CASE REPORT

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A histochemical and electron microscopic study of skeletal and cardiac muscle from a Fabry disease patient and carrier

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Abstract Histochemical and electron microscopic studies were performed in an attempt to clarify the muscle pathology in an 18-year-old man with Fabry disease, showing proximal limb muscle atrophy, and his 52-year-old mother, who is a Fabry carrier with hypertrophic cardiomyopathy. Despite the relatively mild myopathic changes revealed by histochemistry, electron microscopy demonstrated the widespread accumulation of abundant lamellated bodies in myofibers, associated with increased glycogen granules and autophagic vacuoles. The cardiac muscle of the proband’s mother revealed a mosaic pattern of normal-appearing and hypertrophic myofibers containing a number of ring-like, lamellated bodies. Although further studies are necessary to support our findings, skeletal muscle is apparently involved in patients with Fabry disease, and a mosaic pattern of cardiac muscle involvement possibly reflecting Lyonization, may be one of the characteristic findings of a Fabry disease carrier.

Key words Fabry disease · Myopathy · Fabry disease carrier · Lamellated bodies · Mosaic pattern

Introduction

X-linked Fabry disease is caused by mutations of the \( \alpha \)-galactosidase A gene at Xq 22 [3, 5, 8]. Defects lead to the systemic accumulation of glycosphingolipids, including ceramide trihexoside (CTH), ceramide dihexoside (CDH), and blood group B substance, primarily in the plasma and in vascular endothelial lysosomes [4]. The most common clinical manifestation in hemizygotes is the onset of pain in the extremities during childhood or adolescence [4, 12, 18, 21, 26]. According to differences in mutations of the \( \alpha \)-gactosidase gene, there are various clinical phenotypes [6, 9, 10]. We describe here a patient with Fabry disease with proximal muscle atrophy; his mother had hypertrophic cardiomyopathy. Histochemical and electron microscopic studies were performed on skeletal muscle of the proband and on cardiac muscle of his mother.

Case report

An 18-year-old boy was apparently healthy until 2 years prior to evaluation, when he experienced the onset of headaches. Varying degrees of headache crises occurred at any time during the day, and analgesics were ineffective. Two months later, cranial computed tomography (CT) scans led to a diagnosis of multiple cerebral infarctions. The exact cause of the headache was not determined. From the age of 17 years, the patient gradually experienced difficulty in running, walking, and writing at normal speeds. His intellectual functions also deteriorated, and he could not complete his senior year of high school. His mother noted that early in his childhood, he had not perspired much, but had never complained of pain in the extremities. Consanguinity was ruled out. A 41-year-old uncle (the brother of his mother) had been on renal dialysis for the last 7 years and twin male, maternal cousins of the proband had been diagnosed as cases of Fabry disease by a pediatrician at another university.

Physical examination on admission revealed palpebral edema, a saddle-nose, xerotic skin, and small scattered angiokeratoma limited to the scrotum. Neurologically, he was alert and his intelligence quotient (IQ) on the Wechsler Adult Intelligence Scale was 70. His tongue movements were slow, and there was a decrease in spontaneous speech. Examinations for neck stiffness and Kernig’s sign both yielded equivocal results. There was moderate proximal-dominant diffuse muscle atrophy in all limbs, but muscle weakness was relatively slight, except for a mild left hemiparesis. Tendon reflexes were hyperactive in all limbs, and pathological reflexes were elicited on his left side. Slight cerebellar limb ataxia, a slow spastic gait, and dragging of the left foot were present. However, sensory function was normal.

Laboratory studies revealed: serum creatine kinase 42 U/l (normal 32–166 U/l); myoglobin, 37.9 ng/ml (normal 15–77 ng/ml); creatinine, 0.5 mg/100ml (normal 0.6–1.2 mg/100ml); and creatine, 0.5 mg/100ml (normal 0.6–1.2 mg/100ml). Cranial CT and magnetic resonance imaging (MRI) revealed a pattern of multiple cere-
bral infarction. The activities of 4-MU-α-galactosidase in the lymphocytes in the proband and his uncle were less than 5% of normal controls. The activity of 4-MU-α-galactosidase A in the leukocytes was 1.16 nmol/mg protein per h (normal, 42.7–260.9).

The proband’s mother had no subjective complaints but electrocardiograms (ECG) revealed inversion and suppression of the T waves and high voltage in leads V4 to V6. An echocardiogram revealed marked hypertrophy of the ventricular septum (17.3 mm) and posterior wall (18.2 mm). The α-galactosidase activity was 12.1 nmol/mg protein per h. A biopsy was performed on the left biceps brachii muscle of the proband, and on the left and right cardiac muscles from the mother, during cardiac catheterization.

Fig. 1 A transverse section of skeletal muscle obtained from the proband stained with hematoxylin-eosin (H&E); a mild variation in the muscle fiber size and round, atrophic fibers can be observed (A). A 1-μm, longitudinal, epon-embedded section of skeletal muscle obtained from the proband and stained with toluidine blue; an osmiophilic mass can be seen at the subsarcolemmal region or in the midst of the myofibers (arrows) (B). Transverse section of the cardiac muscle obtained from the mother and stained with H&E (C) and NADH-tetrazolium reductase (D); hypertrophic fibers with variously sized vacuoles and normal-appearing fibers appear to be mixed. Following PAS staining of the mother’s cardiac muscle, PAS-positive deposits became evident in the midst of the fibers (arrows) (E). A 1-μm longitudinal, epon-embedded section of cardiac muscle from the mother stained by toluidine blue; osmiophilic, ring-like structures are aggregated in clusters with segmental distribution (F). A × 165, B × 250, C × 190, D × 240, E, F × 245