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A Case of Adult-Onset Centronuclear Myopathy

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Centronuclear myopathy (CNM) is a rare congenital myopathy that is characterized by centrally placed nuclei in the muscle fibers. Based on the time of onset and the mode of inheritance, CNM can be divided into three distinct forms: the severe neonatal form, the childhood onset form, and the adult onset form. This paper describes the case of a female patient with CNM, in whom the disease manifested itself in the fifth decade of life, without any prior family history of such disorders. To the best of our knowledge, this is a rare case of late adult-onset CNM.

Key Words: Centronuclear myopathy, congenital myopathy, myotubular myopathy

INTRODUCTION

Centronuclear or myotubular myopathies form a clinically and genetically heterogeneous group of disorders that share similar histological features, including centrally placed nuclei in the muscle fiber with hypotrophy of the type 1 fibers. Originally termed as myotubular myopathy, centronuclear myopathy (CNM) is now recognized as a distinct clinical entity. Based on the clinical features, CNM is classified into three forms; the severe neonatal form, the childhood-onset form, and the adult-onset form. In this paper, we report on a case of adult-onset CNM, which to the best of our knowledge is the first such case in Korea.

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CASE REPORT

A 49-year-old woman presented with walking difficulties that began at the age of 48 years. She was born via a full term normal vaginal delivery from a 24-year-old mother who had no specific problems during pregnancy. There was no family history of neurological disease (Fig. 1), and she had no history of drug use including steroids. She had shown no evidence of abnormalities until she was 11 years of age. Since that time, she had felt a slight difficulty in running compared to other children. From the age of 28 years, she experienced a mild difficulty in rising from the sitting position and climbing stairs. However, this weakness had not greatly compromised her daily activity. She noted a mild proximal weakness of both lower extremities when she was 48 years of age. Upon a physical examination, we observed lordosis, Gower's sign, waddling gait, right strabismus, and left facial twitching. There was no sign of pseudohypertrophy, winged scapula, muscle atrophy, or fasciculation. The EKG and chest X rays were normal. A neurological examination revealed no abnormalities in her mental status, cranial nerve function, sensation, or coordination. On the MRC (Medical Research Council) grading, she had mild weakness in her neck (MRC grading 4), both proximal upper extremities (MRC grading 4), and both lower extremities (MRC grading 4). There was no facial weakness, and the deep tendon reflexes were preserved. There was no spasticity, Babinski signs, or ankle clonus. The serum CK was 27 IU/L. The thyroid function test and nerve conduction studies were normal. A

needle electromyography study showed the presence of brief, small, and polyphasic motor unit action potentials on the right biceps brachii, the 1st dorsal interosseus, the vastus lateralis, and the tibialis anterior muscles, and an absence of fibrillation, positive sharp waves, and myotonia. A muscle biopsy was performed in the left biceps brachii muscle. There were fiber size variations, increased internal nuclei including the central nuclei (80%), and a large number of myopathic muscle fibers (Fig. 2). Histochemically, the majority of the muscle fibers were type I (80%), which were smaller than the type II fibers (Fig. 2).

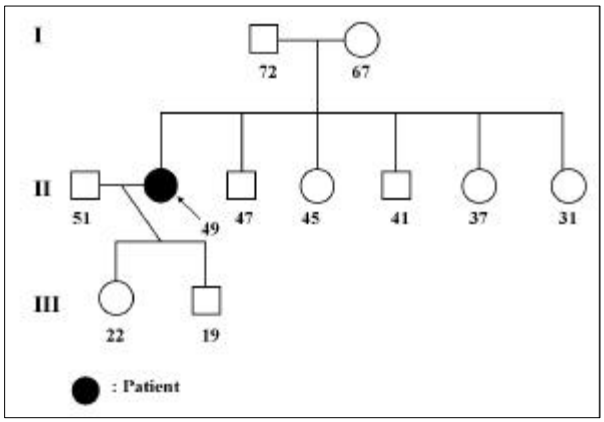

Fig. 1. Pedigree of family.

DISCUSSION

CNM is a rare congenital myopathy, which was first described as myotubular myopathy by Spiro et al.[1] in 1966. They reported the case of an adolescent boy with bilateral blepharoptosis as well as progressive ocular, facial and generalized limb muscle weakness, in whom the central portion of 85% of the muscle fibers was occupied by one or more nuclei lacking myofibrils. The authors suggested that the disease originated from an arrested maturation of the embryonic muscle.

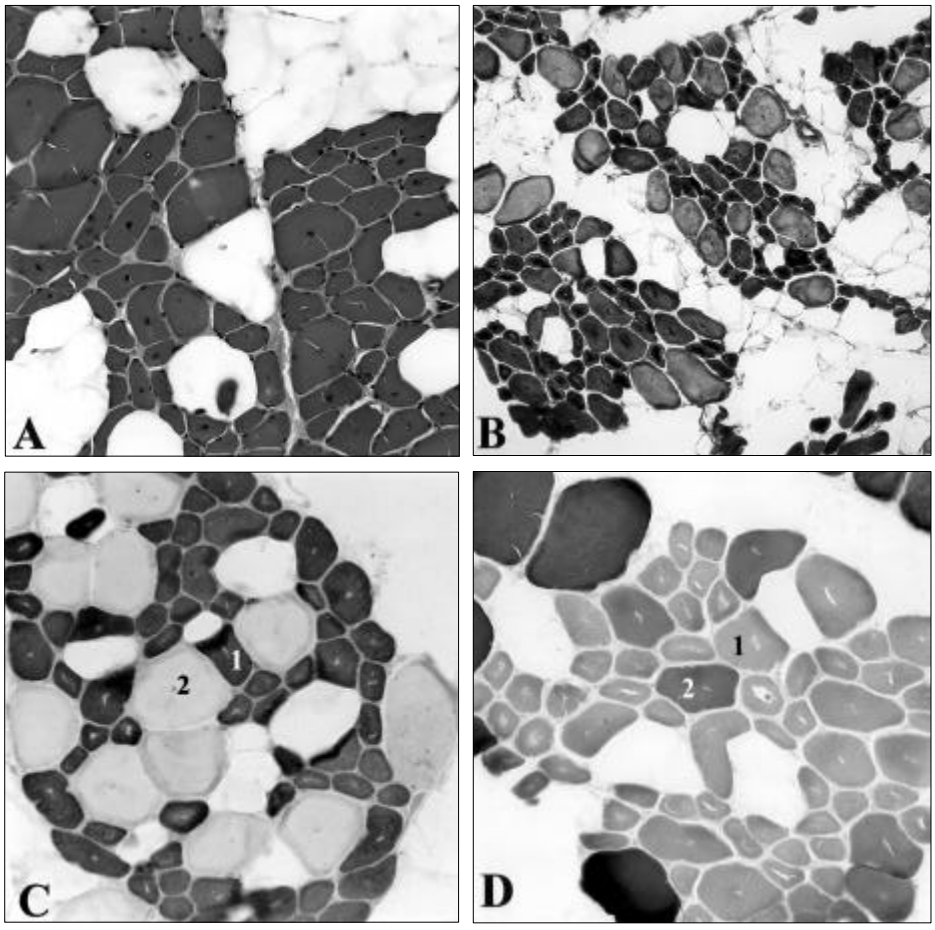

Fig. 2. Pathological findings of muscle biopsy from left biceps brachii muscle. H&E stain shows fiber size variation and central nucleus (A). Histochemical stain shows type II fiber hyptertrophy, type I fiber predominance (80%), and type I fiber atrophy or hypotrophy. (Type I fiber; mean diameter= 31.88 μm, SD=6.82, n=100) (Type II fiber; mean diameter=89.71 μm; SD=13.54, n=60) [B; NADH-Tr, C; ATPase 4.3, D; ATPase 9.4, 1;type I fiber, 2;type II fiber].

Hence, the condition was called myotubular myopathy. The term CNM was introduced to describe the disease in two teenage sisters, who complained of weakness involving the extraocular muscle and impaired motor development.[2] Other denominations have since been used, which include hypotrophy or atrophy of the type I fibers with central nuclei[3,4] and pericentronuclear myopathy.[5] CNM has often been confused with myotubular myopathy. Three forms of the disease were eventually recognized.[6] First, there is a severe, clinically uniform, neonatal form that includes severe hypotonia, and muscular weakness, and causes respiratory failure at birth often leading to early mortality.[7] In this form, the muscular fibers are similar to the fetal myotubes. In addition, there is a recessive X-linked inheritance whose defect was recently identified at Xq28.[8] This form of the disease is presently named X-linked myotubular myopathy. Second, a childhood-onset form, in which the manifestations are observed more frequently in early childhood, is characterized by a slowly progressive diffuse muscular weakness. In this form of the disease, histology shows that the muscle fibers with central nuclei differ from the embryonic myotubes. Third, an adult-onset form fully manifests in the third decade of life, although the incipient clinical signs and symptoms may manifest themselves during the first or second decades.[9] The last form rarely occurs in the sixth decade.[10] Its histological picture is nearly identical to that of the other two forms, but fewer nuclei are restricted to the center of the fiber than in the other two forms of CNM. Most commonly, it is a single nucleus that is affected, but, especially in patients with later onset, a clump of central nuclei is found in some fibers.[11] Opthalmoplegia and bulbar signs are usually lacking in patients with adult-onset CNM, in which ptosis is also rarely present.[9] Our patient showed strabismus, but neither ptosis nor facial weakness. In contrast to the severe neonatal form, the inheritance of the disease is not well defined in the latter two forms, with most cases being sporadic. Nevertheless, an autosomal dominant inheritance may occur in the adult-onset form.[12,13] Both the childhood and adult-onset forms are currently referred to as centronuclear myopathy. The pathogenesis of CNM is unclear. The hypothesis of arrested myofiber maturation is supported by the presence of prenatal myosin isoforms in the muscles from patients with the severe X-linked form of the disease.[14] These isoforms are not found in either the childhood or adult forms of the disease, suggesting that a different pathological mechanism is involved in the autosomal forms. CNM is now recognized as a distinct clinical entity.[15,16] CNM is suspected if the percentage of central nuclei in the muscle biopsy samples is abnormally high (normal range $\leq 3\%$). This suspicion is supported by clinical evidence of facial and limb weakness and the exclusion of other causes of the muscular disorders associated with the central nuclei.[17] Central nuclei are found in the muscle biopsies of patients with inflammatory myopathy, myotonic dystrophy and Charcot-Marie-Tooth disease, and in small amounts in the regenerating fibers of normal muscles.[18] The pathological features of CNM are an increased number of centrally nucleated muscle fibers, a variation in the diameter of the muscle fibers, a type I fiber predominance or atrophy, and a central pallor area of the muscle cell devoid of activity upon reaction with adenosinetriphosphatase (ATPase).[17,19] Herein, we report on a case of adult-onset CNM that fully manifested during the fifth decade of life and for which the muscle biopsy was consistent with the diagnosis of CNM.

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