration pneumonia<sup>[17]</sup>.

### Diagnostic Criteria and Diagnosis

Diagnostic criteria for OPMD on clinical grounds consist of meeting the following 3 parameters: 1) a positive family history of OPMD in two or more generations, 2) at least one palpebral fissure < 8 mm at rest or previous corrective surgery, and 3) taking > 7 seconds to drink 80 mL of ice-cold water<sup>[4,22,24]</sup>. Diagnosis is confirmed with molecular genetic testing of PABPN1 to determine the size of the GCN trinucleotide repeat in the first exon<sup>[7]</sup>, which has close to 100% sensitivity and specificity<sup>[17]</sup>.

Muscle biopsy is reserved for individuals with two normal PABPN1 alleles. Biopsy of affected muscles show intranuclear aggregates that appear as tubular filaments up to 250 nm in length, with an external diameter of 8.5 nm and an internal diameter of 3 nm. Biopsy from clinically affected or unaffected muscle show variation in muscle fiber diameter, atrophic angulated fibers, ragged red fibers, and rimmed vacuoles, however, these findings are nonspecific<sup>[23,25]</sup>.

Electromyography (EMG) of clinically affected muscles shows signs of a myopathic process<sup>[22]</sup>. EMG is not required for the diagnosis of OPMD since this finding is nonspecific.

Elevated serum creatine kinase levels have been reported at two to seven times above the upper limit of normal in individuals with OPMD with severe leg weakness<sup>[26]</sup>, but serum CK levels are usually normally to mildly elevated, thus is not necessary for diagnosis or follow up.

### Management and Treatment

OPMD is managed with supportive treatment, as degeneration is progressive and irreversible. In individuals with moderate to severe ptosis or dysphagia, blepharoplasty and/or cricopharyngeal myotomy can be performed. Surgery is recommended for ptosis when eyelid drooping interferes with vision or if the patient has cervical pain from neck extension compensation for vision<sup>[17]</sup>. Ptosis can be surgically corrected with either resection of the levatorpalpebrae aponeurosis or frontal suspension of the eyelids with minimal complications<sup>[27]</sup>. Resection of the levatorpalpebrae aponeurosis is a relatively easy procedure, but typically needs to be repeated once or twice. Frontal suspension of the eyelids requires using a synthetic sling or a thread of skeletal muscle fascia which is inserted into the tarsal plate of the upper eyelid. The sling is then attached at the ends in the frontalis muscle, which remains relatively preserved in OPMD<sup>[28]</sup>. Its major advantage over resection of the levatorpalpebrae aponeurosis is that it is permanent, however, it does require general anesthesia<sup>[29]</sup>. Contraindications to blepharoplasty include severe ophthalmoplegia, dry-eye syndrome, or poor orbicularis oculi function<sup>[17]</sup>.

Dysphagia should be surgically corrected if there is marked weight loss, near-fatal choking, or recurrent aspiration pneumonia. Cricopharyngeal myotomy is the procedure of choice as it alleviates dysphagia with a low rate of complications<sup>[27]</sup>. Unfortunately, progressive dysphagia recurs within several years in a large proportion of individuals<sup>[30]</sup>. Contraindications to cricopharyngeal myotomy include severe dysphonia and lower esophageal sphincter incompetence<sup>[31]</sup>. Botulinum toxin injections into the cricopharyngeus muscle can be used as an alternative to alleviate dysphagia; however, there is a dose-related risk of dysphonia or worsened dysphagia<sup>[32]</sup>. Repetitive cricopharyngeal dilatations with bougies are another alternative for severe dysphagia and have been shown to be safe and well-tolerated over many years<sup>[33]</sup>.

### Conclusion

Oculopharyngeal muscular dystrophy (OPMD) is an aptly named disease characterized by ptosis and swallowing difficulties with possible subsequent involvement of other proximal skeletal muscles. It is primarily autosomal dominant involving PABPN1 GCN trinucleotide repeats with rare instances of recessive genotypes. Diagnosis is based on history and clinical exam and confirmed with genetic testing, with muscle biopsy being reserved for negative DNA results. Symptom management is the crux of treatment and often involves blepharoplasty and/or cricopharyngeal myotomy.

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