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CASE REPORT

Distal Myopathy with Rimmed Vacuoles and Cerebellar Atrophy

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Distal myopathies constitute a clinically and pathologically heterogeneous group of genetically determined neuromuscular disorders, where the distal muscles of the upper or lower limbs are affected. The disease of a 41-year-old male patient started with gait disturbances, when he was 25. The progression was slow, but after 16 years he became seriously disabled. Neurological examination showed moderate to severe weakness in distal muscles of all extremities, marked cerebellar sign and steppage gait. Muscle biopsy resulted in myopathic changes with rimmed vacuoles. Brain MRI scan showed cerebellar atrophy. This case demonstrates a rare association of distal myopathy and cerebellar atrophy. (Pathology Oncology Research Vol 12, No 2, 115–117)

Key words: ataxia, cerebellar atrophy, distal myopathy, rimmed vacuole

Introduction

Distal myopathies belong to a clinically and pathologically heterogeneous group of genetic disorders, where the distal muscles of the upper or lower limbs are selectively or disproportionately affected.[4]

Distal myopathy with rimmed vacuoles (DMRV) is an autosomal recessively inherited disorder with preferential involvement of the anterior tibial muscles[8] and spares quadriceps muscles.[7] Its most important clinical sign is atrophy of the distal limb muscles, and it has to be differentiated from other myopathic or neuropathic diseases. Recently the gene was mapped to chromosome 9, the same region as involved in hereditary inclusion body myopathy.[1,7] The disease starts in young adults (20-40 years of age, average 26 years), progressive and most of the patients become unable to walk within 12 years after the onset.[8]

Case report

Our patient is a 51-year-old male. Family history was unremarkable. His father had gait difficulties, but no detailed medical report was available. The patient does not have brothers and children, therefore the appearance of the clinical picture was judged as sporadic.

He was first admitted to Neurology Department at the age of 25, because of gait disturbances. We found mild weakness and atrophy of the distal muscles accompanied by increased muscle tone in calf extensors. He was under neurological control since that time. Few years later mild gait ataxia developed, and he experienced difficulties in writing as well.

Neurological examination at this age revealed rotatory nystagmus in all directions, moderate weakness in distal muscles of all extremities, most pronounced in lower arm extensors and calf flexors *(Figure 1)*. No fasciculation, pseudohypertrophy, contractures and myotonia were present. Sensation was normal. Steppage and atactic gait with increased muscle tone was found. Laboratory examinations were normal, except for elevated creatine kinase (CK) level of 1382-1666 U/l, (normal up to 200 U/l) and lactate dehydrogenase (LDH) 714, (normal up to 400 U/l). Brain imaging (MRI) showed marked brainstem and cerebellar (vermis) atrophy *(Figure 2a)*. Electromyography (EMG) was repeated several times, and showed myogenic alterations in both proximal and distal muscles with decreased duration of motor unit potential (MUP, tested muscles and difference from normal: deltoid -23-60%, abductor pollicis brevis -29.8-58%, anterior tibial -39-67%, rectus femoris -35.4%). Electroneuronography (ENG) showed serious axonal damage of motor fibers in median nerve. No sensory changes were detected. Acoustic evoked potential (AEP) showed diffuse axonal and demyelinating brainstem damage. Visual

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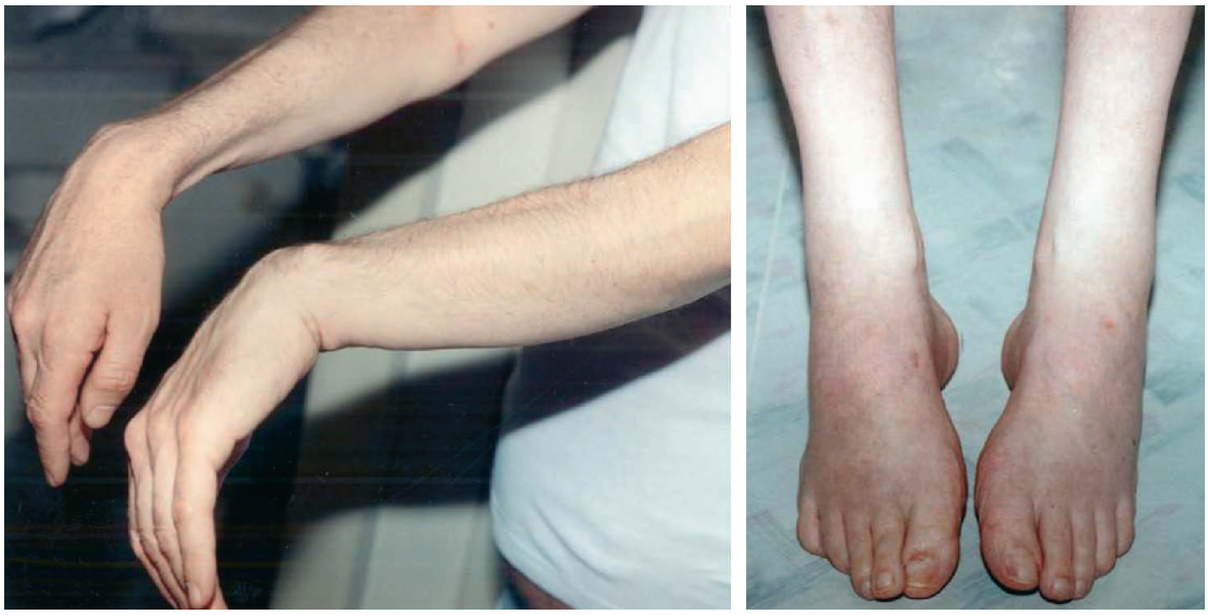

Figure 1. *Atrophy of distal limb muscles*

evoked potential (VEP) revealed bilateral demyelinating lesion of the optic nerve. Somatosensory evoked potential of median nerve (SEP) detected bilateral demyelinating lesion in brainstem and at thalamocortical level. CSF was normal including cell number, protein content and agarose electrophoresis. The following genetic examinations were performed: Frataxin (Fridreich's ataxia), spinal bulbar muscular atrophy (SBMA), spinocerebellar atrophy (SCA) types 1, 2, 3, 6 and 7, dentatorubral-pallidoluysian atrophy (DRPLA), all with normal results.

Skeletal muscle biopsy from anterior tibial muscle revealed myopathic changes. It showed marked variation in fiber size, markedly increased connective tissue, moderately elevated fat content, slightly increased number of central nuclei, many fibers containing rimmed vacuoles, and type 1 fiber predominance (75%) *(Figure 2b).*

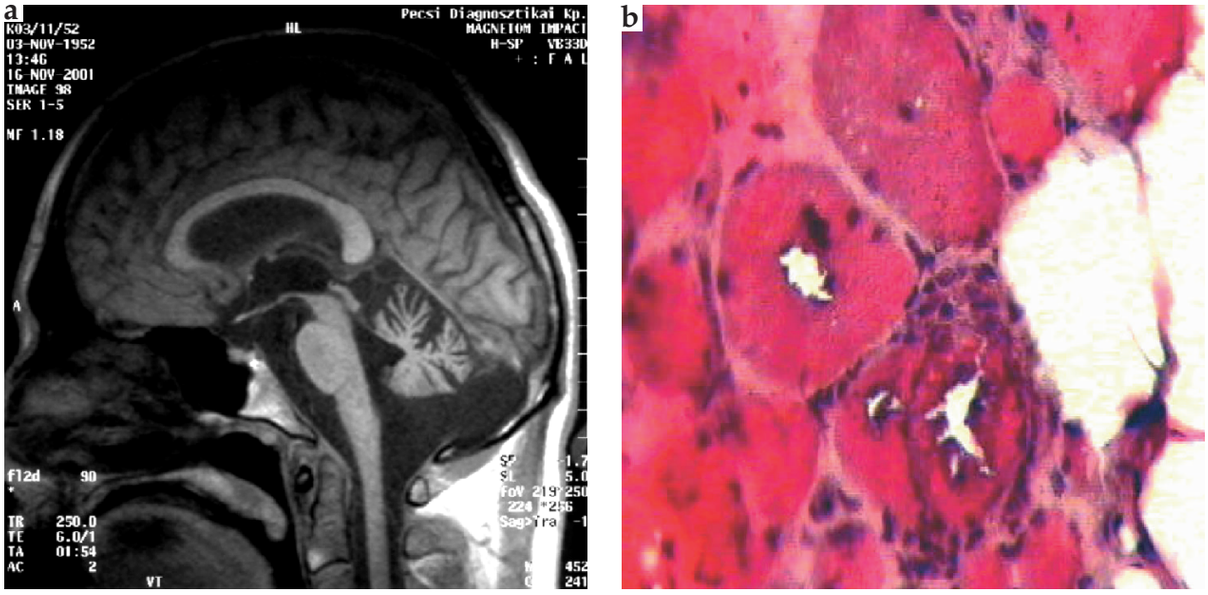

Figure 2. (a) *Severe brainstem and cerebellar atrophy (T1-weighted brain MRI).* ***(b)*** *atrophic fibers and rimmed vacuole formation in the anterior tibial muscle*

The patient was treated with vitamins (B, E) and lipoic acid, but no significant effect was recorded.

Discussion

Distal myopathies are uncommon diseases, therefore, they present difficulties in the classification. Mastaglia et al.[4] distinguished five major forms of distal myopathy (Welander, Myoshi, Finnish/tibial, Nonaka/HIBM2 and Laing). Werneck et al.[10] displayed eight cases of distal myopathy, which had autosomal recessive trait with rimmed vacuole. Kumamoto[2] described three familial cases and one sporadic case of late onset distal myopathy. In the publication of Sunohara et al.[9] the initial symptoms were muscular wasting and weakness in the legs, especially in distal muscles, severe generalized skeletal muscle involvement with sparing of the facial, extraocular, bulbar, intercostal and diaphragm muscles. Nishino et al.[7] examined 27 patients with DMRV, with markedly decreased epimerase activity. DMRV was diagnosed by physical examination, laboratory and histological investigations.

Hereditary inclusion body myopathy (HIBM1) is a rare, autosomal dominant disease involving mainly the distal part of legs.

Rimmed vacuole formation in muscle fibers is not limited to this type of distal myopathy.[5] Beside DMRV, this prominent pathological finding can be seen in inclusion body myositis (IBM), oculopharyngeal muscular dystrophy (OPMD), Marinesco-Sjögren syndrome, reducing body myopathy and rare cases of limb-girdle muscular dystrophy (LGMD 2B) as well. Mizusawa et al.[6] performed an ultrastructural study on muscles in seven patients with DMRV. The earliest changes were focal proliferation of the Golgi's apparatus and mitochondrial degeneration with myofibrillar loss. Later increased number of secondary lysosomes was found, suggesting that an abnormality of the lysosomal system plays an important role in the pathogenesis of DMRV.[3,6]

In our patient neither familial appearance nor inflammatory changes occurred. This clinical picture with peripheral symptoms is very similar to Nonaka type of HIBM, but the cerebellar ataxia is unusual. Genetic examinations excluded the most frequent types of SCA, but other rare types still might be possible. According to our knowledge, no such associations of inherited cerebellar atrophy and myopathy have been reported in the literature. Our case might be a new variant of SCA with DMRV.

References

1. *Ikeuchi T, Asaka T, Saito M, et al:* Gene locus for autosomal recessive distal myopathy with rimmed vacuoles maps to chromosome 9. Ann Neurol 41: 432-437, 1997.
2. *Kumamoto T, Fukuhara N, Nagashima M, et al:* Distal myopathy. Histochemical and ultrastructural studies. Arch Neurol 39: 367-371, 1982.
3. *Kumamoto T, Ito T, Horinouchi H, et al:* Increased lysosome-related proteins in the skeletal muscles of distal myopathy with rimmed vacuoles. Muscle Nerve 23: 1686-1693, 2000.
4. *Mastaglia FL, Laing NG:* Distal myopathies: clinical and molecular diagnosis and classification. J Neurol Neurosurg Psychiatry 67: 703-709, 1999.
5. *Mizusawa H, Kurisaki H, Takatsu M, et al:* Rimmed vacuolar distal myopathy: a clinical, electrophysiological, histopathological and tomographic study of seven cases. J Neurol 234: 129-136, 1987.
6. *Mizusawa H, Kurisaki H, Takatsu M, et al:* Rimmed vacuolar distal myopathy. An ultrastructural study. J Neurol 234: 137-145, 1987.
7. *Nishino I, Noguchi S, Murayama K, et al:* Distal myopathy with rimmed vacuoles is allelic to hereditary inclusion body myopathy. Neurology 59: 1689-1693, 2002.
8. *Nonaka I, Murakami N, Suzuki Y, et al:* Distal myopathy with rimmed vacuoles. Neuromusc Disord 8: 333-337, 1998.
9. *Sunohara N, Nonaka I, Kamei N, Satoyoshi E:* Distal myopathy with rimmed vacuole formation. Brain 112: 65-83, 1989.
10. *Werneck LC, Marrone CD, Scola RH:* Distal myopathies: clinical, laboratory, electromyographic, histologic-histochemical analysis of 8 cases. Arch Neuropyschiatr 51: 475-486, 1993.