OCULOPHARYNGEAL MUSCULAR DYSTROPHY: CLINICAL AND NEUROPHYSIOLOGICAL FEATURES.

Marco Luigetti MD PhD[1], Mauro Lo Monaco MD[1], Massimiliano Mirabella MD[1], Guido Primiano MD[1], Matteo Lucchini MD[1], Mauro Monforte MD[1], Serenella Servidei MD[1].

[1] Dept. Geriatrics, Neurosciences & Orthopedics, Institute of Neurology, Catholic University of the Sacred Heart, Rome, Italy

Introduction:

Oculopharyngeal muscular dystrophy (OPMD) is a late-onset autosomal dominant muscle disorder characterized by progressive ptosis of the eyelids, dysphagia, and muscle weakness in the limbs (Mirabella et al., 2000). Most cases are transmitted in an autosomal dominant fashion, although some occur in a recessive or sporadic pattern (Brais et al., 1999). Autosomal dominant OPMD is caused by short (GCG) 8-13 triplet-repeat expansions in the polyadenylation binding protein 2 (PABP2) gene, which is localized in chromosome 14q11, while autosomal recessive OPMD is caused by a double dose of a (GCG) 7 PABP2 allele (Brais et al., 1999). The histopathologic, molecular, and genetic features of OPMD have become increasingly well-characterized (Mirabella et al., 2000).
Although OPMD is generally considered a muscular pathology, few papers described patients of having clinical and pathological evidence for a concomitant neuropathy. However, the frequency of associated neuropathy varies consistently among different reports from 85% (Hardiman et al., 1993) to 6-7% (Mirabella et al., 2000; Jones and Harper, 2010).

Patients and Methods:

We reviewed neurophysiological reports of OPMD patients admitted at the Neuromuscular Centre of the Catholic University between 2000 and 2013 in order to evaluate electrophysiological pattern, particularly the presence of an associated polyneuropathy. In all patients clinical findings suggested OPMD. Muscle biopsy and genetic analysis confirmed the diagnosis.

Results:

Demographic, clinical and neurophysiological features are summarized in Table 1.

Age at onset varied from 44 to 67 years (mean 54.15, median 53, SD±7.82). The ratio of men to women was 1.6:1 (8/5). Age at neurophysiological examination varied from 55 to 73 years (mean 62.62, median 61, SD±6.73). Ptosis was the main symptom at onset.
With EMG examination, abnormal spontaneous activity was observed in 6/13 patients (46%): fibrillation and positive sharp waves in 6 cases and complex repetitive discharge in 3 cases (31%). The voluntary recruitment revealed a myopathic pattern (early recruitment with small amplitude motor unit potentials [MUPs <200 μV]) in 12 cases (92%), and an additional neurogenic pattern (decreased recruitment with high amplitude [>5 mV] MUPs) in 3 patients (23%), showing a mixed pattern of MUPs.
A sural sensory nerve action of small amplitude was found bilaterally in one case (#4), with no obvious cause other than a possible polyneuropathy. The sural SNAP in all other patients was conspicuously normal, particularly given the average age of our cohort.

Table 1. Demographic, clinical and neurophysiological findings of our cohort.

Case, gender and age at examination	Symptoms at examination	Age at onset	Symptoms at onset	Comorbidities	Sural SNAP (μV)	Tibial CMAP (mV)	Radial SNAP (μV)	EMG (mm)	Abnormal spont. activity		Neurogenic findings	Myopathic findings
									Fibr.; PSW	CRD		
#1M, 60	LL weakness, ptosis, dysphagia	44	LL weakness	HTN, DM, COPD, MI	20	9.4	11	d, bb, vm, ta	absent	-	absent	all muscles
#2M, 69	LL weakness, ptosis, dysphagia	59	ptosis	HCV, arthrosis	21	6.8	11	oo, d, bb, vm, ta	all muscles	-	all muscles	all muscles
#3M, 71	ptosis	68	ptosis	/	15	11.2	8	d, bb	absent	-	absent	absent
#4M, 69	ptosis, dysphagia	50	ptosis	HTN, AF	4	5.9	4	d, bb, vm, ta	bb, ta	ta	ta	bb
#5F, 54	LL weakness, ptosis, dysphagia	48	LL weakness	HTN, breast cancer	13	9.8	11	d, bb, ta	absent	-	absent	d, bb
#6M, 56	LL weakness, ptosis, dysphagia	47	dysphagia	/	21	9.6	14	d, bb, vm, ta	all muscles	ta	ta	all muscles
#7M, 62	ptosis, dysphagia	59	ptosis	HTN	10	9.8	9	oo, d, bb, vm, ta	d, bb, ta	-	absent	all muscles
#8F, 61	ptosis, dysphagia	45	ptosis	COPD, arthrosis	19	11.6	12	d, bb, vm, ta	absent	-	absent	d, bb, vm
#9M, 69	LL weakness, ptosis, dysphagia	67	ptosis	HTN, BPH	15	8.0	8	d, bb, vm, ta	ta, bb	ta, bb	absent	all muscles
#10F, 55	ptosis, dysphagia	53	ptosis, dysphagia	HTN, COPD	20	9.2	13	oo, d, bb, vm	absent	-	absent	all muscles
#11F, 59	ptosis, dysphagia	56	ptosis, dysphagia	/	19	8.4	12	bb	absent	-	absent	bb
#12M, 56	ptosis, dysphagia	50	ptosis	/	20	12.5	12	d, bb	absent	-	absent	all muscles
#13F, 73	LL weakness, ptosis, dysphagia	58	ptosis	HTN, DM	8	6.9	7	d, bb, vm, ta	all muscles	all muscles	absent	all muscles

Abbreviations: M, males; F, female; LL, lower limbs; HTN, hypertension; DM, diabetes mellitus; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; HCV, hepatitis C virus; AF, atrial fibrillation; BPH, benign prostatic hyperplasia; SNAP, sensory nerve action potential; CMAP, compound muscle action potential; mm, muscles; oo, orbicularis oculi; d, deltoid; bb, bicipites brachii; vastus medialis, ta, tibialis anterior; spont., spontaneous; fibr., fibrillation potentials; PSW, positive sharp waves; CRD, complex repetitive discharge. Normal values of SNAP and CMAP amplitude were ≥ 5 μV for sural and radial nerves, and ≥ 5 mV for tibial nerve, respectively.

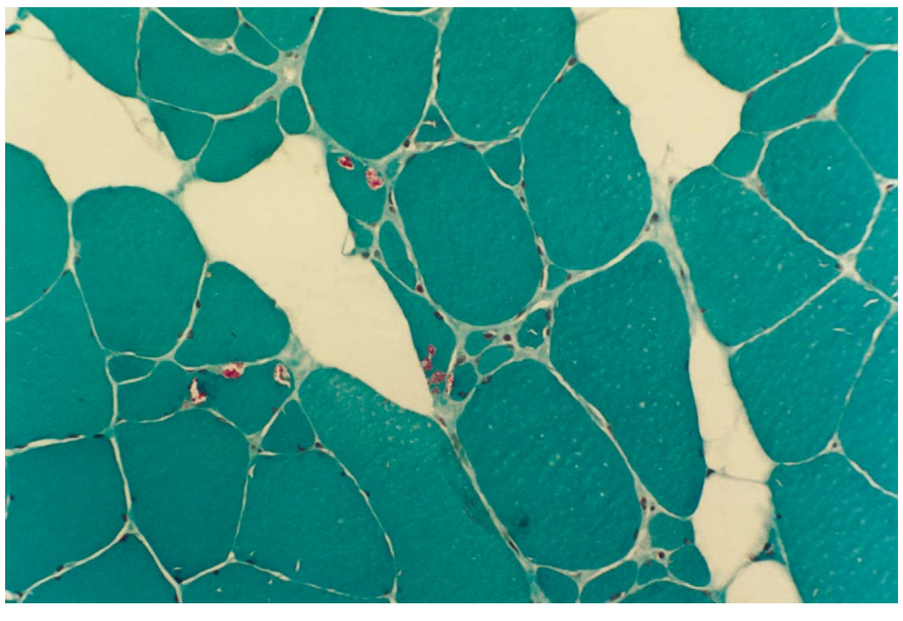

Figure. Cryostat section of a biopsy from deltoid muscle shows variation of muscle fiber size with atrophic and angulated fibers, increased connective tissue and rimmed vacuoles mainly in hypotrophic fibers. Modified Gomori trichrome stain (X250).

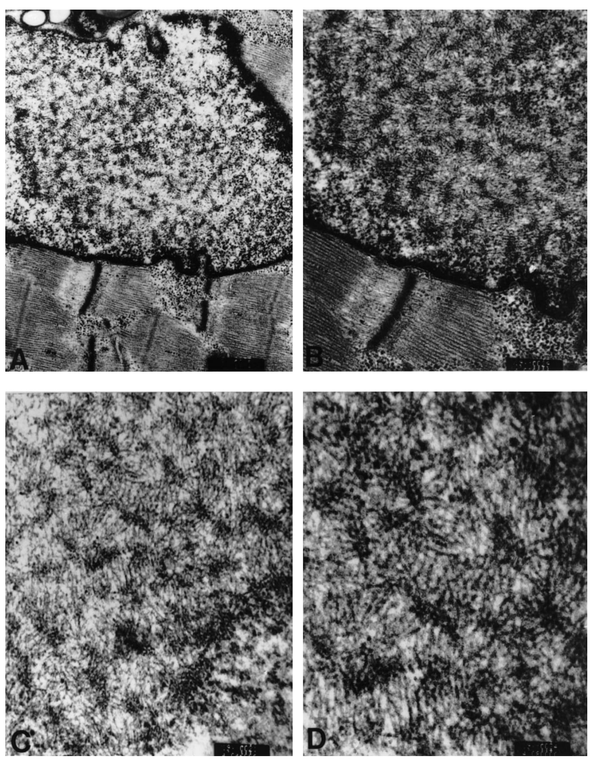

Figure. Biopsy from deltoid muscle. A muscle fiber nucleus containing a large collection of filaments (A, x17,000); at higher magnification (B, x23,000; C, x46,000; D, x80,000) they appear to form tangles or palisades and it is clearly visible in their tubular structure of about 8.5 nm in external diameter.

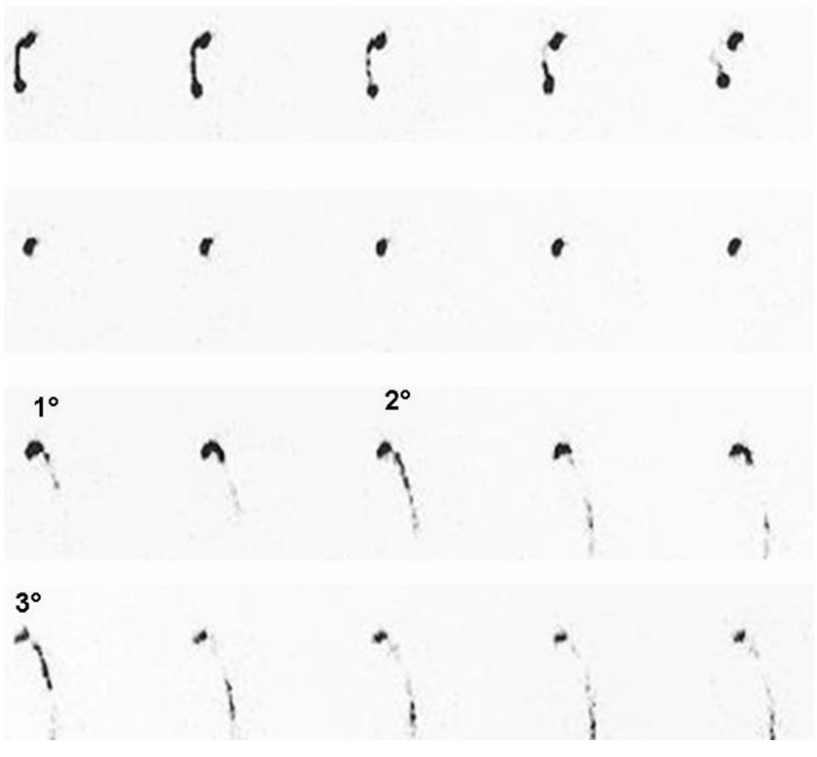

Figure. Oro-Pharyngo-Esophageal Scintigraphy. Dynamic study confirmed a reduction of the suction capacity and normal oral retention of the bolus. Bolus ingestion on command demonstrated greater difficulty in swallowing, which took three non-consecutive deglutitions (1st, 2nd and 3rd), with partial retention of the bolus in the pharynx, due to insufficient glossal and pharyngeal propulsion.

Conclusions:

-Our retrospective analysis confirms that polyneuropathy is not frequently associated with OPMD (Mirabella et al., 2000; Jones and Harper, 2010).

-We also observed in three cases a mixed recruitment: mixed pattern of MUPs has been already described in OPMD (Mirabella et al., 2000) and in other chronic myopathies such as inclusion body myopathy (Blijham et al., 2006).

-Understanding of the spectrum of neurophysiological changes associated with OPMD may help the clinicians to differentiate it from other neuromuscular disorders and to address a correct genetic evaluation, especially in atypical cases or in the absence of a family history.

References:

- Luigetti M, Lo Monaco M, Mirabella M, Primiano G, Lucchini M, Monforte M, Servidei S. Oculopharyngeal muscular dystrophy: Clinical and neurophysiological features. Clin Neurophysiol. 2015 Mar 20. pii: S1388-2457(15)00170-4. doi: 10.1016/j.clinph.2015.03.005
- Blijham PJ, Hengstman GJ, Hama-Amin AD, van Engelen BG, Zwarts MJ. Needle electromyographic findings in 98 patients with myositis. Eur Neurol. 2006;55:183-188.
- Brais B, Rouleau GA, Bouchard JP, Fardeau M, Tomé FM. Oculopharyngeal muscular dystrophy. Semin Neurol. 1999;19:59-66.
- Hardiman O, Halperin JJ, Farrell MA, Shapiro BE, Wray SH, Brown RH Jr. Neuropathic findings in oculopharyngeal muscular dystrophy. A report of seven cases and a review of the literature. Arch Neurol 1993;50:481-488.
- Jones LK Jr, Harper CM. Clinical and electrophysiologic features of oculopharyngeal muscular dystrophy: lack of evidence for an associated peripheral neuropathy. Clin Neurophysiol. 2010;121:870-873.
- Mirabella M, Silvestri G, de Rosa G, Di Giovanni S, Di Muzio A, Uncini A, Tonali P, Servidei S. GCG genetic expansions in Italian patients with oculopharyngeal muscular dystrophy. Neurology. 2000;54:608-614.