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Oculopharyngeal muscular dystrophy in Italy

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Abstract

Oculopharyngeal muscular dystrophy (OPMD) is an autosomal dominant myopathy particularly frequent in Québec. The few Italian cases thus far described with bilateral ptosis, dysphagia and variable muscle weakness, show non-specific dystrophic findings on muscle biopsies by light microscopy. We describe a 70-year-old Italian woman with an adult-onset ptosis, mild dysphagia and proximal muscle weakness belonging to a family segregating OPMD according to an autosomal dominant mode of inheritance. Clinical features of four of her relatives are reviewed. Muscle biopsy studied by electron microscopy showed the typical 8.5 nm in diameter intranuclear filamentous inclusions (INI). To our knowledge, this is the first Italian report of OPMD with INI. The identification of nuclear inclusions is mandatory in order to confirm the diagnosis prior to linkage analysis. © 1997 Elsevier Science B.V.

Keywords: Oculopharyngeal muscular dystrophy; Ptosis; Dysphagia; Intranuclear inclusions; Epidemiology

1. Introduction

Oculopharyngeal muscular dystrophy is an autosomal dominant disease which reveals itself at around the age of 50 with the appearance of two distinct symptoms: bilateral progressive ptosis of the eyelids and dysphagia [1,2], although EMG and muscle biopsies have shown it to be a generalized dystrophy. In fact, as the disease evolves there may be added eye movement impairment, and facial muscle weakness.

Although OPMD is more common in the French-Canadian population probably resulting from a founder effect [2,3], it has a world-wide incidence. A Japanese variant [4] was described with late-onset muscular dystrophy resembling OPMD but associated with selective involvement of the distal limb muscles and, in some cases, with cardiomyopathy [5]. Spanish-American and Eastern European cases with dysphonia, facial muscle involvement, weakness and atrophy of the tongue have also been described [6].

A few cases of OPMD have been reported in Italy. Milleforiori [7] described a family with autosomal dominant inheritance of bilateral ptosis, diplopia, facial muscle involvement and dysphagia. Only later in the disease did proximal muscle weakness appear. Furthermore, psychomotor retardation was observed in an early-onset case. In 1975 [8], an additional family exhibited signs of the French-Canadian type of OPMD. As a matter of fact, two of this family's cases presented an increase in serum IgA and IgG which is in accordance with Barbeau's observations [9]. Vita et al. [10] described a case of familial OPMD with distal muscle weakness in the lower limbs. More recently, Linoli et al. [11] described a sporadic case of OPMD which involved the central nervous system that once again raises a possible neurogenic involvement in OPMD [12–14]. In the above cases, the pathological studies of muscle biopsies, using standard histological and histochemical techniques, showed, in most cases, a non-specific dystrophic process while neurogenic or non-specific changes were noted in others.

Our report deals with the first Italian family to exhibit classical late-onset autosomal dominant ptosis, dysphagia

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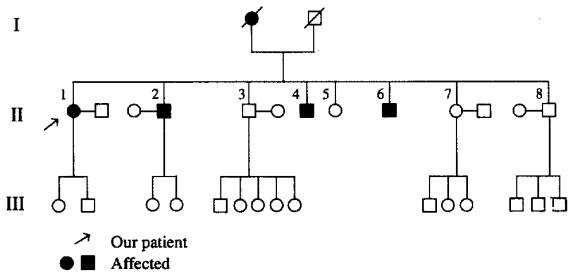

Fig. 1. Pedigree of the Italian OPMD family.

and proximal muscle weakness of variable degree. Furthermore, typical 8.5 nm in diameter intranuclear filamentous inclusions (INI) were demonstrated in muscle biopsy specimens from one family member by electron microscopy. The identification of this first pathologically proven Italian OPMD family opens the way to their inclusion into a molecular genetic study of this disease.

2. Patients and methods

A family with five patients from two generations was investigated and muscle biopsy was performed on patient II-1, as seen on the pedigree (Fig. 1). All family members originate from a small town of central Italy (the Abruzzo region) and some of the proband's relatives (II-3, II-6, II-8) emigrated to Québec after World War II. Clinical features and procedural data are given in Table 1.

Samples of the right deltoid muscle were quick-frozen in isopentane cooled to −160°C in liquid nitrogen, cryostat-sectioned and studied by standard histological and histoenzymologic techniques as previously described [15].

For electron microscopy examination, fragments were fixed in cold 0.1% glutaraldehyde and 2.0% formaldehyde in a 1.12 M sodium cacodylate-HCl buffer at pH 7.3 for a minimum of 2 h, rinsed in a buffer, treated in saturated uranyl acetate for 1 h, dehydrated in graded alcohols and embedded in epoxy resin (Spurr's method).

Semi-thin sections were stained by paraphenylenediamine and/or toluidine blue and examined under light microscope. Thin sections were stained by lead nitrate-sodium citrate and studied by electron microscopy.

3. Results

Patient II-1 is a 70-year-old woman, the oldest member of this family, with a 10-year history of progressive bilateral ptosis which started in the left eye. She never complained of diplopia or dysphagia and she is overweight. Five years ago, she began to experience proximal weakness in the lower limbs and then in the arms.

The neurological examination showed an asymmetrical ptosis of both upper lids (Fig. 2a), but also a partial ophthalmoplegia in all directions, most conspicuous in the upper vertical plane (Fig. 2b–d). A mild weakness of the orbicularis oculi was noted. A mild to moderate muscle atrophy was present and associated with grade 3/5 weakness of the shoulder and pelvic girdle muscles. Rising from a sitting position was only possible with a 'butt-first' maneuver. She is still able to walk short distances unassisted and to climb with the help of a rail a few steps of stairs. Deep tendon reflexes were reduced in all four limbs.

In this family, the mother was symptomatic and died at the age of 77. Four of her eight children are affected (Fig. 1 and Table 1). The onset of the symptoms appears in the sixth decade. The affected members were all examined and presented: (a) an asymmetrical but bilateral, non-fluctuant ptosis; (b) a variable degree of ophthalmoplegia, worse for the elevation of the eyes; and (c) a moderate to severe proximal weakness in the lower limbs. Only two individuals complained of dysphagia, and case II-6, at age 59, was submitted to a myotomy of the upper sphincter of the esophagus in Québec City, where he lives.

The muscle biopsy of case II-1 has shown an increased variability in fiber diameter, an increased number of central nuclei and some rimmed vacuoles located in atrophic fibers (Fig. 3a). An alteration of the oxidative enzyme pattern in small angulated fibers was also observed. The small angulated fibers of both types were not grouped (Fig. 3b). Muscle lipid and glycogen content was normal. The typical INI

Table 1
Clinical data of OPMD patients

Patient	Age	Ptosis	Dysphagia	Proximal weakness[a]	Distal weakness[a]	CK levels (IU)[b]	EMG
I-1	77	Bilateral R > L	Moderate	4/5	4–5/5	Not done	Not done
II-1	70	Bilateral R < L corrected	Mild, absent	3/5	4/5	150	Myopathic
II-2	67	L > R	Moderate	5/5	5/5	170	Not done
II-4	64	L = R	Absent	5/5	5/5	Not done	Not done
II-6	60	L > R	Severe, cricopharyngeal myotomy	3/5	4/5	160	Myopathic

[a]Muscle strength is expressed according to the Medical Research Council (MRC) scale.
[b]Normal value: up to 195 U/l.

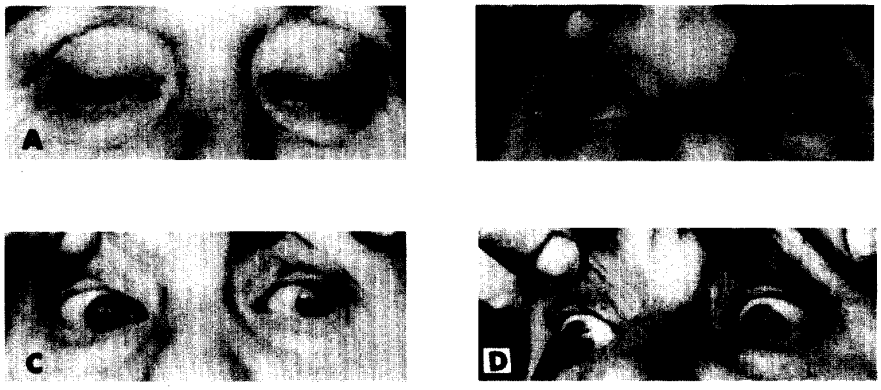

Fig. 2. (a) Characteristic bilateral ptosis: extrinsic ocular movements are reduced upwards (b), to the left (c), and to the right (d) without giving rise to diplopia in this patient.

were seen under electron microscopy (Fig. 4) in about 6% of the muscle fiber nuclei in a given ultrathin section.

4. Discussion

OPMD has a specific histological marker, intermediate-size intranuclear inclusions (INI), made of tubular filaments presenting an outer diameter of approximately 8.5 nm and an inner diameter of about 3 nm [16,17]. These are morphologically distinct from other filamentous structures observed in muscle fibers and, thus far, have been observed in all clinically definite cases of OPMD, not just in French or French-Canadian families [3], but in families of Japanese [18], Bukhara Jewish [19], European, Spanish and South American origins [17,20] as well.

This is the first report of an Italian family with autosomal dominant inheritance of bilateral ptosis and dysphagia with a variable degree of muscle involvement, associated with INI demonstrated by ultrastructural muscle studies. Otherwise, the muscle biopsy of the deltoid muscle was consistent with a dystrophic process.

It has also been suggested that OPMD could have an autoimmune basis because serum immunoglobulin levels were increased in a series of patients, including Italian cases [8]. This was not a constant finding however and in our patient serum immunoglobulin levels were normal suggesting that, when present, they may be secondary to pulmonary infections or other infectious disorder.

Thus far, INI remain the most significant and striking histological change in muscle fibers of OPMD patients described. These inclusions are observed in the Italian family that we have investigated. Immunocytochemical studies with a wide range of well-characterized monoclonal and polyclonal antibodies directed against filamentous proteins (desmin, vimentin, neurofilaments, keratins, laminins, actin, myosin, titin, nebulin, tubulin) fail to label INI and identify the affected nuclei in OPMD [20]. Consequently, the origin and nature of the intranuclear OPMD filamentous inclusions remain unknown. It can be assumed that they represent the expression of an unidentified metabolic disturbance and reflect an intrinsic genetic defect.

Although the significance of these INI is still unclear, their presence is mandatory for diagnosis, especially for those sporadic cases of ptosis and dysphagia or for asymptomatic patients with normal EMG studies and CK levels. Recent molecular studies have shown OPMD linkage on chromosome 14q11.2-q13 close to the region of the cardiac alpha and beta myosin heavy chain genes [21]. The presence of these nuclear filaments in muscle biopsies of more Italian

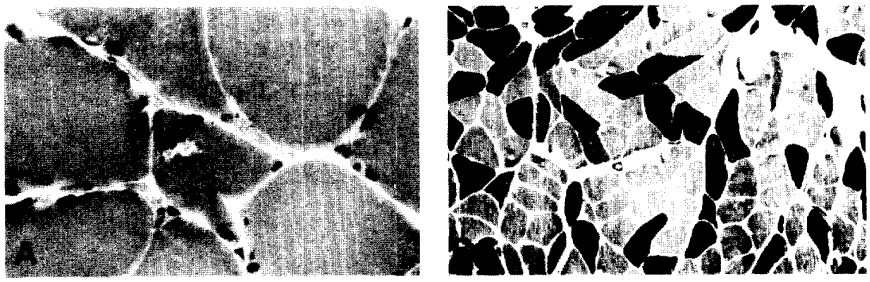

Fig. 3. (a) Central rimmed vacuole in an atrophied muscle fiber shown in a cryostat section. Hematoxylin and eosin (×275). (b) Some atrophied muscle fibers both of type I and II. ATPase after preincubation at pH 9.4 (×110).

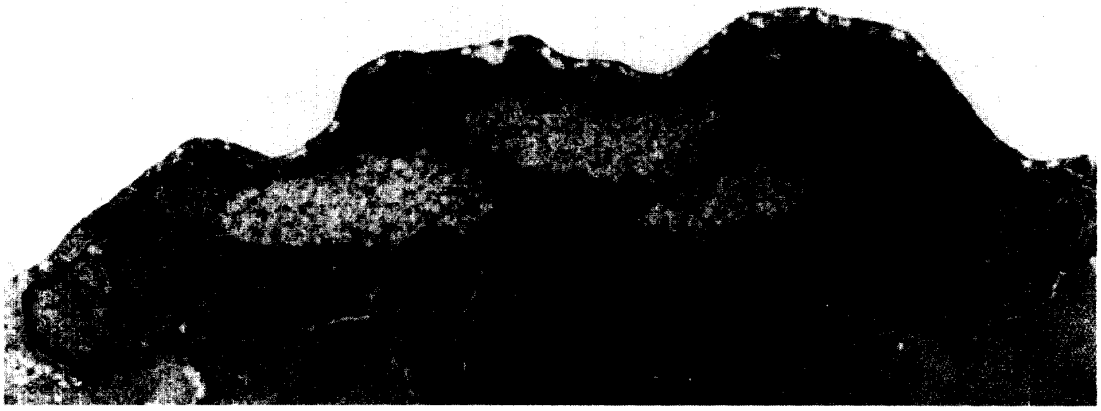

Fig. 4. Subsarcolemmal nucleus presenting clear zones, devoid of chromatin, and containing tubulo-filamentous inclusions. (×17 600).

OPMD families could allow for the selection of a phenotypically homogeneous group of families in linkage analysis. Confirming linkage to chromosome 14q11.2-q13 in our and other non-French-Canadian families will contribute to finding the genetic defect responsible for OPMD.

References

[1] Tomé FMS, Fardeau M. Oculopharyngeal muscular dystrophy. In: Engel A, Franzini-Armstrong C, editors. Myology. New York: McGraw-Hill, 1994:1233–1245.

[2] Griggs RC, Mendell JR, Miller RG. Oculopharyngeal muscular dystrophy. In: Reinhardt RW; Wissler, BM; NcNichols CS, eds. Evaluation and treatment of myopathies. Philadelphia: FA Davis Company, 1995:131–133.

[3] Bouchard JP, Gagné F, Tomé FMS, Brunet D. Nuclear inclusions in oculopharyngeal muscular dystrophy in Québec. Can J Neurol Sci 1989;16:446–450.

[4] Satoyoshi E, Kinoshita M. Oculopharyngodistal myopathy: report of four families. Arch Neurol 1977;34:89–95.

[5] Goto I, Kanazawa Y, Kobayashi T, et al. Oculopharyngeal myopathy with distal and cardiomyopathy. J Neurol Neurosurg Psychiatry 1977;40:600–607.

[6] Weitzner S. Phatosis of the tongue in oculopharyngeal muscular dystrophy: report of two cases. Oral Surg 1969;28:613–615.

[7] Millefiorini M, Filippini C. Oculopharyngeal muscular dystrophy (in Italian). Riv Neurol 1967;37:327–337.

[8] Campanella G, Filla A, Serlenga L, et al. Myopathie oculo-pharyngée: observations histochimiques musculaires et dosage des immunoglobulines du sérum dans une famille italienne. Rev Neurol 1975;131:615–628.

[9] Russe H, Busey H, Barbeau A. Immunoglobulin changes in oculopharyngeal dystrophy. In: Barbeau A, Brunette JR, editors. Progress in neuro-genetics, Vol. 1. Amsterdam: Excerpta Medica, ICS no 175, 1969:62–65.

[10] Vita G, Dattola R, Santoro M, Messina C. Familial oculopharyngeal muscular dystrophy with distal spread. J Neurol 1983;230:57–64.

[11] Linoli G, Tomelleri G, Ghezzi M. Oculopharyngeal muscular dystrophy. Description of a case with involvement of the central nervous system. Pathologica 1991;83(1085):325–334.

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

[13] Schmitt HP, Krause KH. An autopsy study of a familial oculopharyngeal muscular dystrophy (OPMD) with distal spread and neurogenic involvement. Muscle Nerve 1981;4:296–305.

[14] Probst A, Tackmann W, Stoeckli HR, Jerusalem F, Ulrich J. Evidence for a chronic axonal atrophy in oculopharyngeal 'muscular dystrophy'. Acta Neuropathol 1982;57:209–216.

[15] Meola G, Sansone V, Rotondo G, et al. Neural regulation of acid maltase in an unusual adult onset deficiency. Clin Neuropathol 1994;13:286–291.

[16] Tomé FMS, Fardeau M. Nuclear inclusions in oculopharyngeal dystrophy. Acta Neuropathol 1980;49:85–87.

[17] Tomé FMS, Leroy JP, Neville H, et al. Intranuclear tubulo-filamentous inclusions as morphological marker of oculopharyngeal muscular dystrophy (abstract). Muscle Nerve 1986;9(Suppl):212.

[18] Uyama E, Nohira O, Chateau D, et al. Oculopharyngeal muscular dystrophy in two unrelated Japanese families. Neurology 1996;46:773–778.

[19] Blumen SC, Sadeh M, Korczyn AD, et al. Intranuclear inclusions in oculopharyngeal muscular dystrophy among Bukhara Jews. Neurology 1996;46:1324–1328.

[20] Tomé FMS, Gounon P, Collin H, et al. Intranuclear inclusions in oculopharyngeal muscular dystrophy (OPMD): further studies (abstract). Neurology 1989;39(Suppl 1):335.

[21] Brais B, Xie Y, Sanson M, et al. The oculopharyngeal muscular dystrophy locus maps to the region of the cardiac alfa and beta myosin heavy chain genes on chromosome 14q11.2-q13. Human Mol Genet 1995;4:429–434.