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Severe Elevation of Creatine Phosphokinase and the Development of a Honeycomb Structure in a Patient with Progressive Spinal Muscular Atrophy

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Abstract A 22-year-old man was admitted to our hospital for evaluation of muscle weakness. At the age of 14, he noticed difficulty in running and climbing stairs due to muscle weakness; it progressed gradually with age. On admission, he displayed waddling gait, showed moderately severe muscular atrophy, especially in proximal portion of the extremities, and had decreased tendon reflexes. Serum examination showed severe elevation of creatine phosphokinase. Muscle biopsy specimen revealed neuropathic and myopathic changes, and there were many necrotic fibers. Moreover, honeycomb structures were observed electronmicroscopically. It is extremely rare to observe a severely increased serum creatine phosphokinase activity more than ten time the normal level in progressive spinal muscular atrophy, and this is the first report of honeycomb structure in progressive spinal muscular atrophy. We suggested that severe elevation of creatine phosphokinase and honycomb structures might be due to long administration of phenytoin sodium.

Key Words : Progressive spinal muscular atrophy, Honeycomb structure, Kugelberg-Welander disease, Creatine phosphokinase, Phenytoin

Introduction

Abnormal increases in serum creatine phosphokinase (CPK) activity have recently been observed in patients with motor neuron disease[1,2]. However, patients with neurogenic muscular atrophy rarely exhibit more than ten times the normal level of CPK activity[1]. Moreover, except in some myopathies, tubular aggregates that resemble honeycomb structures are rarely observed[3,4,5].

We experienced a patient with progressive spinal muscular atrophy, presenting with severe increased serum CPK activity and honeycomb structures on electronmicroscope.

Case Report

Our patient was a 22-year-old man who was born to healthy parents at full term. His development was normal. At the age of 14 years, he noticed difficulty in running and climbing stairs due to muscle weakness; this problem gradually progressed with age. There was no consanguinity. In the same year, he began to suffer from generalized cerebral seizures that were treated with phenytoin sodium and carbamazepine. He had been taking 200 mg of phenytoin sodium daily for 8 years prior to hospitalization for

evaluation of the muscle weakness.

On admission, his body weight was 58 kg and his height was 172cm. He displayed waddling gait, showed moderately severe muscular atrophy, and had decreased tendon reflexes. He was unable to rise from a squatting position. Bilateral finger tremor was observed, but sensory and cerebellar disturbances were not detected. There was no dysarthria, dysphagia, or urinary disturbance. Electromyographic investigation showed fibrillation and sharp positive waves and polyphasic and high-amplitude potentials. Nerve conduction velocity was normal. Electroencephalography demonstrated slow- and high-amplitude waves originating in the frontal to parietal regions. Cerebral CT scan and vertebral X-rays were normal. Peripheral blood examination yielded no further examination. The results of analysis were as follows: glutamate oxidative transaminase, 28 IU (normal: 1-20); glutamate pyruvate transaminase, 15 IU (normal: 1-15); lactate dehydrogenase, 42 IU (normal: 130-240); alkaline phosphatase, 29 IU (normal: 44-260); and aldolase, 32.7 IU (normal; 0.7-4.4). Cerebrospinal fluid appeared normal. Serum luteinizing hormone, follicle-stimulating hormone, estrogen, prolactin, and 17-KS were normal. The quadriceps muscle demonstrated fiber size variability, internal nucleoid fibers, group atrophy, pyknotic nuclear clumps, and scattered necrotic fibers with a central vacuole (Fig. 1). Oxidative enzyme activity was centrally increased in the fibers with vacuoles (Fig. 2), shown to be necrotic in longitudinal sections (Fig. 3). These necrotic fibers were observed in both type 1 and 2 fibers. Nemalin rods, ragged red fibers and rimmed vacuoles were not seen. Ultrastructural examination showed separation of myofibrils and widening of the subsarcolemmal space, whorl membranous debri, and tubular aggregates in the form of honeycomb structures (Fig. 4).

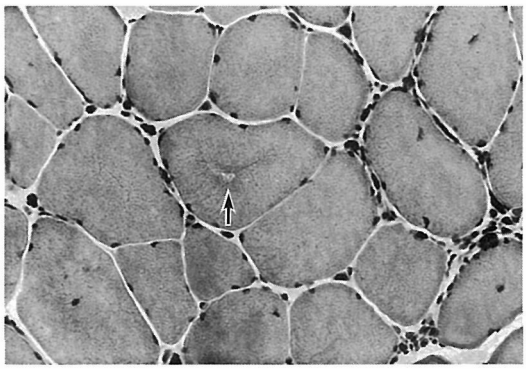

Fig. 1 Hematoxyline and eosin staining showing fiber size variability, internal nucleoid fibers, pyknotic nuclear clumps, fibers with a central vacuole (arrows), and widening of endomysial space. (× 250)

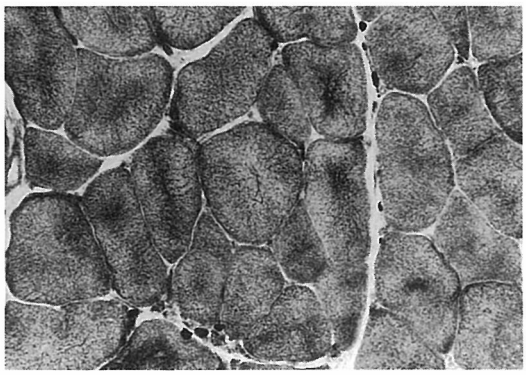

Fig. 2 Histochemical staining of NADH-TR showing the increased activity in or around the center of the muscle fibers. (×250)

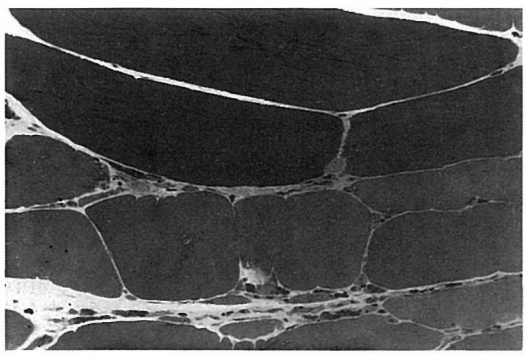

Fig. 3 Longitudinal section of the muscle fibers showing severely necrotic fibers. (toluidin blue, ×250)

Discussion

We diagnosed this patient having a Kugelwerg-Welander disease from the clinical and histological features, if he had a heredity[1].

Pearce et al.[5] reported that serum CPK is useful in differentiating the Duchenne type of dystrophy and other dystrophic states of primary muscle disease from neurogenic muscle atrophy. Elevated CPK has also been found in neurogenic atrophy, and an increase

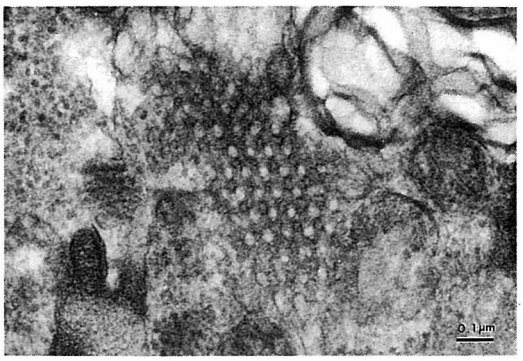

Fig. 4 Electron micrograph showing a honeycomb structure.

in serum CPK has commonly been observed in Kugelwerg-Welander disease[6], amyotrophic lateral sclerosis[1], and progressive spinal muscular atrophy[2]. However, as in our patient, CPK activity rarely exceeds twelve times the normal value. The mechanism of CPK elevation in motor neuron disease is unknown. Some authors have found that patients with increased CPK levels had both denervation atrophy and associated myopathic changes in muscle biopsy samples[1,2]. Our patient also experienced denervation atrophy and myopathic changes, and had many fibers that were centrally necrotic in cross-section and displayed honeycomb structures on electronmicroscope. Honeycomb structures have been seen in patients with alcoholic myopathy[3], or osteomalacic myopathy due to anticonvulsantdrugs[4]. Engel et al.[7] described that the origin of tubular aggregates was not unknown, but they were postulated to be proliferated sarcoplasmic reticulum, and tubular aggregates were formed in response to exogenous endogenous toxins. The diameter of opening, seen circle, of honeycomb structures in our patient was about 300-400 Å, and it is morphologically compatible with reported honeycomb structures[3,4] or tubular aggregates[7]. Therefore, the honeycomb structures of this patient may be composed of sarcoplasmic reticulums, and exogenous toxin, that is phenytoin, may contribute to a formation of them. Moreover, phenytoin may certainly contribute to increased serum CPK activity.

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