Oculopharyngeal muscular dystrophy

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Abstract
Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant form of late-onset slowly progressive myopathy characterized by eyelid ptosis, dysphagia and, sometimes by other cranial and limb-muscle involvement. Most early cases were reported in the French Canadian population but the disease was subsequently found to be ubiquitous. From a clinical perspective, this disorder presents in the fourth to the sixth decade with progressive often asymmetrical ptosis resulting in a compensating contraction of the frontalis muscle and therefore a suggestive posture with retroflexion of the neck. Dysphagia is also an early symptom and can lead to nasal regurgitation and severe episodes of aspiration if overlooked. Limb-girdle muscle weakness, especially in the pelvic girdle, is often noted but varies widely among individuals without any correlation with the severity of ptosis or dysphagia. Creatine kinase (CK) levels are slightly elevated and electromyogram (EMG) studies suggest a mild myopathic process. The best clue to the diagnosis, after the clinical distribution of muscle weakness, is the presence of intranuclear inclusions in the muscle fibers. Rimmed vacuoles are often seen but are less specific. Genetic studies are now available and can establish the molecular signature of the disease. A short GCG-triplet repeat expansion in the gene encoding the PABPN1 protein (on chromosome 14q) is pathognomonic of OPMD. However, the disease pathogenesis remains unclear. Supportive treatment is available and consists of eyelid surgery and myotomy of the cricopharyngeal muscle in carefully selected cases.

Keywords
Oculopharyngeal muscular dystrophy, OPMD, muscular dystrophy, ptosis, dysphagia, intranuclear inclusions, rimmed vacuoles, triplet repeat expansion, polyalanine, PAPBN1, PAPB2, 14q11.2-q13.

Disease name and synonyms
Oculopharyngeal muscular dystrophy (OPMD)
Barbeau's disease.

Definition/Diagnosis criteria
Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant form of late-onset slowly progressive myopathy. The diagnosis is firmly

established on the basis of the combination of clinical, pathological and molecular findings.
- Clinical criteria: male or female patient over 45 years of age, with slowly progressive eyelid ptosis and dysphagia, occasional limb-girdle muscle weakness (notably in the pelvic girdle). Ptosis can be measured and is regarded as positive when one palpebral fissure measures less than 8 mm at rest. Drinking 80 ml of ice-cold water in more than 8 seconds is an objective measurement of dysphagia. A positive family history with autosomal dominant transmission is strongly suggestive but may be absent in sporadic cases.
- Histology: Electron microscopy detects the presence of intranuclear inclusions in muscle fibers.
- Molecular studies: pathological allele with 8 to 13 GCG-triplet repeats in the *PABPN1* gene.

Excluded diseases
The following diseases have to be considered mainly in atypical or sporadic cases without any positive family history:
- myotonic dystrophy
- oculopharyngeal distal myopathy
- autosomal distal myopathy with vocal cord paralysis
- mitochondrial myopathy with or without progressive external ophthalmoplegia (PEO)
- mitochondrial neurogastrointestinal encephalomyopathy syndrome (MNGIE)
- myasthenia gravis
- congenital myasthenic syndrome (notably the slow channel syndrome, which is also autosomal dominant)
- progressive bulbar palsy or polymyositis
- late-onset isolated familial ptosis

Prevalence
OPMD is a rare but ubiquitous disorder, which has been reported in many countries across the 5 continents to date. Of particular interest is the existence of several clusters: the largest one is found in the Canadian province of Quebec with a prevalence of 1:1000. A founder effect originating from the first French settlers has been clearly established. In Bukhara Jews now settled in Israel, the prevalence is close to 1:600. In the French general population, some studies suggest a prevalence of 1:100.000, similarly to the rest of Europe.

Clinical description
OPMD is a late-onset myopathy. Patients become symptomatic from the 5th or more often 6th decade onwards. Earlier onset is possible as seen, in the very few reported homozygotes. Presenting manifestations consist of ptosis and/or dysphagia. Ptosis is noted in 100% of cases after the age of 60 years. Eye-duction abnormalities are rarely seen and usually consist of incomplete and non-progressive ophthalmoparesis. The rest of the facial musculature is spared untill a later stage. Swallowing difficulties are an almost constant feature and may become debilitating by pooling the secretions in the nasopharynx and sometimes result in severe episodes of aspiration. Dysphonia is noted in 50% of cases. Limb-girdle muscle weakness, mostly in the lower segment, is not correlated to disease duration. It can occur quite early in the disease and is generally more proximal than distal. No other primary symptoms, particularly of the cardiac, respiratory or central nervous systems, have been reported to date. Disease progression varies widely from one individual to another, even within the same family. A few patients (less than 10%) become wheelchair bound, due to marked proximal limb-muscle weakness combined to dysphagia-related cachexia and aging.
Homozygotes for the condition exhibit an earlier onset and a more severe disease course.

Management including treatment
In the absence of any new insights into the pathogenesis, the treatment is purely supportive.

Surgical correction of ptosis
Two types of procedures are available: the resection of the levator palpebrae aponeurosis and the frontal suspension of the eyelids. The latter procedure provides a permanent correction but requires general anesthesia. Such interventions are recommended when the ptosis interfers with vision, or when compensatory neck postures become painful. Conversely, surgery is contraindicated in case of marked ophthalmoplegia. Alternatively, the intermittent use of glasses with eyelid props can prove useful.

Surgical correction of dysphagia
Even if a relative consensus exists on the technique (myotomy of the cricopharyngeal muscle) to alleviate symptoms related to dysphagia, the timing of such a procedure remains controversial. In that context, substantial weight loss, numerous episodes of choking as well as frequent episodes of aspiration pneumonia should prompt the surgeon to intervene rapidly. In the long term, the key-issue remains the risk of recurrence. Alternatively, repeated dilatations of the upper-esophageal sphincter with bougies can sometimes be beneficial to the patient.

Etiology / Heredity
The autosomal dominant type is by far the most frequent. Occasional cases of autosomal recessive inheritance have been reported.
OPMD is caused by mutations of the *polyadenylate binding protein nuclear* 1 gene, *PABPN1* (previously called *PABP2*), located on chromosome 14q. The first exon of this gene normally contains one expansion of 6 GCG trinucleotide repeats [(GCG)6]. Autosomal dominant pathological alleles consist of expansions greater than 7 and up to 13 GCG repeats. The [(GCG)9] allele is particularly frequent in French-Canadian OPMD patients. The [(GCG)7] allele is a bit peculiar and corresponds, in association with an allele with the same or more rarely, a larger pathological segment of 8 or more repeats, to the very few autosomal recessive cases reported to date.

Diagnostic methods
The muscle biopsy is no longer essential for the diagnosis but can provide helpful information, especially in clinically atypical cases. Two main histological changes are noted in the muscle fibers of OPMD patients: rimmed vacuoles and tubulofilamentous intranuclear inclusions. Conversely, the dystrophic aspect of the muscle, if any, is usually very mild. Intranuclear inclusions (INIs) are pathognomonic of OPMD and consist of tubular filaments, with an outer diameter of 8.5 nm and 0.25 nm long, exclusively within in the nuclei of muscle fibers. Only visible under electron microscopy, they require careful examination and expertise due to their relative paucity (they are present only in 3 to 6% of the muscle fibers). Rimmed vacuoles are less specific and are also seen in the cytoplasm of a small percentage of muscle fibers.

DNA studies
DNA studies are highly sensitive and specific, even though less than 1% of OPMD cases do not exhibit a pathological GCG expansion. Unlike many other triplet-expansion diseases, the mutation is quite stable over generations and does not lead to clinical anticipation.
DNA studies are now recommended as a first-line diagnostic method when OPMD is clinically suspected. If no mutation is found, a muscle biopsy with the search for specific intranuclear inclusions is required before confirming or ruling out the diagnosis of OPMD.

Genetic counseling
In autosomal dominant OPMD, which represents the predominant situation in clinical practice, the risk of transmitting the genetic defect to the next generation is 50%, irrespective of the gender. The rate of *de novo* mutations is still unknown.
Testing of potentially at-risk asymptomatic adults is possible. However caution is recommended regarding the psychological impact of such a disclosure on a given individual.
Despite the advent of molecular testing, the clinical severity over time is not predictable. In the Canadian experience, and when different clinical courses coexist in a given family, patients with a severe form are not more likely to transmit the severe phenotype than those affected by a more benign form.
In autosomal recessive OPMD, the parents are obligate carriers and, as such, do not exhibit any particular symptoms. The risk of transmitting the disease to the next generation is 25%, with a 50% of the other offspring being asymptomatic carriers.
Predictive testing is not recommended for asymptomatic children.
When no pathological allele is found, genetic counseling can be hampered, but also questions the accuracy of the diagnosis and suggests a possible genetic heterogeneity in this disorder.

Antenatal diagnosis
Prenatal testing is theoretically possible. However, given the late-onset and the generally mild course of the disease, requests for such a procedure, usually performed on chorionic villus sampling or amniocentesis material, are quite uncommon.

Unresolved questions
The establishment of genotype-phenotype correlations is still in progress. To some extent, severity of muscle weakness and age of onset depend on the size of the triplet expansion. However, many exceptions to this rule remain. Even with the same genotype and within the same familial background, significant clinical variations have been reported, thereby suggesting the existence of epigenetic or non-genetic modifying factors. In the most severe autosomal dominant cases, it seems as if the presence of an additional [(GCG)7] allele potentiates the clinical severity. Autosomal recessive cases with a [(GCG)7], [(GCG)7] genotype usually have a late onset and a milder disease course.
Pathogenesis is still obscure: The mutated PAPBN1 protein harbors an expanded polyalanine domain. The mechanism by which this change induces toxicity gain-of-function is still unclear. INIs contains not only the mutated *PAPBN1* but also ubiquitin, proteasome subunits, HSP 40, HSP 70 and many poly(A) – mRNA. A transgenic mouse model expressing the mutated *PABPN1* has just been generated

and showed a myopathic phenotype. This may provide news insights into the pathogenesis.

References

Barbeau A. The syndrome of hereditary late onset ptosis and dysphagia in French Canada. In Progressive Muskeldystrophie. Myotony. Myasthenia (ed. E. Kuhn), pp. 102-109. Springer-Verlag, Berlin.

Blumen SC, Nisipeanu P, Sadeh M, *et al*. Clinical features of oculopharyngeal muscular dystrophy among Bukhara Jews. Neuromuscul Disord, 1993;3:575-577.

Blumen SC, Brais B, Korczyn AD, *et al*. Homozygotes for oculopharyngeal muscular dystrophy have a severe form of the disease. Ann Neurol 1999;46:115-118.

Bouchard JP, Brais B, Tomé FMS. Oculopharyngeal muscular dystrophy. In "Neuromuscular disorders: clinical and molecular genetics." Emery AEH, Editor. Wiley. 1998. pp. 157-179.

Brais B. Oculopharyngeal muscular dystrophy: a late-onset polyalanine disease. Cytogenet Genome Res, 2003;100:252-60.

Brais B, Bouchard JP, Xie YG, *et al*. Short GCG expansions in the PABP2 gene cause oculopharyngeal muscular dystrophy. Nat Genet 1998;18:164-167.

Brais B, Xie YG, Sanson M, *et al*. The oculopharyngeal muscular dystrophy locus maps to the region of the cardiac alpha and beta myosin heavy chain genes on chromosome 14q11.2-q13. Hum Mol Genet, 1995;4:429-434.

Brunet G, Tomé FMS, Samson F, *et al*. Dystrophie musculaire oculopharyngée. Recensement des familles françaises et études généalogiques. Rev Neurol, 1990 ;146 :425-429.

Duranceau A. Cricopharyngeal myotomy in the management of neuromuscular dysphagia. Neuromuscul Disord, 1997;7(suppl. 1):85-89.

Fried K, Arlozorov A, Spira R. Autosomal recessive oculopharyngeal muscular dystrophy. J Med Genet, 1975;12:416-418.

Hino H, Araki K, Uyama E, Takeya M, Araki M, Yoshinobu K, Miike K, Kawazoe Y, Maeda Y, Uchino M, Yanamura KI. Myopathy phenotype in transgenic mice expressing mutated PABPN1 as a model of oculopharyngeal muscular dystrophy. Hum Mol Genet, 2004;13:181-190.

Mathieu J, Lapointe G, Brassard A, *et al*. A pilot study on upper oesophageal sphincter dilatation for the treatment of dysphagia in patients with OPMD. Neuromuscul Disord, 1997(suppl. 1):100-104.

Rodrigue D, Molgat YM. Surgical correction of blepharoptosis in OPMD. Neuromuscul Disord, 1997, 7, (suppl. 1):82-84.

Taylor EW. Progressive vagus-glossopharyngeal paralysis with ptosis: a contribution to the group of family diseases. J Nerv Ment Dis, 1915;42:129-139.

Tomé FMS, Fardeau M. Nuclear inclusions in oculopharyngeal dystrophy. Acta Neuropathol, 1980;49:85-87.

Victor M, Hayes R, Adams RD. Oculopharyngeal muscular dystrophy. A familial disease of late life characterized by dysphagia and progressive ptosis of the eyelids. N Engl J Med, 1962;2677:1267-1272.