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Oculopharyngeal muscular dystrophy – an under-diagnosed disorder?

Stephan Rüegg[a]*, *Monique Lehky Hagen*[a]*, *Ursula Hohl*[a], *Ludwig Kappos*[a], *Peter Fuhr*[a], *Martina Plasilov*[a, b], *Hansjakob Müller*[b], *Karl Heinimann*[b]

[a] Department of Neurology, University Hospital Basel, Basel, Switzerland
[b] Division of Medical Genetics, University Children's Hospital Basel, Basel, Switzerland

Summary

Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant muscle disorder, usually of late onset. OPMD is among the few triplet repeat diseases/ polyalanine (poly(A)) expansion diseases for which the function of the mutated gene is quite well established. The disease is characterised by slowly progressive bilateral ptosis, dysphagia and proximal limb weakness, appearing after the age of 40 years. Prevalence and incidence of OPMD are low, but the disease occurs all over the world. The pedigrees of two Swiss kindred have been previously reported in Switzerland. In the last 2 years, accumulation of newly diagnosed cases in North-West Switzerland have been observed, which suggests that OPMD may be more prevalent than previously thought. Primary care providers, opthalmologists and neurologists that are alert for the almost specific combination of clinical signs, together with the availability of reliable genetic testing may help to recognise currently undiagnosed patients. They can advance knowledge and the characterisation of the OPMD population in Switzerland. Since the number of disorders linked to poly(A) expansions is growing rapidly, the study of OPMD may contribute to the understanding of a large group of other developmental and degenerative diseases. On the basis of a patient with "classical" OPMD, this review summarises the clinical, therapeutic, epidemiological, pathomechanistic and genetic aspects of OPMD, provides practical information about the differential diagnosis of OPMD, and presents a survey of different investigational methods.

Key words: oculopharyngeal muscular dystrophy; OPMD; muscle disorder

Introduction

Slowly progressive weakness of ocular muscles was first reported as "progressive external ophthalmoplegia" (PEO) by von Graefe in 1868 [1]. But it was only in 1962 when Victor recognised a unique association of PEO with insidious pharyngeal weakness and subsequently introduced the term "oculopharyngeal muscular dystrophy" (OPMD) [2]. The report by Taylor in 1915 and some other case reports had been overlooked before [3]. The largest clusters of OPMD were observed by Barbeau in Quebec [4] with an estimated prevalence of 1:1000 in the late sixties, and in 1997 by Blumen, who found a prevalence of 1:600 in Bukhara Jewish immigrants in Israel [5]. Recently, by analysing local hospital records, Becher and colleagues have revealed an unexpected large OPMD population of Hispanic offspring living in New Mexico (USA) [6]. Eventually, patients with OPMD have been reported in more than 30 countries on all five continents (for review, see [7]). In Switzerland, Graf published the first family with OPMD in 1971 [8]; another family with 7 symptomatic members within 3 generations was described by Knoblauch in 1984 [9].

No case of OPMD was observed during the last 20 years at a tertiary care hospital in North-

Abbreviations:

CPEO	chronic progressive external ophthalmoplegia
CSF	cerebrospinal fluid
EDTA	ethylene-diamino-tetraacetic acid
ENT	ear-nose-throat
INIs	intranuclear inclusions
KSS	Kearns-Sayre syndrome
MG	myasthenia gravis
MRI	magnetic resonance imaging
OPMD	oculopharyngeal muscular dystrophy
PABP2	poly-adenylate binding protein-2
PABPN1	poly-adenylate binding protein nuclear gene-1
poly(A)	poly(alanine)

* Both authors equally contributed to this work

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West Switzerland. However, since 2003 the diagnosis of OPMD of six non-related cases from this region has been genetically confirmed at the Division of Human Genetics of the University Children's Hospital of Basel (UCHB). Although all these patients had a combination of ptosis, dysphagia and/or limb weakness, most of them were primarily seen by an ophthalmologist and treated only for their ocular problems. The disease remained undiagnosed for a substantial period of their life. All but one patient had a positive family history; however, none of their relatives received a diagnostic work-up. Routine genetic testing to confirm the diagnosis of OPMD has been established in 2003 at the Division of Human Genetics of the UCHB. Thus, reporting on our index patient, this review summarises the current knowledge of the clinical, pathological, and genetic features of OPMD. We intend to review the differential diagnosis of OPMD and to discuss the literature with special emphasis on the diagnostic and therapeutic advances in the field of OPMD. Increased awareness of OPMD by primary care physicians, ophthalmologists and ENT doctors may facilitate and speed up earlier diagnosis of OPMD.

Clinical features

The symptoms of OPMD usually start insidiously and become manifest in the fifth or sixth decade, with a slowly progressive course; eventually, beyond the age of 70, all patients are symptomatic [10]. The main symptoms are ptosis and dysphagia due to weakness of the levator palpebrae and pharyngeal muscles. Although other extraocular muscles may become gradually involved, complete external ophthalmoplegia is rare and intrinsic eye (ciliary, sphincter) muscles are not affected [11]. Ptosis is always bilateral, but may be asymmetrical. Upon progression of ptosis, patients try to compensate their limitation of the visual field by contracting the frontal muscle and reclining the head, holding their head in the so-called "astrologist's" posture. This posture may aggravate the dysphagia. The symptoms of dysphagia in OPMD typically are noticed first for solid foods. Later on, fluids may become difficult to swallow, too. Weakness and atrophy of the tongue can be observed in the vast majority of patients [12]. Consecutive aspiration pneumonia, together with malnutrition or even starvation, are the leading causes of death in patients with OPMD. However, these events mostly occur at higher age and life expectancy seems not to be shortened, although quality of life may be substantially impaired during the last years of life.

The myopathic process may become manifest with several other symptoms which are listed in table 1 (modified from [13]). Some patients eventually may become wheelchair-bound [12]. Interestingly, a recent study of Dutch patients reported substantial limb-girdle weakness – even as the first manifestation of OPMD – in a high percentage of patients [13].

The existence of an additional axonal sensorimotor neuropathy in OPMD patients has been reported several times [12, 14–21] and even one case with involvement of the CNS [22]. Nevertheless, it remains unclear whether the neuropathy is causatively related to OPMD or whether it is a coincidental disorder in OPMD patients, or simply a process of ageing. Another possibility in such patients may consist in a purely neuropathic process involving the limbs and extending to the cranial nerves. However, in such cases, additional neurophysiological, laboratory, histopathological and genetic examinations may allow to specifically determine the cause of the suspected neuropathic process (see below).

Table 1

Frequency of clinical signs of OPMD according to different studies [5, 6, 12, 13, 18, 19, 92–95]; (modified from [13]).

Study	New Mexico (n = 49)	Israel (n = 117)	Québec (n = 72)	France (n = 29)	Uruguay (n = 65)	Italy (n = 18)	Germany (n = 16)	The Netherlands (n = 16)	UK (n = 31)
Symptom/sign									
Ptosis	92%	98%	100%	97%	91%	100%	100%	100%	100%?
Dysphagia	76%	73%	100%	69%	>40%	67%	63%	100%	100%?
Dysarthrophonia	41%	70%	67%	34%	n.s.	n.s.	25%	75%	n.s.
Proximal weakness	65%	20%	38/71%*	52%	34%	61%	56%	81%***	n.s.
Facial weakness	n.s.	17%	43%	n.s.	66%	11%	13%	81%	n.s.
Abnormal gait	35%	n.s.**	n.s.	n.s.	n.s.	n.s.	38%	n.s.	n.s.
eye motility disorder	n.s.	21%	61%	55%	68%	5%	31%	25%	50%

* upper/ lower extremity; ** n.s.: not specified; *** including additional limb-girdle weakness

Illustrative case

History

The 65-year-old male patient was referred by his ophthalmologist for neurological evaluation of ptosis. The patient himself noticed slight ptosis in 1995, more pronounced on the right eye. The ptosis had become a handicap to him since 2002, forcing him to recline his head in order to see (figure 1). Because of progressive fatigue he had to walk slowly. Since 2002, he additionally became aware of a slurred speech and had the impression of a heavy, awkward tongue. He found swallowing of saliva difficult and started to choke when eating too fast. He had to eat extremely slowly so that even small meals lasted more than an hour. Although he trained for taking small bites and subsequent rinsing with water, he reported needing to cough after swallowing. Despite these difficulties, his weight remained stable. Personal history was notable for palpitations suggestive of re-entry tachyarrhythmias during his twenties; however, they ceased at age 30 without treatment. He had hearing loss resulting from exposure to shooting noise. He took no medication and did not drink alcohol.

Family history was remarkable in that his mother (figure 2) and one of his two older brothers had already been successfully operated for ptosis by tarsorrhaphy. One sister and one brother seemed to be unaffected and healthy. One older sister had severe multiple sclerosis and died at age 40 because of secondary pulmonary problems. The mother died at age 81, probably due to pneumonia. According to the patient, she was almost unable to eat during the last period of her life, except for a daily small amount of yoghurt. Her ptosis relapsed some years after the operation; she had substantial difficulties to talk and was nearly deaf. One of the patient's brothers had been operated because of bilateral ptosis several years ago with good results so far. No family member had paid attention to the speech- and deglutition problems, nor had linked it to the ptosis. Additionally, one brother and one sister of the patient's mother suffered from identical symptoms.

Physical examination

The patient was in good general condition. He showed marked bilateral palpebral ptosis (right > left) and the width of eyelid clefts were 3 mm (right) and 5 mm (left) (figure 1). He also showed bilateral minimally restricted upward gaze. He had slight left-sided intentional tremor. Deep tendon reflexes were symmetrically reduced on all four limbs. Muscle strength and sensibility were normal. He had impaired hearing and Unterberger's test showed a deviation to the left of 90°. The neurological examination was otherwise normal.

Figure 1

Progression of ptosis in OPMD: evolution of the patient reported, at age 20 (left), and at age 64 (right). The photographs are published with the informed consent of the patient.

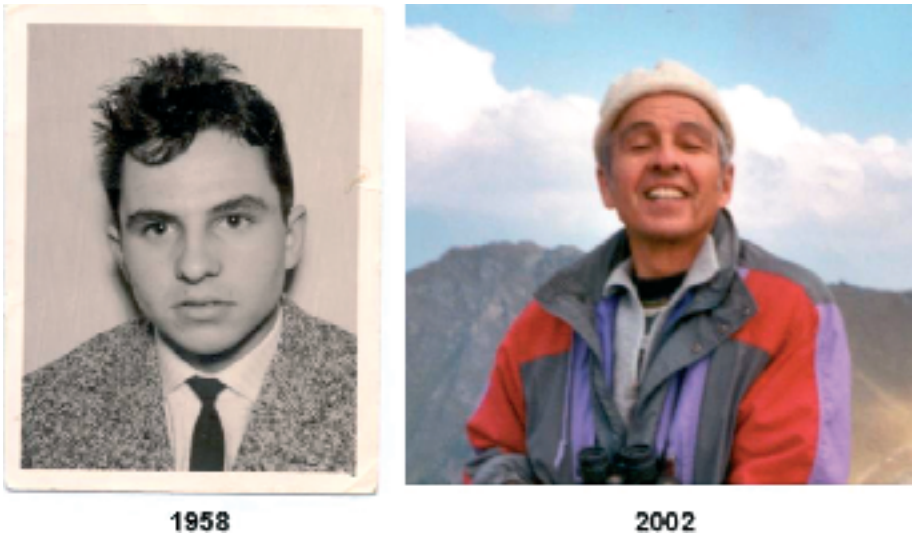

Figure 2

Autosomal-dominant inheritance of OPMD: the patients' mother at his wedding day; note the marked ptosis (circle/arrow). The photograph is published with the informed consent of the patient.

Investigations

At first appreciation, the personal and familial history of the patient together with the clinical findings strongly suggested OPMD. Electromyography showed mild bilateral myopathic signs in the orbicularis oculi and tibial anterior muscles. Repetitive electrical stimulation of the facial and accessory nerves and an ice water test performed in order to exclude altered neuromuscular transmission were normal. Because of the reported muscular exhaustibility we performed an ischaemia test with measurement of lactate concentrations, which showed no signs suggestive of a metabolic myopathy.

Nasopharyngeal videoendoscopy revealed dysphagia for foods and fluids because of dysfunction of all phases of deglutition, with delayed triggering and insufficient relax-

ation of the upper oesophageal sphincter, and paresis of the tongue and the posterior wall of the hypopharynx. Consecutively, solid foods rather than fluids were pooled in the epiglottic valleculae and the piriform recessus from which they could be only removed by repetitive swallowing. Reclination of the head aggravated deglutition problems. Coughing started with significant delay after the penetration of fluids into the larynx; however, there were no signs of aspiration.

Blood tests showed normal haematological cell counts; creatinine phosphokinase (CK) (371 U/L [<200]), γ-glutamyltransferase (116 U/L [<66]), and IgA (6.94 g/L [0.3–3.8]) were mildly elevated.

An MRI of the head performed because of the pathological Unterberger's test and near-deafness, revealed unspecific subcortical microangiopathic changes and specifically ruled out an ischaemic, neoplastic or inflammatory lesion of the brainstem. Since the patient mentioned tachyarrhytmias during adolescence, an ECG was made which showed normal sinusal rhythm without signs of aberrant conduction or bundle branch blocks.

Subsequent molecular genetic analysis of leukocyte-derived DNA from the patient revealed an expansion of the GCG triplets from 6 (wild-type) to 9 repeats in the PABPN1 gene confirming the clinically suspected OPMD in our patient.

Initially no muscle biopsy was performed. However, a muscle specimen taken during tarsorrhaphy lacked, not unexpectedly, the typical histological pattern of OPMD (see below), while important but unspecific tissue changes were present.

Clinical and videoendoscopic reevaluation one year later showed further deterioration of swallowing. However, the functional situation is currently stable under intensive training of swallowing by a speech therapist and adaptations of life-style.

Genetics, pathogenesis and molecular diagnosis of OPMD

General considerations

Oculopharyngeal muscular dystrophy (OMIM 164300) is caused by expansions in a 6 GCG trinucleotide repeat tract ([GCG]6) located in the first exon of the polyadenylate binding protein nuclear 1 gene (PABPN1) on chromosome 14q11.2–q13 [23]. In the vast majority of patients the disease is inherited in an autosomal dominant fashion with heterozygous mutation carriers displaying alleles in the range from 8 to 13 GCG repeats [(GCG)8–13]. Thus far, autosomal recessively inherited OPMD has only been observed in a single patient being homozygous for the (GCG)7 allele [23]. Due to its prevalence of 1 to 2% in the Western world, the (GCG)7 allele per se is considered a polymorphism.

The expansion of GCG triplet repeats, encoding the amino acid alanine, leads to an elongation of the N-terminal polyalanine tract in the PABPN1 protein. In contrast to disorders with comparatively large triplet repeat expansions (so-called "dynamic" mutations) within coding sequences (eg polyglutamine disorders like Huntington or Kennedy disease) PABPN1 mutations are mitotically and meiotically stable. The causal mutational mechanism still remains to be determined: recent studies, however, suggest that OPMD mutations occur through unequal crossing-over rather than the initially proposed DNA slippage during replication. In view of these important mechanistic differences compared to "classical" triplet repeat expansion disorders, OPMD is better referred to as a polyalanine (domain expansion) disease (for review see [7, 10]).

PABPN1 protein is part of the mRNA processing machinery which adds the poly(A) tail to the newly transcribed mRNA [24]. The protein is exclusively localised in the nucleus and is present in all tissues, particularly highly expressed in skeletal muscle. Similar to studies on other polyalanine disorders (eg the ARX gene in X-linked mental retardation and epilepsy) as well as polyglutamine disorders, current theories suggest that the pathologically expanded polyalanine domain confers cell toxicity by rendering the protein resistant to nuclear degradation. The resulting formation and accumulation of intranuclear filaments, seen in OPMD muscle as intranuclear inclusions (INIs), may thus interfere with normal cell homeostasis eventually leading to cell death [25–28]. Recent work in a cell model of OPMD showed that the protein aggregates directly impair the ubiquitin-proteasome pathway, thereby inhibiting clearance of the unfolded polypeptides and enhancing the accumulation of INIs. In addition, these INIs seem to reduce the induction of molecular chaperons, ie heat-shock proteins, another cellular safe-guard protecting cells from noxious protein aggregates [29]. Another study showed an interaction of the mutated PABPN1 protein of OPMD patients with the two nucleocytoplasmic exotransporter proteins hnRNP A1 and hnRNP A/B; these results help to further explain how the intranuclear inclusions typical for OPMD may accumulate [30, 31]. It is of note, however, that other, intranuclear inclusion-independent mechanisms have been proposed, eg interference with (tissue-specific) transcriptional coactivators resulting in disruption of gene expression. Recent work has suggested that the nuclear inclusions could also be dynamic structures [32].

Genetic testing

To confirm the diagnosis in patients clinically suspected of having OPMD molecular genetic testing is performed. Following genetic counselling and informed consent given by the patient, a peripheral venous blood sample (2 to 5 ml EDTA blood) is drawn. Subsequently, genomic DNA is extracted from leukocytes and analysed by specific amplification and direct sequencing of the first exon of PABPN1 in order to determine the size of the GCG trinucleotide repeat. The costs of the analysis amount to approximately CHF 500.

Rarely, other permutations than GCG triplet repeat expansions have been described (eg a GCA(GCG)2 insertion in Cajun OPMD patients) with all of them resulting in a polyalanine tract expansion, too. Considering DNA sequencing as the analytical gold standard, it is estimated that >99% of patients with severe, autosomal dominant OPMD actually carry a pathogenic PABPN1 triplet repeat expansion.

Genotype-phenotype correlations in OPMD

Based on a study on French-Canadian (GCG)9 mutation carriers, penetration of dominant OPMD has been estimated to be nearly complete past age seventy [33]. In the majority of patients and families, the genetic factor(s) modifying disease expression are not known and are subject of intense research. Due to the often considerable intra-familial variability, knowledge of the size of the GCG repeat expansion does not allow to predict disease severity or rate of progression in asymptomatic mutation carriers. Nevertheless, 20% of patients with severe OPMD are either homozygotes or compound heterozygotes ([GCG] 7 allele in combination with an autosomal dominant mutation), having both alleles mutated [23]. The worst OPMD phenotype has been observed in patients homozygous for an autosomal dominant mutation in PABPN1 [34].

Furthermore, it currently remains elusive why the ubiquitously expressed PABPN1 protein affects, when mutated, some muscles with exquisite predominance.

Molecular genetic testing of asymptomatic at-risk individuals

In autosomal dominant OPMD, 50% of offspring are at risk of having inherited the disease allele from the affected parent. Provided that adequate genetic counselling was given to the person to be tested and written informed consent obtained, genetic testing for diagnostic confirmation in symptomatic individuals poses few ethical problems per se.

Predictive genetic testing of asymptomatic family members, however, warrants extensive pre- and post-test counselling of the proband, similar to Huntington's disease, since the disease occurs only late in life (usually after age 45) and no cure exists to date. In addition, the impact of the test result on the psychological as well as the socio-economic level (eg private insurance coverage, employment) needs to be addressed before a test is performed. Due to the implications of a positive or a negative test result, the molecular genetic analysis should be confirmed on a second, independently drawn blood sample to exclude any potential sample mix-up. As put forward in national and international guidelines, no molecular genetic investigation should be performed during childhood as this would remove the child's choice (right to ignorance) and could result in serious psychosocial stigmatisation and impact future life plans [35].

The role of ancillary investigations for the diagnosis of OPMD

Before genetic testing became available, the diagnosis was made on purely clinical grounds. The presence of slowly progressive ptosis and dysphagia, an onset of symptoms after age 40, and a positive family history were pathognomonic. Later on, light and electron microscopy studies of muscle biopsy specimens provided further diagnostic confirmation by the presence of rimmed vacuoles within muscle fibres and OPMD-specific nuclear inclusion bodies. Additionally, electro(neuro)myographic studies tried to exclude other neuromuscular disorders. Eventually, genetic testing fundamentally changed the diagnostic process and the degree of diagnostic certainty as described above. Following, some of the diagnostic tools and their clinical, diagnostic and prognostic impact will be discussed.

Neurophysiology

Electromyography (EMG) usually is performed on proximal (deltoid, rectus femoris, tibial anterior) and distal (extensor digitorum brevis) muscles of the limbs. Though clinically most evident, the extraocular muscles are not easy to analyse because they have very small motor units generating action potentials of short duration and making the interpretation of EMG findings difficult. Most of the changes recorded in proximal limb muscle are myopathic with a polyphasic motor unit potential that is small in amplitude and of short duration. However, polyphasic motor unit potentials of high amplitude and long duration have been observed suggesting an additional neurogenic component. Single muscle fibre EMG yielded equivocal results because normal as well as abnormal pairs of jitters have been recorded [12, 36]; thus, the usefulness of this test remains to be determined. By electroneurography (ENG), repetitive supramaximal stimulation of single peripheral nerves has to be normal in patients with OPMD, thereby excluding the presence of a disorder of neuromuscular transmission like myasthenia gravis (MG), botulism, and Lambert-Eaton myasthenic syndrome. Mild neuropathic findings may be seen (see above), but they are considered to be related to older age or concomitant disease in most cases. In clinically obvious cases of OPMD, electromyography studies are not mandatory, but they may be helpful for corroboration of the diagnosis and serve as an objective parameter of disease

evolution when repeatedly performed. In patients where MG cannot be ruled out by clinical means, repetitive stimulation is essential in the diagnostic process.

Laboratory features

Laboratory features except for genetic testing are not specific.; creatinine phosphokinase may be normal or slightly elevated (up to 500 U/L [normal <200 U/L]); the same is true for muscular aldolase. Hypothyroidsm has to be ruled out. Elevated levels of IgG and/or IgA (as in our patient) does not seem to reflect an autoimmune mechanism in OPMD, but most likely may result from repetitive upper airway infection triggered by dysphagia. Thus, the IgA levels were significantly higher in patients with marked progression of ptosis and dysphagia over the last five years [37]. The pattern of results of repetitive lactate and ammonia testing before, during, and after moderate physical exercise (ischaemia test) should remain within normal limits what supports the differentiation of OPMD from metabolic or mitochondrial myopathies. Normal biochemical activities of mitochondrial oxidative (cytochrome C) complexes in muscular biopsy specimens help to exclude mitochondriopathies, especially chronic progressive external ophthalmoplegia (CPEO) and Kearne-Sayre syndrome (KSS). Testing for enzyme deficiencies specific for metabolic muscular disorders, like glycogenoses (McArdle's disease, phosphofructokinase deficiency, etc.), alterations of lipid (carnitine-palmitoyl-transferase type-I and -II deficiency) or nucleotide (myoadenylate deaminase deficiency) metabolism is only rarely warranted when the patient presents with unspecific or very atypical symptoms and signs of OPMD.

Cardiac exploration

Routine ECG in OPMD patients is almost always sufficient to exclude branch bundle blocks, which were reported in a few patients with OPMD [11]. Holter ECG and echocardiography should only be performed when the patient presents with symptoms and/or signs of cardiac arrhythmias or failure. These symptoms, however, may also represent a comorbidity unrelated to OPMD.

Investigations of swallowing

Radiologically documented swallowing and videoendoscopy are important tools to assess the severity of dysphagia in the course of the disease [38]. In these studies, palatal mobility is reduced and the gag reflex can be impaired, so that pools of saliva tend to accumulate in the nasopharynx, leading to tracheobronchial aspiration. Additional manometric and radiological studies of pharyngeal and oesophageal motility show weak, prolonged and repetitive pharyngeal contractions, but contraction of the upper oesophageal sphincter is normal. However, sphincter relaxation itself is delayed and incomplete due to the weakness of the hypopharyngeal muscles. One study reported additionally significant dysmotility of the whole oesophagus leading to non-propulsive or even retrograde transport, suggesting an important contribution of oesophageal smooth muscles to the dysphagia of OPMD patients [39]. To conclude, the inability of the pharyngeal musculature to build up sufficient pressure may explain the mechanism of dysphagia in patients with OPMD.

Histopathology

The histology of muscle biopsy specimen shows some particular, but non-specific changes: 1) small angulated fibres which may represent an ageing-related concomitant denervation process, and 2) rimmed vacuoles within the muscle fibres which most probably derive from an autophagic process; (similar vacuoles are seen in inclusion body myositis). Electron microscopy reveals tubulofilamentous inclusions of about 8.5 nm in diameter within the nuclei of muscle fibres which represent the INIs and seemed to be the most specific diagnostic sign of OPMD except for genetic testing; however, these inclusions tend to be easily overlooked [40]. These inclusions consist of mutated PABPN1 (see genetics above) that is not degradable by the proteasome machinery [29].

Other histological changes are not specific and common to many muscular dystrophies (loss of muscle fibres, abnormal variation in fibre size, increase in the number of nuclei, expanded interstitial fibrous and fatty connective tissue). Although probably all skeletal muscles are affected, the histologic changes were most pronounced in extraocular, lingual, pharyngeal and diaphragmatic muscles in autopsy findings [11].

When the clinical history, family history and genetic testing are compatible with OPMD, muscle biopsy is currently no longer indicated. However, muscle biopsy may help to clear diagnostic troubles when genetic testing is negative though clinical suspicion is high or when puzzling findings concerning laboratory values (like a creatinine phosphokinase elevation >1000 U/L, a positive ischaemia test etc.) or an unexpected (eg, myotonic) electromyography pattern are present. The detection of a mutation of unknown pathogenic significance may provide another indication for muscular biopsy in order to properly characterise the genotype-phenotype correlation. However, the value of muscular biopsies is essentially dependent on a sufficient amount of muscular tissue in the specimen taken from a clearly affected muscle to avoid sampling error, and on a neuropathologist experienced in ultrastructural examination techniques. The often focal accentuation of the myodystrophic process in OPMD experimentally allows to perform a CT of the clinically most affected part of one limb in order to identify the optimal spot for a muscle biopsy or for neurophysiologcal studies. Typical changes corresponding to muscular fibre loss and fatty degeneration are reported for the semimembranous, semitendinous, and biceps femoris muscles [41].

Table 2.

Overview of OPMD and the differential diagnostically most important diseases with respect to their key features.

disorder	OPMD	myasthenia gravis[1]/LEMS[2]	MMD[1]/ PROMM[2]	Kearns Sayre syndrome[1]/ CPEO[2]	OPDM	late-onset LGMD	IBM	desmin myopathy	myofibrillary myopathies[§] (corresp. to 1,2,3)	late-onset distal myopathies (Welander[1]/ Markesbery[2])	SMA IV[1]/ SBMA[2] feature
ptosis	+	+[1]/+[2] use-dependent[1]	+[1]/(+)[2]	+[1]/+[2]	+	–	–	+	+	– –	((+))[1]/+[2] very rare
dysphagia/ dysarthria	+	+/+ use-dependent[1]	+[1]/ (+)[2]	+/–	+	very rarely	+	+	+	–	((+))[1]/+[2]
proximal weakness	+	+/+ use-dependent[1]	+/+	+/(+)	+ (end-stage)	+	+	+	+[1, 2]/–[3] (at late stage)	(+)	+
cardiac involvement	(+)	–	+[1]/ (+)[2]	+/(+)	–	very rarely	–	+	+[1, 2]/–[3]	–	(+)
neuropathy	(+)	very rare[1]/(+)[2]		very rare	–	–	occasionally	+	+[1]/(+)[2, 3]	–	((+))
other clinical signs	none	use dependent muscular impairment[1]; dysautonomia, hypo-/areflexia; underlying SCLC in ca. 40%[2]	cataracts, diabetes mellitus, hypogonadism, dysmenorrhea, insomnia, hollow temples, stiffness, pain, cholecystitis[1]; less frequent or milder in [2] myotonia[1, 2]	retiniti pig mentosa, ataxia, deafness, (dementia)[1]	prominent distal weakness	hyporeflexia/ areflexia	distal weakness: flexors > extensors; often no pain	respir. failure intestinal hypomotility; fast progression; areflexia	respir. failure[3]; cataracts[2]	arflexia (ankle tendon reflex) at late stage	fascicul.[1, 2], esp. perioral[2], gynecomastia, sensory neuropathy[2]
EMG	unspecific myopathic signs	jitter in SFEMG, decrement of CMAP during repetitive stimulation (RS), ice-pack-test positive[1]; increment of CMAP during RS/exercise[2]	almost pathognomonic spontaneous bursts ("dive bombers, motorcycle") when inserting the needle[1, 2]	normal or unspecific myopathic signs	unspecific myopathic signs	short duration, low-amplitude potentials in proximal muscles	like in polymyositis; sometimes signs of neuropathy	myopathic pattern; complex-repetitive dischargres	myopathic and neurogenic pattern; partly also myotonic	myopathic or mixed neuromyopathic pattern	chronic>>> acute denervation; ENG: red. CMAP, normal SMSV
CK (no: <200)	no/<500	no	<1000[1, 2]	no	no/<800	<1000	<500	<1000	<500	<500	<1500[1]/2500[2]
important lab tests	none/IgA?	positive edrophonium chloride test, anti-AChR-Ab; if neg.: antiMusK-Ab, anti-Titin-Ab[1]; positive anti-N- or P/Q-type voltage-gated Ca^{2+}-channel-Ab[2]	insuline (insensitivity), FSH (elevated), testosterone (low) , γGT (high), IgG, IgM (low)[1, 2]	lactate (may be elevated); CSF protein increased; CSF folate reduced	none	LDH increased (up to 900 U/L)	none	none	none	none	none
ischemia test	no	no/no	no/no	pathologie	no	no	no	no	no	no	no
histopathology	rimmed vacuoles in muscle fibres; "typical" nuclear inclusion biodies: tubulofilamentous of 8.5 nm in diameter variations in fibre size, interstitial fibrosis, fatty tissue replacement	early: unspecific late: atrophy; degeneration of muscular endplate[1]; progressive atrophy and loss of type 1 muscle fibres[2]	myopathic pattern: central nuclei, angulated atrophic hypertrophic or necrotic muscle fibres, fibrosis, fatty tissue[1, 2]	red-ragged muscle fibres impaired activities of muscular cytochrome C oxydases	rimmed vacuoles, variations in fibre size, interstitial fibrosis, fatty tissue replacement	rimmed vacuoles, variations in fibre size, interstitial fibrosis, fatty tissue replacement β_1-laminin red.	rimmed vacuoles (= "inclusions") paired helical structure, amyloid-, tau-, ubiquitin-containing; marked invasion of $CD8^+$T-cells	rimmed vacuoles granulofilamentous desmin depositis next to sarcolemma	myofibrillary structures with amorphous, granular/hyaline structures; vacuolisation; amyloid deposits; signs of denervation present	dystrophic; central nuclei, splitted fibres, increased connective tissue. some[1]/excess[2] of rimmed vacuoles; filaments (15–18nm)	signs of de- and reinnervation; large + small group atrophy of fibre types, along with type grouping. (myopathic)

Table 2 cont.

Overview of OPMD and the differential diagnostically most important diseases with respect to their key features.

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disease onset (yr)	40–50	20–80[1] 30–70[2]	childhood* up to ~35[1]; 20–60[2]; * severe form	5–40/various*	40–75	>50	>(30–) 50	5–50	55–80[1]/30–40[2]/ childhood–50[3]	>(30–) 45[1] >40[2]	mid-30s[1] >30[2]
inheritance	AD/(AR)	very rare[1] acquired[2]	AD[1, 2]	sporadic/ maternal* rarely: AD**	AD/ar/ sporadic	ar	sporadic	AD/ar	AD[1](?)/AD[2]/ AD3	AD[1, 2]	AR (70%)/ AD (30%)[1]; X-linked[2]
genetic defect/ mutated protein	PABPN[1] (minimal expansion of GCG trippletts (>7; 6 are normal)	AChR$_e$receptor subunit/rapsyn[1]; none[2]	DMPK[1] (myotonic dystrophy protein kinase; CTG triplet) ZNF9[2] (zinc finger protein 9; CCTG tetra-nucleotide repeats)	large scale deletions or duplications/ mtDNA point mutations or multiple deletions*, ie ANT1, C10ORF[2], POLG[1]	?	?	?	desmin	myotilin[1] αB-crystallin[2] ?[3]	?[1, 2]	SMN1/SMN2[1] microdeletion or gene conversion[1], androgen receptor gene[2] (CAG triplet expansion 40–65 [17–26])[2] VABP[2]
chromosomal locus	14q11.2–q13	17p/ 11p11.2–p11.1[1]; none[2]; very rarely inherited forms	19q13.3[1]; 3q212	mtDNA (COXIII)/ mtDNA A3243G, C3256T, T4285C, A5692G, C5703T, A12308G, T12311C, G12315A* and 4q34–35, 10q24, 5q25 (nuclear)**	?	?	?	2q35	5q31[1] 11q22.3–q23.12[2] 2q21/2q24–31[3]	2p[1] q31–33[2]	5q13[1] Xq11–12[2]
genetic testing	available	exp.[1]; none[2] (but, test for VGCC-Ab's available)	available[1]; exp.[2]	available for most common mutations	?	?	?	exp.	exp.	exp.	available
prevalence (per 100'000)	1 (up to 1:600 in specific populations)	10–15[1] 0.5[2]	2–14[1,2]	not available (rare)	very rare (not available)	very rare (not available)	0.5 – 1	very rare	very rare	very rare	0.32[1]/2.5[2]

Abbreviations: [§] ie:myotilinopathy[1] / αB-crystallinopathy[2] / myopathies with proximalweakness and early respiratory muscle involvement[3];
Ab: antibody; AChR: acetylcholine receptor; AD: autosomal-dominant; ar: autosomal-recessive; CK: creatinine phosphokinase; CMAP: compound muscle action potential; CPEO: chronic progressive external ophthalmoplegia; esp.: especially; exp.: experimentally; IBM: inclusion body myositis; LEMS: Lambert-Eaton myasthenic syndrome; LGMD: limb-girdle muscular dystrophy; no: normal; MMD: myotonic muscular dystrophy; OPDM: oculopharyngodistal myopathy; OPMD: oculopharyngeal muscular dystrophy; PABPN1: polyadenylate binding protein nuclear-1 gene; PROMM: proximal myotonic myoptahy; red.: reduced; RS: repetitive motor nerve stimulation; SBMA: spinal bulbar muscular atrophy; SCLC: small-cell lung cancer; SFEMG: single fibre electromyography; SMA IV: adult-onset spinal muscular atrophy; SMSV: sensorimotor conduction velocity; VABP: vesicular associated protein B (synaptobrevin)

To date, there are no reports on the use of MRI for planning of the muscle biopsy; however, some centres experimentally use MRI to guide muscle biopsy in order to minimise the extent of sampling errors [reviewed by 42]. Biopsy of the clinically, electromyographically and radiologically most affected and easiest accessible muscle is recommended.

Differential diagnosis

The combination of the cardinal features of slowly progressive late-onset ptosis, dysphagia and dysarthria, proximal limb weakness and a positive family history (figure 3) already allow the diagnosis of OPMD to be made, which can be definitively confirmed by genetic testing. However, if the patient does not present with all the cardinal signs and symptoms (for example, at an early stage) of OPMD, disorders that should be considered for differential diagnosis are shown in table 2 which offers an overview of their key features. The particular muscles involved, histopathology, age of clinical onset, and genetic testing allow to distinguish OPMD from other muscular dystrophies. Clinically, two major differential diagnoses of OPMD to be considered are disorders of neuromuscular transmission, especially MG, and mitochondriopathies, especially, late-onset KSS [43, 44].

Most patients with MG have the typically fluctuating, use-dependent symptoms and signs of muscular weakness and exhaustion worsening towards evening. They usually show good response to acetylcholine-esterase inhibitors and are positive in up to 80% when tested for anti-acetylcholine receptor antibodies. However, there are cases of myasthenia gravis without fluctuating signs and symptoms. Some may have atrophy of limb muscles, some are tested negative for acetylcholine receptor antibodies and respond poorly to anticholinesterase drugs. In this situation, electrodiagnostic testing with electromyography (EMG), repetitive stimulation, and single fibre EMG demonstrating defective neuromuscular transmission may help to corroborate the diagnosis of MG. Additionally, radiological evidence of a mediastinal mass compatible with thymoma supports a diagnosis of MG.

The paraneoplastic LEMS in patients with small cell lung cancer may present with ptosis, dysphagia and prominent proximal weakness [45]. The typical increment or facilitation after exercise or repetitive nerve stimulation and a positive test for antibodies against presynaptic voltage-gated P/Q-type Ca^{2+}-channels allow the correct diagnosis of LEMS [46, 47].

Kearns-Sayre syndrome is a rather rare mitochondriopathy with mainly bulbar myopathy (manifesting as CPEO), often proximal limb weakness, retinitis pigmentosa, and cardiac abnormalities like conduction blocks. Since the different mitochondriopathies often clinically overlap, visceral and stroke-like signs or symptoms, dementia, ataxia, seizures, and lactic acidosis may occur. Protein in the CSF is increased in many of the patients. The syndrome first manifests itself within early childhood and age 20, and has a very serious prognosis; however, some cases start in adult life only and then take a milder course; they can present also with severe dysphagia. These cases were sometimes very difficult to differentiate from OPMD before genetic testing had become available. Muscle biopsies show the typical red-ragged or, at least,

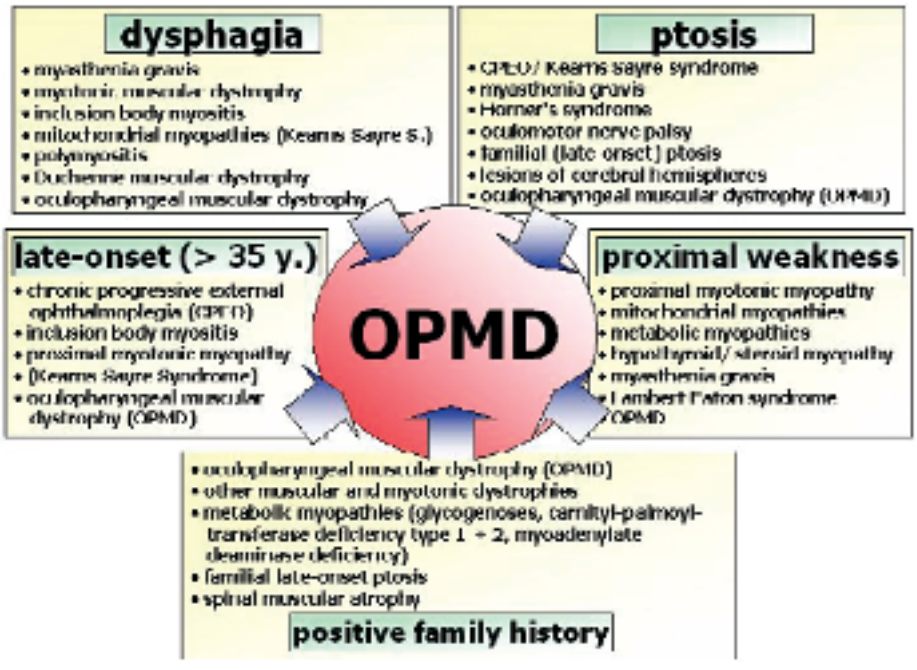

Figure 3

Differential diagnosis of OPMD dependent on its key features (dysphagia, ptosis, proximal weakness, late-onset (>35 y.), and positive familial history).

red-rimmed fibres in KSS whereas the histopathological hallmark of OPMD consists of rimmed nuclear vacuoles and tubulofilamentous inclusions. However (and even more confusing), mitochondrial abnormalities were reported by Wong and colleagues [48]. While OPMD is genetically a well defined autosomal dominantly inherited disease, KSS is almost always sporadic and results from large duplications and deletions of mitochondrial DNA; on the other hand, various point mutations in the mitochondrial genome were sometimes associated with KSS. The syndrome is only rarely inherited in an autosomal dominant way. Linkage analysis indicated predisposition loci on chromosomes 4q34–35, 10q24, and 15q25 but the genetic basis of the disease remains to be elucidated [49–51].

Other differential diagnoses include myotonic muscular dystrophy (Curschmann-Steinert; MD1) [52] and the proximal myotonic myopathy (PROMM; DM2) [53, 54], the oculopharyngodistal myopathy variant [55–58], a very rare late-onset variant of limb-girdle muscular dystrophy with autosomal recessive inheritance [59], sporadic inclusion body myositis [60], desmin myopathy [61–64], different types of myofibrillary myopathies [65–67], late-onset distal myopathies sometimes spreading to more proximal and bulbar muscles [68, 69], and eventually spinal muscular atrophy [70, 71] and X-linked spinobulbar muscular atrophy (Kennedy's disease) [72]. More detailed information on these disorders is presented in table 2. There may be more disorders to be evaluated in the differential diagnosis of OPMD, like polymyositis or the bulbar form of amyotrophic lateral sclerosis [60, 73, 74]. However, ptosis is almost always absent in these diseases.

The group of mainly inherited disorders of lid cleft abnormalities (ie, blepharophimosis, late-onset isolated familial ptosis and extraocular muscle fibrosis) lack dysphagia and proximal weakness, often start to become manifest at very young age, and are frequently associated with other dysmorphous traits.

One of the clinically most valuable observations in patients with OPMD was recently reported by van der Sluijs and colleagues: they noted that more than 40% of their patients complained from limb-girdle weakness as the first symptom of OPMD; thus, OPMD should be included into the differential diagnosis of some forms of the limb-girdle dystrophies, especially at the begin of symptoms [13].

Therapeutic options

Despite significant progress in the understanding of the pathomechanism and genetic background of OPMD, causative treatment is still lacking and there are no reports on drugs effective in OPMD. Thus, the mainstay of therapy consists in symptomatic interventions in order to reduce the impact of muscular weakness leading to ptosis and dysphagia with subsequent malnutrition. While there are almost no established medications to alleviate symptoms, corrective (plastic) surgery interventions on the upper eyelid (blepharoplasty) and on the upper oesophageal sphincter (cricopharyngeal myotomy) have been reported to be effective. Surgical correction of ptosis is indicated when the patient starts to suffer from neck pain secondary to the maximal reclination posture for the compensation of the impaired visual field or when he is esthetically challenged. Two different surgical techniques sometimes dependent on the levator palpebrae function (more/less (4)/8 mm) are currently used [75]: the resection of the levator palpebrae aponeurosis is easily performed in local anaesthesia, but often has to be repeated once or twice because of relapsing ptosis [76]. The fixation of the tarsus at the frontal muscle results in more durable, almost permanent effect, but requires general anaesthesia [75, 76].

Corrective or compensatory interventions of dysphagia are prompted when the patients lose weight, nearly choke or repeatedly suffer from pneumonia. Although there are no prospective studies available and most data were extrapolated analogously to dysphagia in stroke patients, optimisation of the swallowing process (choice of food consistency, positioning of the head, stimulation of pharyngeal sensibility, and strengthening of oropharyngeal muscles) by logopeadic training always should be the first therapeutic step which may result in a subjectively significant improvement for the patient [77]. A high-protein diet was recommended for preventing weight loss and starvation [7, 10]. A Cochrane review about the treatment of swallowing difficulties in non-inflammatory chronic muscle diseases identified no randomised controlled trials. The challenges encountered and the tools needed for a correct evaluation of outcome and benefit of various treatments of dysphagia are analysed in this comprehensive review. Percutaneous gastrostomy might be the most adequate feeding strategy in advanced cases. Additionally, observational studies suggest that people with moderate or severe dysphagia secondary to OPMD could benefit from either cricopharyngeal myotomy or upper oesophageal dilatation [78]. The most favourable results were seen in patients without weight loss and preserved pharyngeal propulsion; contrarily, the intervention should be avoided when aperistalsis is present. About 75–80% of patients benefited from cricopharyngeal myotomy in three series of nearly 300 patients [79–81]. However, these reports have to be read with caution because apart from publication bias

they are from single institutions, the information whether and how long the patients were followed by a neurologist were not clearly specified, and this procedure did not change the final course of the disease. Neurologists caring for patients with neuromuscular disorders may be reluctant to interventions that irreversibly abolish function in a continuously deteriorating neuromuscular disease. Another non-surgical intervention may be tested experimentally: the dilatation of the upper oesophageal sphincter by a Maloney bougie or an achalasia dilator was performed in 14 patients. The procedure yielded a substantial improvement in nine patients (64%) after three months of follow-up and this effect persisted in three patients (21%) for more than 18 months. The intervention showed good feasibility and safety, but further well conducted studies are needed [82].

Therapeutic perspectives

High-dose creatine-monohydrate (initial phase with 5–10 g daily, then tapering to lower maintenance dosage) showed inconsistent effects ranging from no to moderate effect dependent on the type of muscular dystrophy [83–88]. However, creatine monohydrate has not been evaluated yet in patients with OPMD. Steroids may be another therapeutic option since they proved effective in Duchenne muscular dystrophy [89]. As a future perspective from the bench-side, Davies and colleagues elegantly showed in a transgenic mouse model of OPMD that the well known drug doxycycline substantially delayed and attenuated the formation of the typical intranuclear protein aggregates in muscle fibres as a result of its anti-aggregative and antiapoptotic properties [90]. Tetracyclines are an attractive therapeutic option in OPMD since their long-term use seems to be safe as shown for example in patients with acne. Additionally and unlike in other neurological disorders (ie, Huntingtons disease, multiple sclerosis, parkinsonism, etc.) where it has been experimentally tested [91], the drug does not have to cross the blood-brain barrier and should easily penetrate the muscle tissue. Given the availability of genetic testing for OPMD in asymptomatic patients, a "preventive" trial evaluating tetracyclines (doxycycline or minocycline) for the delay and attenuation of symptomatic OPMD is an attractive and clinically important goal.

Conclusions

Oculopharyngeal muscular dystrophy is an autosomal dominant inherited slowly progressive, late-onset, degenerative muscular disorder with currently no causative and only modest symptomatic treatment options.

The disorder is one of the few triplet repeat diseases / polyalanine expansion diseases for which the function of the mutated gene is comparatively well established. As the number of diseases found to be linked to polyalanine expansions steadily increases and there seems to be a pathological overlap with CAG triplet/polyglutamine disorders, further studies of OPMD could potentially lead to a better understanding of a much larger group of developmental and degenerative diseases. Gain of further insight into the molecular and pathophysiologic disease mechanisms will inevitably result in re-classification of many neuromuscular disorders in the not too distant future.

Clinically, the art of medicine in the future will involve bridging the gap between the overwhelming wealth of new information from basic research and the urgent needs of the patients. With regard to OPMD, strategies to block the accumulation of the detrimental INIs at a very early stage may prove essential. Specifically designed new drugs targeting altered molecular pathways as well as already available drugs, such as tetracyclines, represent promising therapeutic avenues to be assessed in prospective clinical trials.

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Correspondence:
Stephan Rüegg MD
Division of Clinical Neurophysiology
Department of Neurology
University Hospitals
Petersgraben 4
CH-4031 Basel
Switzerland
E-Mail: srueegg@uhbs.ch

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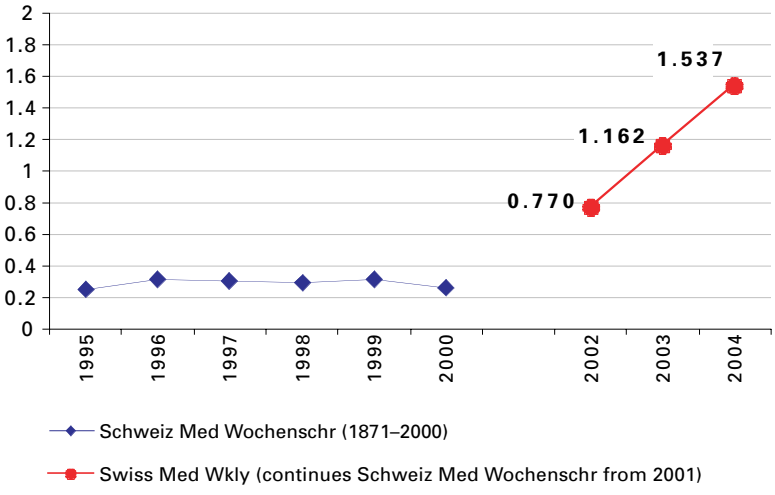

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