Type 2 Fiber Predominance in Patients with Muscle Cramp and Exertional Myalgia

-A Report of Three Cases-

Na Rae Kim, Sung-Hye Park, Yeon-Lim Suh, Byung Joon Kim

Department of Pathology, Kangnam General Hospital Public Corporation, Seoul, Korea; Departments of Pathology and Neurology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; Department of Pathology, Ilsan Paik Hospital, Inje University School of Medicine, Koyang, Korea

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Among the patients with muscle cramps or exertional myalgia, underlying muscular or systemic diseases such as McArdle's disease and rarely tubular aggregate myopathy may be encountered in biopsy findings. However, a significant number of cases with no significant changes in laboratory and biopsy studies have been left undiagnosed. Telerman-Toppet et al. initially described thirteen cases of type 2 fiber predominance in patients with muscle cramp and myalgia. No such cases have been described in Korean literature. Here we report three typical cases and briefly review our observation.

Case Report

Case 1

A 19-year-old man with muscle cramps, stiffness and exertional myalgia for 7 years presented himself. The stiffness was also provoked by cold temperature. The average duration of muscle cramps and myalgia was one to three minutes. Six years ago, he had been stranded while mountain climbing because of an attack of muscle cramps and exertional myalgia. At that time he was rescued by an emergency team. The frequency of the attacks increased, ranging from 5 to 6 times per month. The pattern of paralysis progressed from the upper arm to the lower limbs. The initial clinical impression was periodic hypokalemic paralysis. A muscle biopsy from his vastus medialis was obtained. He was exempt from the military service because of the disease. During the 3 years of follow-up visits, he did well by avoiding vigorous exercises.

Case 2

A 22-year-old male with occasional fasciculation in the thigh...
and calf for 17 years presented himself. The frequency was 5-6 times per month. The cramps and myalgia began from the upper arms down to the lower extremities. Physical examination and laboratory findings were not contributory. He had neither family history of other neuromuscular disorders nor perinatal problems, such as developmental delay. A muscle biopsy was taken from the vastus lateralis. During the 3 years of follow-up periods, he has avoided vigorous exercise and has not complained of severe myalgia during normal life conditions.

Case 3

An 18-year-old male suffering from muscle cramps and exertional myalgia for a 2-year-duration presented himself. Except for a mild ankle contracture, he showed no abnormal findings on physical examination. A muscle biopsy was taken from the vastus lateralis. During the 2 year of follow-up periods, he did well by avoiding vigorous exercises.

In all three cases, the facial expression muscles were spared. Pseudohypertrophy of the calf muscle or true hypertrophy was absent. Sensation and coordination were unaffected. Their Gower signs were negative. Deep tendon reflexes were normal. Full ranges of movement were achieved. Perinatal events or developmental delay was denied. None of the patients had a history of alcohol or medication intake. Physical examination and laboratory findings showed no systemic diseases. Laboratory findings including serum creatine kinase, aldolase, lactate dehydrogenase, electrolytes and the thyroid function test were within the normal range. Blood lactate levels increased during ischemic exercise, which ruled out glycogen storage diseases, such as McArdle’s disease. Electromyograms of the skeletal muscle showed no myopathic or neurogenic discharges. Nerve conduction velocity and Jolly tests revealed no abnormal findings. None of their siblings and parents had histories of exertional cramps and myalgia. Cases 1 and 2 showed no contractures or atrophy of the muscles during their follow-ups. Case 3, who showed a mild ankle contracture, did not display a further progression of ankle contracture.

Biopsied muscle samples were treated as follows: 1) snap-frozen in isopentane pre-cooled in liquid nitrogen, and stored at -80°C until use; 2) placed in formaldehyde fixative and paraffin embedded for routine histology; 3) for conventional transmission electron microscopy (TEM), specimens were fixed in 2.5% glutaraldehyde in 0.1 M phosphate-buffered saline, post-fixed with 1% osmic acid and embedded in Epikote (Epok 812, Oken Shoji, Tokyo, Japan). The thin sections (1 μm) were stained with toluidine blue and Azure B solution to ascertain that the desired cells were in the block. Ultrathin sections were double stained with uranyl acetate and lead citrate, and examined with a TEM (H-7100, Hitachi High-Technologies, Tokyo, Japan). Six-micron cryostat sections were processed, using the usual histologic stains (HE stain, phosphotungstic acid hydrogenase, modified Gomori’s trichrome, and periodic acid-Schiff and enzyme histochemistry (adenosine triphosphatase [ATPase] preincubated at pH 4.3, 4.6, and 9.4, succinyl dehydrogenase, and nicotinamide adenine dinucleotide-tetrazolium reductase [NADH-TR]). Immunohistochemistry using a monoclonal antibody for dystrophin (MS/486/P1, 1:20, NeoMarkers, Fremont, CA, U.S.A.) was also performed.

All three cases showed no significant abnormalities, except for a mild size variation of myofibers (Fig. 1). There were a few scattered small fibers in case 3. Enzyme histochemistry revealed focally increased subsarcolemmal stainability for NADH-TR in cases 2 and 3 (Fig. 2). And the proportion of type 2 fibers was consistently increased in all patients, and accounted for 75% in case 1, 80.2% in case 2, and 75% in case 3 (reference range in quadriceps muscle: 52-70%, Fig. 3). In myofibrillar ATPase preincubated at pH 9.4, there was a marked reduction of type 1 fibers and a subpopulation of type 2 fibers was composed of intermediately and darkly stained fibers. Neither fiber type grouping nor necrotic/regenerative fibers was observed. Ultrastructural examination revealed no significant alterations. Immunohistochemical study showed normal expression of dystrophin along the sarcolemmal membrane in all cases.
Muscle cramps and exertional myalgia are manifestations of various myopathic disorders, either primary or secondary. Sometimes, muscle cramps or exertional myalgia may fail to clarify the underlying cause, despite meticulous investigation of the systemic disease and muscle biopsy. Some patients have even been misdiagnosed as having psychosomatic problems, and referred to the department of psychiatry, and some have remained undiagnosed. In 1985, Telerman-Toppet et al. first introduced the phenomenon of “type 2 fiber predominance” in thirteen patients showing muscle cramp and exertional myalgia, but otherwise no...
abnormalities on examinations. The only pathologic finding was a decrease in the type 1/type 2 ratio, due to the increased proportion of type 2 fibers; 72.91% of type 2 fibers in the affected group versus 59.9% in the control group. Although the inverse relationship existed between ATPase at pH 9.4 and NADH-TR, in myofibrillar ATPase preincubated at pH 9.4, intermediate and dark type 2 fibers were frequently observed, as compared to the usual uniformly dark type 2 fibers observed in normal biopsies. In their report, biopsied muscles for the control study were not restricted to the vastus medialis. All of the reported cases occurred among young men except for two patients aged 42 and 48 years. Familial occurrences have not yet been reported. Unfortunately, follow-up data were not recorded in the report.

The proportions of the myofiber types vary with sites and age. In adults, the proportion of type 2 fibers ranges from 52 up to 70% in the quadriceps, 16-38% in the tibialis anterior, 37-57% in the deltoid, 49-66% in the biceps, and 49-63% in the gastrocnemius. Therefore, a caution must be exercised when myofiber predominance is evaluated. Paraplegia, hemiplegia or hyperthyroidism can also show myofiber type predominance. Usually, paraplegia or hemiplegia reveal predominate type 1 fibers, while hyperthyroidism shows type 2 fiber predominance. In these circumstances, type 2 fiber predominance may result from physiologic fiber type conversion without any physical remodelling of motor units. The pathogenesis of type 2 fiber predominance in muscle cramp and exertional myalgia remains unsettled. Two theories have been suggested. One is that there is a selective deficiency of an oxidative enzyme affecting type 1 fibers and the relative predominance of type 2 fibers, which were presumed to have resulted from fiber switching of type 1 fibers to a glycolytic type 2 fibers. However, in such circumstances rather than type 2 being predominate, hypertrophy of type 2 fibers is common. Second, abnormal stimulation of muscle fibers could be responsible for the conversion from type 1 to type 2 through a modification in the pattern of muscle fiber activation. However, the second theory goes against the fact that determination of fiber type distribution is dependent on innervated nerves. Therefore, these theories are just hypotheses, and the exact pathogenesis has not yet been clarified.

The real existence of this entity is quite doubtful. It is still unestablished as to whether this condition is an independent entity unrelated to other musculoskeletal disorders, because follow-up information is generally incomplete. Furthermore, inadequate sampling or sampling errors of the skeletal muscle should be excluded. A prospective study using a larger series of muscle biopsies is mandatory in order to trace clinical courses of the patients with this disease. For the treatment, proven methods of management have not yet been suggested.

In summary, muscle cramps and exertional myalgia can lead to chronic disability in otherwise healthy patients. However, the definite diagnosis can often hardly be made due to nonspecific or normal neurologic features and muscle biopsy findings. However, to avoid underestimation or misdiagnosis of symptomatic patients and to predict the outcome of this disorder, pathologists’ and clinicians’ recognition of this rare category of type 2 fiber predominance with muscle cramp and exertional myalgia is potentially important.

REFERENCES