LAMP-2 Positive Vacuolar Myopathy with Dilated Cardiomyopathy

Seiichiro Sugimoto¹, Kazutaka Shiomi², Ayaka Yamamoto³, Ichizo Nishino³, Ikuya Nonaka¹ and Takekazu Ohi⁴

Abstract

We report a 46-year-old male patient with late-onset vacuolar myopathy and dilated cardiomyopathy. Acid maltase activity of the muscle was normal, but the biopsied muscle specimen stained for lysosome-associated membrane protein-2 (LAMP-2), which has recently been reported to be deficient in muscles of patients with Danon disease. The clinical features of the patient are distinct from X-linked myopathy with excessive autophagy, infantile autophagic vacuolar myopathy and autophagic vacuolar myopathy with late-onset and multiorgan involvement (Kaneda).

Key words: vacuolar myopathy, lysosome-associated membrane protein-2, dilated cardiomyopathy

(DOI: 10.2169/internalmedicine.46.6265)

Introduction

Autophagic vacuolar myopathy has been classified into 3 types: Danon disease (1), X-linked myopathy with excessive autophagy (XMEA) (2) and infantile autophagic vacuolar myopathy (AVM) (3). These myopathies share a unique pathologic feature: vacuolar membranes with sarcolemmal features. In addition to these three well-characterized diseases, there are likely to be more myopathies in this category. One of them is autophagic vacuolar myopathy with late-onset and multiorgan involvement (Kaneda) (4). The vacuolar membranes of them are immunostained with antibodies to various sarcolemmal proteins and have acetylcholinesterase (AChE) and nonspecific esterase (NSE) activities. We report another type of autophagic vacuolar myopathy with sarcolemmal features in 46-year-old man with late-onset myopathy and dilated cardiomyopathy.

Case Report

A 46-year-old Japanese man was admitted to our hospital because of gait disturbance. He had a normal birth after an uneventful pregnancy and delivery. He was a slow runner in a short distance in his childhood. He had a history of right pontine hemorrhage and a resulting left hemi-sensory-motor paresis with soft palatal myoclonus at age 33. At the age of 36, he exhibited a mild gait disturbance. Prior to admission he had fallen down stairs due to weakness of his waist, hips and legs. The patient’s family has a history of intermarriage with both maternal and paternal grandmothers being siblings. However, the family history revealed no neuromuscular disorders except for cerebral hemorrhage suffered by the patient’s father. His older brother is normal and healthy.

On admission, the patient's blood pressure was 118/60 mmHg, pulse 58/min, height 180 cm and weight 68 kg. Head, neck and abdomen were negative. Respiratory sound was vesicular and a third heart sound was detected. On neurological examination, he showed palatal myoclonus, proximal dominant upper limb weakness and lower limb weakness except for calf muscles. Moreover, he showed Gowers’ sign, waddling gait and left hemisensory impairment. He had normal intelligence.

On laboratory examination, creatin kinase (1259 IU/L; normal value 40-167), alanine aminotransferase (52 IU/L; 3-33), lactic dehydrogenase (590 IU/L; 222-401) and aldolase (29.6 IU/L; 4.1-11.8) were elevated. Blood glucose (206 mg/dl; 69-107), triglyceride (238 mg/dl; 37-161) and hemo-
globin A1c (7.8%; 4.3-5.8) were also elevated, but blood cell count was normal. Serum lactate and pyruvate were both normal. The alpha-glucosidase activity in white blood cells was normal (28.5 nmol/mg protein/h; 13.1-46.3). Uric analysis showed no abnormality and creatinine clearance was 107.1 ml/min.

Needle EMG showed short duration and low amplitude motor unit potentials. Nerve conduction studies were normal. Electrocardiogram showed multifocal ventricular premature beats. Echocardiography showed left atrio-ventricular dilatation [LAD (left atrial distance): 78 mm; (normal: 25-40); LVDD (diastolic left ventricular diameter): 58 mm; (39-55); LVDds (systolic left ventricular distance): 48 mm; 21-37; LVWTds (diastolic left ventricular wall thickness): 12 mm; (7-12); LVWTd (systolic left ventricular wall thickness): 12 mm; (11-18); IVSTd (diastolic inter ventricular septal thickness): 9 mm; (6-11)] and increased ejection fraction (40%; 65-88). Cardiac scintigram using MIBG revealed decreased accumulation in the anterior, apex and postero-inferior regions of cardiac muscles. Echocardiography showed normal pulmonary function (vital capacity: 3.30 L, FEV1.0%: 94.3%).

Brain MRI on T2-weighted image showed small high signal intensity area in the right dorsal pons and right ventral medulla oblongata.

Muscle biopsy was performed on the left femoral rectus muscle with the patient’s consent. Light microscopic findings of HE staining of biopsied muscle specimen revealed variable size in the diameter of muscle fiber and slightly rimmed vacuoles (Fig. 1a). These vacuoles were positive for acid phosphatase (Fig. 1b) and positive for periodic acid-Schiff (PAS) (Fig. 1c). These findings slightly mimic those of glycogen storage disease type IIb (acid maltase deficiency). However, the acid maltase level and neutral maltase level in biopsied muscles were both normal [5.2 (7.3 ± 2.2) and 14.2 (18.1 ± 5.1) mmol 4 MU/mg/30min, respectively]. The rims of vacuoles in the specimen were immunostained with anti-dystrophin antibody (Fig. 1d) and had AChE (Fig. 1e) and NSE (Fig. 1f). The clinical features and the findings of muscle biopsy suggested a diagnosis of lysosomal glycogen storage disease with normal acid maltase (Danon disease). However, the muscle specimen was stained with lysosome-associated membrane protein-2 (LAMP-2) antibody (Fig. 1g), which negated the possibility of Danon disease. Furthermore DNA analysis of this case revealed no LAMP-2 genetic mutation (data not shown).

In October 1999 (51y.o.), he was admitted to our hospital again with exertional dyspnea and pretibial pitting edema. General physical findings at the second admission revealed arrhythmia and generalized edema. Routine chest X-ray showed high cardio-thoracic ratio (>60 %) and Carley B line in the lung field. Echocardiography showed left ventricular dilatation (LAD: 41.7 mm; 25-40; LVDD: 63.5 mm; 39-55; LVDs: 58.1 mm; 21-37; LVWTd: 11.2 mm; 7-12; LVWTs: 14.4 mm; 11-18; IVSTd: 9.4 mm; 6-11) and decreased ejection fraction (18%; 65-88). ECG showed couples and triplets of VPC. Cardiac scintigram with MIBG revealed decreased accumulation in postero-inferior, apex and antero-apical region of cardiac muscle, and scintigram with thallium revealed diffuse hypoperfusion in cardiac muscles. Based on these findings, the patient was referred to cardiologists. Cardiac catheter evaluation revealed no stenosis of left or right coronary arteries. Cardiac muscle biopsy was not performed because the patient disapproved. The patient’s congestive heart failure and arrhythmia were then treated with furosemide, imidapril hydrochloride, mexiletine hydrochloride, metprolol hydrochloride and amiodaron hydrochloride resulting in an improvement of the treated disorders.

**Discussion**

Danon disease, which was originally reported as lysosomal glycogen storage disease with normal acid maltase, shows a triad of cardiomyopathy, myopathy and mental retardation (1). Nowadays, it is found that Danon disease is not a glycogen storage disease because glycogen is not always increased and because the primary defect resides in LAMP-2, a lysosomal structural protein rather than a glycolytic enzyme (5, 6). The patient showed late-onset vacuolar myopathy and cardiomyopathy, which suggested the possibility of Danon disease. However, the age of onset of the patient is over 30 and the cardiomyopathy is not the hypertrophic but dilated type. The age at onset of male patients with Danon disease was under 20 and they died before age of 30, with most patients showing hypertrophic cardiomyopathy (7). Furthermore, the presence of LAMP-2 and the absence of the LAMP-2 gene mutation excluded this diagnosis. We did not perform C5b-9 staining of muscle specimen, but cardiomyopathy of the patient excluded XMEA, which is characterized by slowly progressive muscle weakness and atrophy that spares cardiac and respiratory muscles. Infantile AVM, another disease to be differentiated, was definitively excluded by the age at onset of the patient. In 2003, Kaneda et al reported autophagic vacuolar myopathy with late-onset and multiorgan involvement (4). In addition to skeletal and cardiac muscle disorders, their case has retinal pigmentary degeneration, hepatic histological disorder, renal dysfunction, immunoglobulinopathy and accumulation of Gallium-67 citrate in lungs and skeletal muscles. Except for skeletal and cardiac muscle disorders, the patient did not show visual disturbances, renal dysfunction and immunoglobulinopathy. Liver biopsy and Gallium-67 scintiscan were not performed in the patient because of no clinical necessity. Although muscle pathology of the patient showed the character of autophagic vacuolar myopathy, clinical features were distinct from the other known autophagic vacuolar myopathies. The patient showed brain stem hemorrhage at age 33. Two autopsy cases of adult type acid maltase deficiency were reported to show vacuolation of the smooth muscle cells in the media of the cerebral arteries (8). The patient was different from adult type acid maltase deficiency. But vacuolation of the smooth muscle cells in the
Figure 1. Muscle pathology. Mild fiber size variation and intracytoplasmic vacuoles are seen on hematoxylin and eosin staining (a). Acid phosphatase activity is increased in the vacuoles (b). Vacuoles are stained with periodic acid Schiff (c). Vacuolar membrane is immunostained with anti-dystrophin antibody (d). Vacuolar membranes show activities for acetylcholinesterase (e) and nonspecific esterase (f). Immunohistochemistry for lysosome associated membrane protein-2 (LAMP-2) shows the presence of LAMP-2 (g). Bar shows 50 micrometer and b through g are same magnification.

media of the cerebral arteries could be speculated. During five years, cardiac function of the patient severely decreased. Echocardiography showed increased dilatation of left ventricular diameter. Cardiac scintigram with MIBG showed almost no progression during five years, but scintigram with thallium showed diffuse hypoperfusion of cardiac muscles. However cardiac catheterization showed no coronary artery disorders. These facts revealed that dilated cardiomyopathy of the patient gradually progressed for five years. Treatment for the cardiomyopathy was continued and he can now walk by himself.

The present case could not be completely differentiated from that of Kaneda et al. However, late-onset vacuolar myopathy and dilated cardiomyopathy with consanguinity, early onset cerebrovascular disorder and possibly diabetes mellitus may compose one type of autophagic vacuolar myopathy.
References


© 2007 The Japanese Society of Internal Medicine
http://www.naika.or.jp/imindex.html