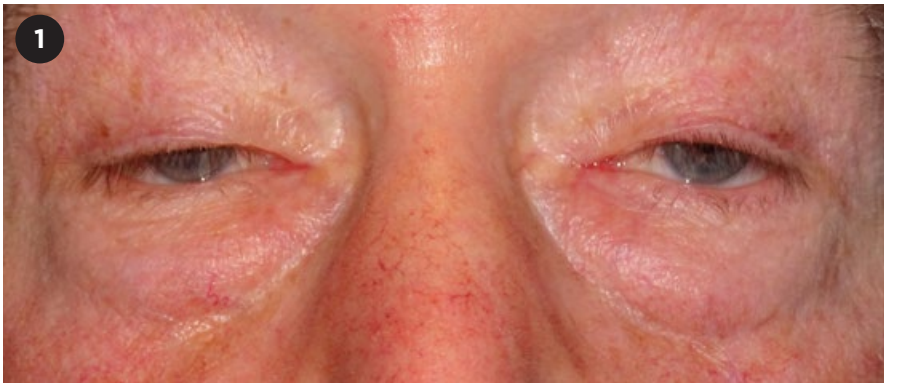
# The Case of Ptosis With a Pedigree

Seventy-year-old Orville Packard* thought that his problem with droopy eyelids was behind him after he had ptosis surgery 10 years ago. Yet he found himself struggling to see the road on the perilous 4-hour drive to our oculoplastics clinic for evaluation.




***EYELID EFFECT.*** *Photograph of patient at presentation demonstrating severe bilateral ptosis, which interfered with his vision.*

## First Impressions

Mr. Packard was relieved to arrive in one piece. He started by telling us how fearful he had been about driving for the last 2 years because of declining vision, which he attributed to his drooping lids.

During the interview, Mr. Packard had to tilt his head back to see us. He described a constant aching of his head and brows. He denied any fluctuation in his symptoms; they were present "all the time." He was disheartened that the first surgery—a bilateral levator resection he had undergone at the age of 60 with another provider—had failed.

On examination, Mr. Packard's visual acuity was normal, but he had superior visual field deficits bilaterally on confrontation testing. His upper margin–reflex distance (MRD-1) was 0 in both eyes (Fig. 1). The rest of the anterior and posterior segment exams, including pupils and ocular motility, were normal.

## Digging Deeper

We considered the differential diagnosis —Was this simply recurrent aponeurotic ptosis? Could it be myasthenia gravis? During the discussion, Mr. Packard added, "The same thing happened to my dad when he was my age." We pressed him for a more detailed family history. After thinking about his extended family, he identified 6 individuals on the paternal side, including himself, with severe ptosis (Fig. 2).

On further review of systems, Mr. Packard reported bilateral leg weakness. He added, "I also have trouble swallowing, which runs in my family, too." The patient's ethnicity cinched the diagnosis: His family had strong French Canadian roots. All the evidence pointed to oculopharyngeal muscular dystrophy (OPMD).

## Discussion

OPMD is an inherited disorder characterized by new onset of bilateral ptosis and dysphagia in the fifth to sixth decades of life. The disease is slowly progressive and may eventually spread to include the extraocular and limb girdle muscles.

The earliest symptoms of OPMD may include slowed eating and pooling of saliva. Patients may be observed to tilt their head back as levator weakness becomes more prominent, which is further exacerbated by progressive restriction of upgaze.

In most patients, the prognosis is dependent on the magnitude of dysphagia, with risks of aspiration and malnutrition increasing with age and disease progression. Less commonly, patients with severe disease may become wheelchair dependent.

**Genetics.** Although there are several subtypes of OPMD, including severe and autosomal recessive forms with associated phenotypic variations, the most common is autosomal dominant type. It has been attributed to an expansion of the trinucleotide repeat in the

BY **MATTHEW R. DENNY, MD,** AND **RONA Z. SILKISS, MD, FACS.** EDITED BY STEVEN J. GEDDE, MD.

Rona A. Silkiss, MD, FACS

first exon of *PABPN1*, a ubiquitous gene thought to be involved with mRNA processing throughout the body.

**Histology.** Histologically, the disease shares many features with other common muscular dystrophies but is characterized more specifically by filamentous intranuclear inclusions in skeletal muscle fibers. These inclusions consist of aggregations of abnormal PABPN1 protein and appear to be more pronounced in extraocular, lingual, pharyngeal, and diaphragmatic muscles.[1]

**Epidemiology.** The prevalence of OPMD is estimated to be 1/100,000 in Europe, affecting men and women equally. However, several groups around the world are disproportionately affected by the disease. The largest such group is the French Canadian population of Quebec, with a prevalence of 1/1,000. This increased prevalence is thought to result from a founder effect that has been traced to a single French couple who immigrated in 1634.[2]

## Diagnostic Criteria

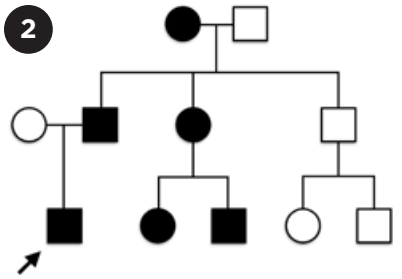
A diagnosis of OPMD is suggested by 1) a positive family history spanning at least 2 generations, 2) progressive ptosis or history of ptosis repair, and 3) dysphagia, elicited with a questionnaire or demonstrated by the length of time needed to finish a glass of water.

Historically, diagnosis was confirmed by histology, but in the era of genetic testing, muscle biopsy is reserved for individuals found to have 2 normal *PABPN1* alleles. Today, diagnosis can be confirmed with direct detection of the trinucleotide repeat expansion: 10 repeats of the GCN codon are found in the normal allele, and variable numbers of additional repeats are pathogenic. Patients with a longer *PABPN1* expansion or with 2 expanded alleles may have earlier onset and increased severity of symptoms.

## Treatment

Patients with a new diagnosis of OPMD should consider formal dysphagia and neuromuscular evaluations to assess the extent of disease at presentation. Management is based on severity of symptoms.

**Dysphagia.** When dysphagia becomes debilitating, cricopharyngeal myotomy (a surgical sectioning of the upper esophageal sphincter) can improve swallowing. Unfortunately, in many patients, this procedure may only be temporizing, as there is a high recurrence rate for dysphagia following myotomy.




***FAMILIAL CONDITION.*** *Patient's family pedigree, consistent with autosomal dominant inheritance pattern spanning 3 generations. Circles represent women, squares represent men, and black color indicates affected individuals. The arrow points out the patient.*

**Ptosis.** The most common procedures for ptosis repair are resection of the levator aponeurosis and frontalis suspension. A case series of 82 patients who underwent primary ptosis repair for OPMD found a recurrence rate of 4.9%, usually occurring a decade after primary repair. Most of these recurrences were bilateral and affected patients who had presented with moderate to severe ptosis (at least 3 mm).[3]

**Muscle inclusions.** While it remains unclear whether the protein aggregates themselves are pathogenic, several therapies have been proposed to target their accumulation. For example, intracellular PABPN1 antibodies in a cell model have been shown to reduce aggregation in a dose-dependent manner. Doxycycline therapy has also been used in a mouse model to delay and attenuate signs of disease.[1]

**Looking ahead: gene therapy?** Going forward, there may be a role for gene therapy in the management of OPMD. A recent study in a mouse model used an adeno-associated virus vector to simultaneously inhibit the presumed pathogenic protein and induce a functional replacement. After treatment, the affected muscles had substantial reduction in intracellular aggregates, decrease in fibrosis, and reversion to normal strength. OPMD could be a suitable target for gene therapy because of the limited range of muscle groups affected, allowing for in vivo muscle injections rather than whole body therapy, as may be needed in other types of muscular dystrophy.[4]

## Our Patient's Course

We counseled Mr. Packard on the genetic implications of this diagnosis so that he can discuss them with his family, and we recommended that he undergo a formal swallowing evaluation. He is scheduled for bilateral frontalis suspension to address his recurrent ptosis.

*Patient name is fictitious.


1 Abu-Baker A, Rouleau GA. *Biochim Biophys Acta.* 2007;1772(2):173-185.

2 Trollet C et al. *Oculopharyngeal Muscular Dystrophy.* Updated Feb. 20, 2014. In: Pagon RA et al., editors. GeneReviews. Seattle: University of Washington; 1993-2017. www.ncbi.nlm.nih.gov/books/NBK1126/.

3 Molgat YM, Rodrigue D. *Can J Ophthalmol.* 1993;28(1):11-14.

4 Malerba A et al. *Nat Commun.* Published online March 31, 2017. www.nature.com/articles/ncomms14848.



**Dr. Denny** is a first-year ophthalmology resident, and **Dr. Silkiss** is the Service Chief of Oculoplastic Surgery; both are at California Pacific Medical Center, in San Francisco. *Relevant financial disclosures: None.*




Matthew R. Denny, MD