Oculopharyngeal Muscular Dystrophy Associated with Dementia

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Abstract

We report genetically confirmed heterozygote oculopharyngeal muscular dystrophy (OPMD) accompanied by dementia, suggesting a possible causal association between OPMD and dementia. The proband first noticed bilateral ptosis, dysphagia, and proximal dominant muscle weakness in the lower extremities at age 53. Ten years later, she was found to have dementia with a score of 10/30 on the mini-mental state examination (MMSE). On PABPN1 gene analysis, the GCN repeat was expanded 17 times in one allele. In addition, the proband’s younger brother exhibited myopathy and dementia. To our knowledge, this is the first report of genetically confirmed heterozygote OPMD associated with dementia.

Key words: oculopharyngeal muscular dystrophy (OPMD), heterozygote, expanded PABPN1 (GCN) 17 mutation, dementia

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Introduction

Oculopharyngeal muscular dystrophy (OPMD) (1) is an autosomal dominant muscle disease caused by an increase in GCN repeats in the polyadenylate binding protein nuclear 1 (PABPN1; also called PABP2) gene (2), which is located on 14q11.2-q13 (3). Normally there are 10 GCN repeats, but they are increased 12-17 times in OPMD (4).

The disease usually starts in the fifth decade of life or later, and is clinically characterized by ptosis, mild ophthalmoplegia, dysphagia, and generalized muscle weakness and atrophy. Little attention has been paid to central nervous system (CNS) involvement in OPMD. To our knowledge, two reports have described OPMD patients with mental retardation (5, 6), one with cognitive impairment (7), one with spinal cord involvement (8).

Here, we report genetically confirmed heterozygote OPMD accompanied by dementia.

Case Report

Patient 1 (proband)

A 63-year-old woman without an informative medical history and with no vascular risk factor profiles (e.g., diabetes mellitus, hypertension, smoking) was admitted to the hospital due to symptoms of progressive ptosis, dysarthria, and limb muscle weakness in the lower extremities for 6 weeks before admission. At one point, she had received a diagnosis of progressive supranuclear palsy or myasthenia gravis at another hospital; however, she refused further investigation. According to her husband, her intelligence seemed normal at that time. She had also been suffering from arteriosclerosis obliterans (ASO) with an infection and skin ulcer in the lower extremities for 6 weeks before admission.

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With regard to family history, the father of Patient 1 had generalized muscle weakness and was wheelchair-bound in his fifth decade; he died in his seventh decade. Her three siblings (two brothers, ages 66 and 61, and a sister, age 65), were reported to have muscle weakness, suggesting autosomal-dominant inheritance. Her younger brother (patient 2) was admitted to another hospital at age 45 due to muscle weakness. (Information on patient 2 is provided below.) Her husband did not supply further information about her educational background or cognitive impairment of her family members.

On admission, Patient 1 had gangrene on the bilateral distal lower extremities with ASO. She was conscious and alert. She had to lift her eyelids with her fingers due to marked bilateral ptosis and external ophthalmoplegia (Fig. 1). She also had facial muscle weakness, a nasal voice, dysarthria, and dysphagia, which necessitated the insertion of a nasogastric tube. Diffuse limb muscle weakness and atrophy were noted and respiratory function was normal. Her intellectual level was markedly decreased with severe disorientation in regard to time and place. She also had poor word recall, comprehension, and calculation; her mini-mental state examination (MMSE) was 10/30. Her level of cooperation did not allow further cognitive evaluation.

Blood chemistry was uninformative; values of electrolytes, CK, AST, ALT, thyroid hormones, thiamine, lactic acid, pyruvic acid, acetylcholine receptor antibody, and Jo-1 antibody were all within normal ranges. Arterial blood gas and cerebrospinal fluid were normal. Total tau-protein and amyloid beta protein in the cerebrospinal fluid (9, 10) were also within normal ranges.

On electromyography, the facial muscles, upper extremi-
ties, and diaphragm showed short-duration, polyphasic motor unit potentials with early recruitment. Motor and sensory conduction studies revealed normal results. No epileptiform waves were identified on electroencephalogram. Orbital CT and brain MRI showed no abnormalities (Fig. 2). Hippocampal volume was normal on voxel-based specific regional analysis for Alzheimer’s disease (VSRAD) (11). $^{123}$I-meta-iodobenzylguanidine (MIBG) myocardial scintigraphy (12, 13) did not reveal cardiac sympathetic denervation. Single photon emission tomography (SPECT) with easy Z-score imaging system (eZIS) (14) revealed a decrease in cerebral blood flow at the bilateral parietal and occipital lobe and a relative increase at the bilateral basal ganglia, thalamus, and cerebellum (Fig. 3).

Doppler ultrasonography, enhanced CT, and MRI of the body showed occlusion in the distal abdominal aorta and bilateral common iliac arteries, and arterial flow on the distal portion of her bilateral legs was extremely decreased, indicating Leriche syndrome due to ASO. Doppler ultrasonography of the upper extremities was relatively normal. Concerning the carotid arteries, an intimal-medial thickness at the right common carotid artery was 3.3 mm, and that at the left was 1.7 mm, suggesting mild arteriosclerosis. Axillo-bifemoral bypass was immediately performed, and with written informed consent, a muscle biopsy was taken from the left pectoralis major muscle.

Muscle pathology revealed scattered rimmed vacuoles in addition to fiber size variation (Fig. 4). There were no visible ragged red fibers, cytochrome c oxidase deficient fibers, or strongly succinate dehydrogenase-reactive blood vessels. The analysis of the GCN repeats region in PABPN1 gene by capillary electrophoresis of PCR products revealed 17/10 GCN repeats [(GCG)$_6$ GCA (GCG)$_6$ (GCA)$_3$ GCG]/[(GCG)$_6$ (GCA)$_3$ (GCG)], leading to a diagnosis of OPMD. The two daughters of Patient 1, aged 35 and 32, had normal neurological physical examinations. The other family members were uncooperative and did not agree to gene tests.

**Patient 2 (younger brother of Patient 1)**

Patient 2 developed muscle weakness of the extremities with distal dominance at age 43, and was admitted to another hospital 2 years later, in January 1992. After finishing high school, he worked as a taxi driver. Patient 2 did not give a detailed family history. On admission, he was con-
scious and alert. He did not show any obvious blepharoptosis, external ophthalmoplegia, dysarthria, or difficulty swallowing, but diffuse, mild muscle weakness and atrophy were present. He walked with a waddling gait, and Gowers’ sign was positive. Blood chemistry and cerebrospinal fluid were uninformative. Muscle biopsy from the left biceps brachii muscles revealed scattered fibers with rimmed vacuoles in addition to variation in fiber size, which led to a diagnosis of distal myopathy with rimmed vacuoles (DMRV) at that time. Gene analysis for OPMD had not yet been established. He also had dementia with a total IQ of 72 (verbal 80; performance 68) on the Wechsler Adult Intelligence Scale-Revised. Brain MRI showed no particular abnormalities, but SPECT revealed a diffuse decrease in cerebral blood flow before eZIS was established.

### Discussion

To our knowledge, this is the first report of genetically confirmed heterozygote OPMD with CNS involvement. Patient 2 did not show a typical clinical picture with ophthalmoplegia or dysphagia, but he likely had OPMD, as his muscle pathology was identical to that of OPMD.

The dementia in Patient 1 was likely caused by a unique pathomechanism. Alzheimer’s disease, dementia with Levy bodies, vascular dementia, and metabolic dementia were clinically unlikely and all laboratory indicators for these dementias were negative. The fact that her brother also had similar clinical and pathological manifestations, though genetically unconfirmed, raises the possibility that OPMD and genetically unconfirmed, raises the possibility that OPMD and similar clinical and pathological manifestations, though genetically unconfirmed, raises the possibility that OPMD and similar clinical and pathological manifestations, though genetically unconfirmed, raises the possibility that OPMD and similar clinical and pathological manifestations, though genetically unconfirmed, raises the possibility that OPMD and similar clinical and pathological manifestations, though genetically unconfirmed, raises the possibility that OPMD and similar clinical and pathological manifestations, though genetically unconfirmed, raises the possibility that OPMD and similar clinical and pathological manifestations, though genetically unconfirmed, raises the possibility that OPMD.

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