Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 25 (2015) 869–872

www.elsevier.com/locate/nmd

Case report

Dropped-head in recessive oculopharyngeal muscular dystrophy

Matteo Garibaldi [a,*], Elena Maria Pennisi [b], Mirella Bruttini [c,d], Veronica Bizzarri [c,d], Elisabetta Bucci [a], Stefania Morino [a], Caterina Talerico [e], Antonella Stoppacciaro [e], Alessandra Renieri [c,d], Giovanni Antonini [a]

[a] *Unit of Neuromuscular Diseases, Department of Neurology Mental Health and Sensory Organs (NESMOS), Faculty of Medicine and Psychology, Sapienza University of Rome, Rome, Italy*

[b] *Department of Neurology, San Filippo Neri Hospital, Rome, Italy*

[c] *Medical Genetics, University of Siena, Siena, Italy*

[d] *Genetica Medica, Azienda Ospedaliera Universitaria Senese, Siena, Italy*

[e] *Anatomical Pathology, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy*

Received 1 February 2015; received in revised form 25 August 2015; accepted 26 August 2015

Abstract

A 69-year-old woman presented a dropped head, caused by severe neck extensor weakness that had started two years before. She had also developed a mild degree of dysphagia, rhinolalia, eyelid ptosis and proximal limb weakness during the last months. EMG revealed myopathic changes. Muscle MRI detected fatty infiltration in the posterior neck muscles and tongue. Muscle biopsy revealed fiber size variations, sporadic rimmed vacuoles, small scattered angulated fibers and a patchy myofibrillar network. Genetic analysis revealed homozygous $(GCN)_{11}$ expansions in the *PABPN1* gene that were consistent with recessive oculopharyngeal muscular dystrophy (OPMD). There are a few reports of the recessive form, which has a later disease onset with milder symptoms and higher clinical variability than the typical dominantly inherited form. This patient, who is the first Italian and the eighth worldwide reported case of recessive OPMD, is also the first case of OPMD with dropped-head syndrome, which thus expands the clinical phenotype of recessive OPMD.

Keywords: Oculopharyngeal muscular dystrophy; Recessive OPMD; Dropped-head

1. Introduction

Oculopharyngeal muscular dystrophy (OPMD) is a late-onset myopathy that has been reported worldwide. It is characterized by eyelid ptosis and pharyngeal muscle involvement, associated with varying degrees of proximal and symmetrical limb weakness, prevalently in the pelvic girdle [1]. Muscle biopsy reveals 'rimmed' vacuoles [2] and characteristic intranuclear inclusions (INIs) within the muscle fibers [3]. The classic form of this disease is caused by a short, stable, dominantly inherited, expansion $(GCN)_{12–17}$ of the wild-type $(GCN)_{10}$ allele, which results in a pathological poly-alanine tract in the polyadenylate-binding protein nuclear 1 gene (*PABPN1*) on chromosome 14q11 [4,5], corresponding to the characteristic nuclear inclusion in skeletal muscle nuclei [6].

The $(GCN)_{11}$ micro-expansion is found in 2% of the healthy population and is carried with the wild-type allele $[(GCN)_{11}/(GCN)_{10}]$ [5,7]. The $(GCN)_{11}$ allele is consistent with a polymorphism, which may act as a phenotype modifier when it is carried in a dominant classic expansion $[(GCN)_{11}/(GCN)_{12–17}]$ [5] or as recessive mutation when it is present in a homozygous status $[(GCN)_{11}/(GCN)_{11}]$ [5]. Both the compound heterozygotes for the dominant mutation and polymorphism $[(GCN)_{11}/(GCN)_{12–17}]$ [5,8] and the dominant homozygotes $[(GCN)_{13}/(GCN)_{13}]$ [5,9] manifest a severe phenotype with earlier disease onset. By contrast, the recessive homozygotes $[(GCN)_{11}/(GCN)_{11}]$ manifest a milder phenotype with a later disease onset [5,10–12].

2. Case report

A 69-year-old woman had progressively worsening drop head in the two years before coming to our attention, associated with a slight difficulty in swallowing liquids and dysphonia in the previous months.

* Corresponding author. Unit of Neuromuscular Diseases, Department of Neurology Mental Health and Sensory Organs (NESMOS), Sant'Andrea Hospital, 'Sapienza' University of Rome, Via di Grottarossa 1035-1039, 00189 Rome, Italy. Tel.: +39 (0)6 33775937; fax: +39 (0)6 33775900.

E-mail address: matteo.garibaldi@uniroma1.it (M. Garibaldi).

http://dx.doi.org/10.1016/j.nmd.2015.08.011

0960-8966/

The patient had one brother and three sisters. Two of her sisters and she had been suffering from schizophrenia since their adolescence. Neither the patient's parents nor her siblings suffered from known neuromuscular disorders though one of the sisters (not examined) had gait disturbances.

At the clinical examination, the patient presented a severely dropped head (Fig. 1). The neuromuscular examination showed severe weakness of the neck extensor muscles (MRC 1/5), mild eyelid ptosis without ophthalmoplegia, bilateral orbicularis oculi weakness (MRC 4/5), mild rhinolalia and dysphagia for liquids. Tongue strength was reduced. Slight symmetrical proximal weakness in both the upper and lower limb muscles (MRC 4/5) was also detected. Both the respiratory and cardiac assessments were normal. Neither the symptoms nor signs fluctuated, and the patient did not complain of fatigue. No signs of abnormal fatigability were detected. The patient died few months after our observation because of respiratory complication related to pneumonia.

The patient's creatine kinase (CK)levels ranged from normal to 2–3-fold normal values. Acid alpha-glucosidase activity tested on peripheral blood sample was normal. The electromyography (EMG) revealed myopathic changes. A neuromuscular transmission disorder was ruled out by normal repetitive nerve stimulation and single-fiber electromyography (SFEMG), negative blood testing for anti-AChR and anti-MuSK antibodies and ineffective treatment with pyridostigmine. T1-weighted MRI sequences revealed fatty infiltration in the posterior neck muscles and tongue (Fig. 1).

An open deltoid muscle biopsy revealed increased fiber size variability with a mild degree of necrosis and regeneration, several small angulated fibers darkly stained with oxidative enzymes and a patchy intermyofibrillar network. Rare small rimmed vacuoles were only present in isolated non-atrophic fibers (Fig. 1). Some ragged red fibers (RRF), devoid of cytochrome c oxidase, were also detected (not shown). No inclusions or glycogen accumulation were present. No inflammatory infiltrates were detected, nor was MHC-I over-expressed. The ultrastructural study was not available.

Based on clinical and neuropathological data atypical OPMD was suspected.

The molecular test was performed on genomic DNA isolated from an EDTA peripheral blood sample using the QiAmp DNA Blood Kit, according to the manufacturer's protocol. OPMD samples and normal controls were analyzed by PCR amplification. PCR products were analyzed by means of the GA 3130 Genetic Analyzer (Lifetechnologies), while the fragment size in the base pair was analyzed by means of GeneScan software.

Our patient displayed a homozygous $(GCN)_{11}/(GCN)_{11}$ genotype confirmed by an independent Sanger sequencing analysis.

In order to rule out the presence of copy number variants (CNVs) in the genome, a whole-genome array CGH analysis was performed using 1500 ng of genomic DNA and a 60 K oligonucleotide array (Agilent Technologies, Santa Clara, CA, USA) according to protocols provided by the manufacturer. The results were visualized by means of the Genomic Workbench software v. 6.5.0.18 and ADM1 algorithm. The results of the

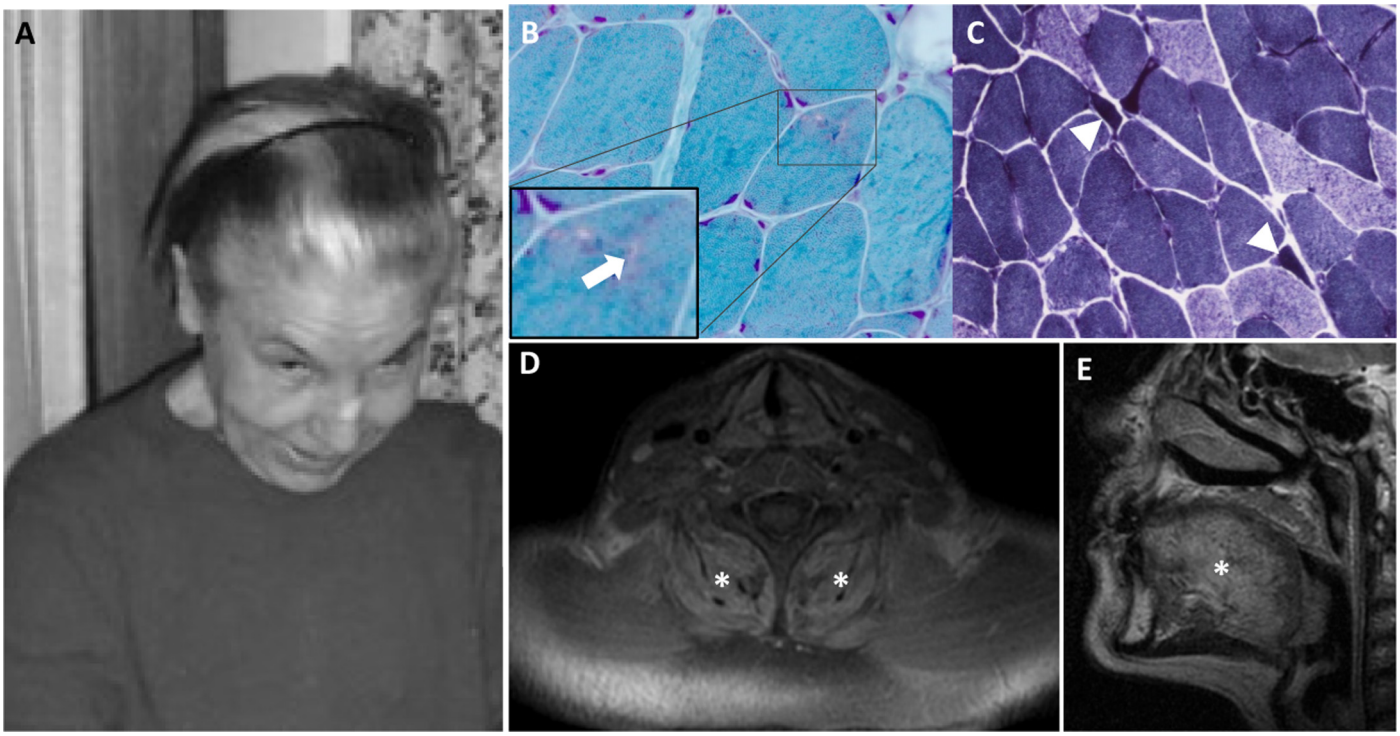

Fig. 1. Index patient (A), small vacuoles in non atrophic fibers with Gomori Trichrome (mGT) stain (B, arrow), angulated darkly stained fibers with reduced nicotinamide adenine dinucleotidedehydrogenase-tetrazolium reductase (NADH-TR) stain (C, arrow heads), fatty replacement of cervical and tongue muscles by MRI (D and E, asterisks).