Arq Neuropsiquiatr 2003;61(4):946-949

# MYOPATHY OF DISTAL LOWER LIMBS

## The clinical variant of Miyoshi

*Cristiane N. Soares[1], Marcos R.G. de Freitas[1], Osvaldo J.M. Nascimento[2], Lenilda Ferreira da Silva[1], Andréa R. de Freitas[3], Lineu C. Werneck[4]*

ABSTRACT - Miyoshi distal dystrophy is a rare myopathy characterized by an autosomal recessive pattern of inheritance and it is prevalent in Japan. Onset of disease is in early adult life with weakness and atrophy of the leg muscles. Recently gene linkage to chromosome 2p12-14 has been established. We report three sisters, born of consanguineous parents. All of them noticed weakness and atrophy of leg muscles, and could not walk on their heels. In all of them the creatine kinase concentrations were very high. The electromyography showed myopathic patterns and the muscle biopsy disclosed dystrophic changes and an absence of dysferlin. There are few cases reported of Miyoshi distal dystrophy in Latin America. The Miyoshi myopathy may be distinct among the hereditary distal myopathies.

KEY WORDS: distal muscular dystrophy, myopathy, Miyoshi myopathy, dysferlin.

**Miopatia distal dos membros inferiores: variante de Miyoshi**

RESUMO - A distrofia muscular de Miyoshi é doença rara, descrita inicialmente no Japão e de herança autossômica recessiva. Caracteriza-se por fraqueza e atrofia muscular acometendo inicialmente e às vezes exclusivamente a musculatura do compartimento posterior das pernas, com evolução lentamente progressiva. Recentemente verificou-se alteração genética no cromossomo 2p-12-14. Referimos a três pacientes do sexo feminino, irmãs e filhas de pais consangüíneos de primeiro grau. Todas apresentaram como sintoma inicial fraqueza nas pernas com dificuldade para andar, sobretudo na ponta dos pés. A flexão dorsal dos pés estava preservada. Todas exibiam níveis elevados de creatinoguinase. A eletromiografia em todas mostrou padrão miopático. A biópsia muscular revelou alteração da disferlina. Poucos casos de miopatia de Miyoshi são relatados na América Latina. Realçamos seus critérios diagnósticos necessários para o diagnóstico desta afecção dentre as miopatias geneticamente determinadas.

PALAVRAS-CHAVE: distrofia muscular distal, miopatia, miopatia de Miyoshi, disferlina.

Myopathies usually present weakness and proximal atrophy[1,2], involving mainly pelvic and escapular muscles. However, there is a group of rare myopathies with different characteristics that affect specially distal muscles. They can be identified by the following features: autosomic dominant or recessive genetic inheritance, early or late onset distal muscle atrophy, increased creatine kinase (CK) and abnormal muscles biopsy[1,3].

Miyoshi myopathy involves mainly distal and posterior leg muscles, with an early onset and an autosomic recessive inheritance. This myopathy was first described in Japan, in 1967, by Miyoshi and col.[2,4]. It occurs mainly in young adults between 15-30 years old.[1,3], without sex preference[1]. It has an autosomic recessive transmission, with complete penetrance. Difficulty in tiptoeing and climbing stairs is the initial symptom, with involvement of gastrocnemius and soleus muscles[2,5]. There is a slowly progressive weakness and the proximal muscles may be involved lately[3,6,7]. The CK is usually high[1,3-6]. The electromyograhy (EMG) shows a myopatic pattern and the muscles biopsy reveals dystrophic changes without the presence of rimmed vacuoles[1,4]. Recently it has been shown that dysferlin, one of the components of muscular fiber membrane is decreased or absent. Bejaoui and col.[1] studied 20 pedigrees with Miyoshi myopathy emphasinzing the genetic aspect.

Departamento de Neurologia, Hospital Universitário Antonio Pedro, Universidade Federal Fluminense (UFF), Niterói, Brasil: [1]Médica Residente; [2]Professor Titular de Neurologia; [3]Neurologista;[4]Chefe de Departamento de Neurologia do Hospital de Clínicas da Universidade Federal do Paraná, Curitiba PR, Brasil.

Received 10 February 2003, received in final form 11 June 2003. Accepted 4 July 2003.

*Dra. Cristiane N. Soares - Rua Aureliano Coutinho 81/605 - 25625-000 Petrópolis RJ - Brasil. E-mail: mendoncapereira@uol.com.br*

In this disorder there is involvement of chromosome 2p 12-14. It has been also described in USA, Italy, Spain, Germany, The Netherlands[4], Africa[1] and Brazil[2]. In Japan its incidence is approximately from 1 case to 440 000 inhabitants[1], which is similar to hypercalemic periodic paralysis[1,3].

We describe three sisters with Miyoshi myopathy, whose unaffected parents are first degree cousins. The muscle biopsy showed absence of dysferlin.

## CASES

*Case 1*. This is a 30 year old female. She is the oldest of three sisters and manifested weakness of lower limbs at the age of 12 years, with difficulty to run and climb stairs. She had progressive weakness and atrophy of lower limbs and at the age of 25 she could neither walk nor stand without aid. There were weakness and atrophy of the calves (the posterior part of the legs). The proximal muscles were relatively spared. Dorsal flexion of the feet was preserved as well as the strength of upper limbs. The

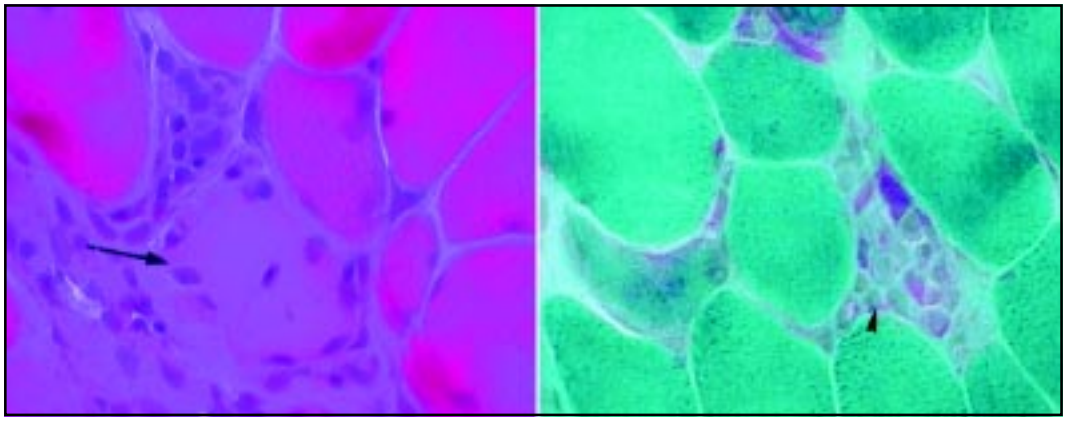

*Fig 1. Case 3. A - Important variation in fiber diameter with round, necrotic and poliedric atrophic fibers (arrow). (H&E 400x) B-Necrosis of fibers in the milddle of the figure (arrow). (TG 400x).*

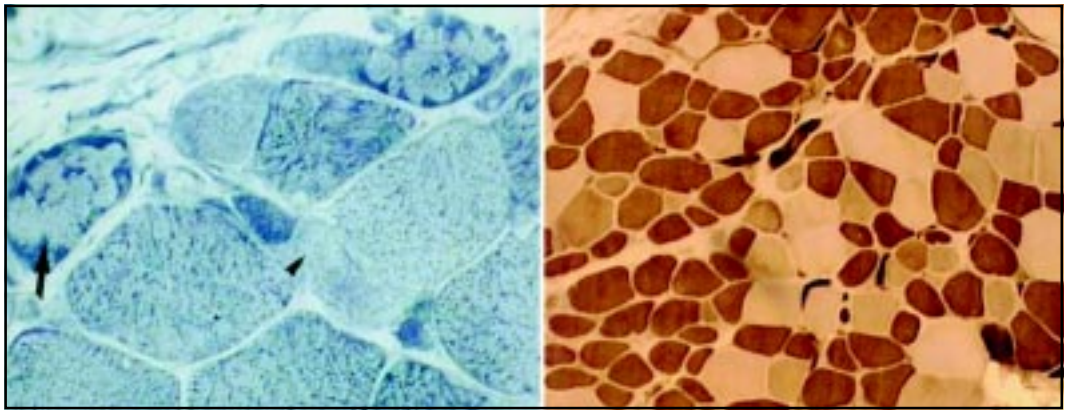

*Fig 2. Case 3. A- Some fibers show focal enlargement, there are two "moth-eaten" (arrow) and a whorled fiber (arrow-head) (NADH-TR 400x). B-Normal type 2 fibers. Predominance of atrophic type 1 fibers (ATPase 25x).*

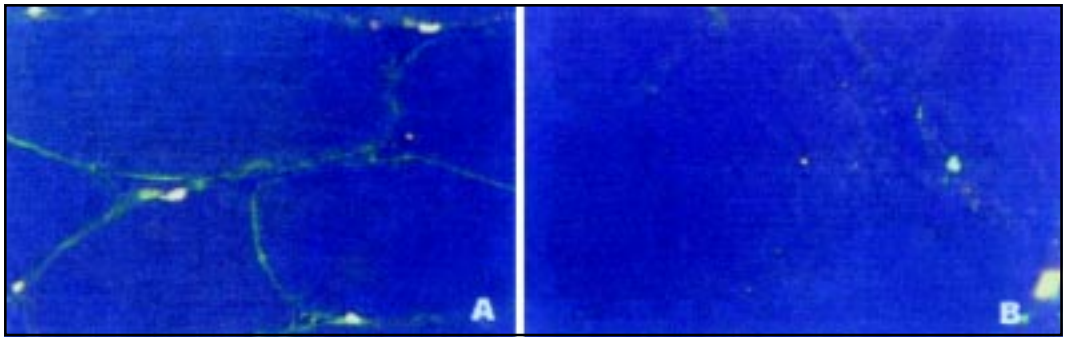


*Fig 3. A-Dysferlin: normal control (100x). B-Case 3. Deficiency of dysferlin (100x).*

tendon reflexes were present and symmetric. The CK was 2850U/l, aldalose 273U/l, LDH 747U/l. The EMG showed a myopathic pattern. The muscle biopsy showed unspecific myopathy characterized by round fibers of different sizes, rare images of necrosis, fibrosis and core centralization.

*Case 2.* A 22-year-old female patient. At the age of 19 she manifested weakness of distal lower limbs, mainly in the right one, with difficulty to tiptoe. The physical examination showed mild weakness in flexion of the feet. The ankle jerks were abolished. The CK was 4905U/l, LHD 505 U/l and liver function, hemogram, sugar, creatinine were normal. The EMG showed myopatic changes: positive waves, incomplete recruitment and polyphasic potential motor unities of short lasting and short amplitude in lower limbs and in deltoid, triceps and brachioradial muscles in upper limbs. The patient refused to have a muscular biopsy as her two sisters had already been tested for it and had confirmed the same diagnosis.

*Case 3.* An 18-year-old female patient presented weakness of lower limbs two years before. She could not run and climb stairs. Physical examination revealed weakness in feet flexion. The patellar and ankle reflexes were mild. Her CK was 4000 U/l, LDH 600 U/l. The EMG showed incomplete recruitment of motor unities and polyphasic potential with short amplitude in gastrocnemius, quadriceps femoris, anterior tibial, triceps and biceps muscles. Biopsy specimen was taken from the left rectus femuris muscle. Cryostat or parafin sections were stained with hematoxylin and eosin (H&E), modified Gomori trichrome (GT), NADH-tetrazolium reductase (NADH-TR) and adenosine triphophatase (ATPase). They showed: variation in fiber size (Fig 1A), presence of some necrotic fibers (Fig 1B), focal enlarged fibers with disruption of intermyofibrillar network pattern ('moth-eaten' and whorled fibers) (Fig 2A) and predominance of type 1 atrophic fibers (Fig 2B). The indirect immunofluorescence test (epi-ilumination) was done with dysferlin antibody from Novocastra, (Newcastle upon Tyne, UK.) (100x). The dysferlin antibody concentration of was 1/10. The sections were of 4 micra thick. There was absence of dysferlin in the fiber membrane (Fig 3). The other immunohistochemical methods (dystrophin, laminin, merosin, sarcoglican) were normal.

## DISCUSSION

We report three sisters with distal Miyoshi's myopathy (MM). All of them had the same phenotype, however there was a difference in the clinical severity. The oldest sister was more severely affected. In all of them the onset was in young ages, between 12 and 19. The main symptom was distal lower limb weakness, with difficulty to tiptoe. In the oldest patient there was a gradual evolution and she could not walk without aid. There was a severe atrophy in gastronemius muscles. This progression has been described in MM and it is the only distal myopathy that begins in the posterior part of the legs . The proximal lower limbs muscles may be involved after many years and the anterior tibial and the peroneal muscles are almost normal[8]. However, it is known that the earlier the onset, the faster is the progression.The inheritance was autosomic recessive: their parents were first degree cousins and they didn't have the disease. Recently it has been described that MM is due to the absence or decrease of a protein in the muscles membrane called dysferlin. The function of this protein of 273k DA, made of 2080 aminoacids is unknown, but it might function in calcium mediated membrane fusion or trafficking[5,7,9,10]. The coding for dysferlin has 55 exons and its mutation would probably due to a change in one nucleotide[9]. The limb girdle muscular dystrophy 2B (LGMD 2B) has the same dysferlin locus than MM[9]. Meugfatt and col described a new method to differenciate MM from LGMD 2B. In the MM there is a lack in blood dysferlin, as it exists in monocytes. The technique would permits a less invasive, faster and cheaper diagnosis and allows to quantify dysferlin levels when new treatments would be tested[9]. The high levels of CK in MM is due to great muscular lesion. Miyoshi and col and Barohn[8,11] reported high level of this enzyme in asymptomatic patients' relatives. Probably they were pre-clinical individuals or were heterozigotics. Besides enzymatic increase, the EMG also confirms myopatic pattern with brief lasting potential, with small amplitude and poliphasic potentials. Although fibrilation discharges have been described in this illness, that's not the pattern that usually happens. The imunocitochemistry on muscle biopsy performed in one of our patients showed absence of dysferlin in muscle membrane. There were also necrosis and phagocytoses in few fibers. These dystrophic characteristics with fiber necrosis and regeneration without the presence of vacuoles have been revealed in other cases of MM[12,13]. There are other distal myopathies that look like MM. They can have dominant or recessive autosomic patterns. The Nonaka's myopathy is a recessive autosomic disorder with the onset in young adults. This myopathy shows weakness in feet dorsiflexors muscles and toe extensors (fallen feet). The CK is high and on muscle biopsy there are rimmed vacuoles, focal myofibrilar destruction and autophagocytoses[14]. The lysossomal system is activated with myofibrilar destruction that cleans the destroyed material[13]. The vacuoles are surrounded by a granular basofilic material[13].Among dominant autosomic distal myopathies, the myopathy described by Lisa Welander[15,16] is the most

common hereditary distal muscle disorder. It is a dominant autosomic disease with the onset in the later adult age with weakness and atrophy of feet and toes extensors. The anterior tibial is the most affected[15]. The CK is almost normal and there is no genetic known location. Muscular biopsy shows dystrophic pattern, often with rimmed vacuoles and no inflammatory infiltration[15]. As well as Welander's myopathy, the Markesberg-Grigg's myopathy or tibial muscular dystrophy[13] begins in the later adult age, with weakness in the anterior leg muscles. The CK is normal or slightly elevated. In this disease the frozen muscle biopsy shows unique or multiple fiber muscles vacuoles .Another distal autosomic dominant myopathy is the form described by Lang and col. In this disorder there are weakness in the anterior leg muscles and in neck flexors with the onset in childhood. Genetic location is in chromosome 14q11[17]. The CK is slightly high and there are no vacuoles in the muscular biopsy.

Other distal myopathies are the inclusion body myositis, myotonic dystrophy and some metabolic myopathies. However they have distinct clinical and histological features.

In our cases all sisters were affected and the parents were first degree cousins. The absence of dysferlin in muscle confirm the diagnosis of MM. In Brazil[2] and Latin America there are only five cases described of MM. We think that in patients with hereditary distal muscle weakness it is mandatory to perform genetic tests and muscle biopsy with immunohistochemical techniques.

## REFERENCES


1. Bejaoui K, Hirabayashi K, Hentati F, et al. Linkage of Miyoshi myopathy (distal autosomal recessive muscular dystrophy) locus to chromosome 2p12-14. Neurology 1995;45:768-772.
2. Werneck L, Marrone CD, Scola RH. Distrofias musculares: análise clínica, laboratorial, eletromiográfica, histológico-histoquímica de oito casos. Arq Neuropsiquiatr 1993;51:475-486.
3. Flachenecker P, Kiefer R, Naumann M, Handwerker M, Reichmann H. Distal muscular dystrophy of Miyoshi type: report of two cases and review of the literature. J Neurol 1997;244:23-29.
4. Linssen WHJP, Notermans NC, Van der Graaf Y, et al. Miyoshi type distal muscular dystrophy: clinical spectrum in 24 patients. Brain 1997;120:1989-1996.
5. Aoki M, Liu J, Richard I, et al. Genomic organization of the dysferlin gene and novel mutations in Miyoshi myopathy. Neurology 2001;57:271-278.
6. Griggs RC, Markesbery WR. Distal myopathies. In Engel AG, Franzini-Armstrong C (eds). Myology. New York Mc Graw Hill 1994:1246-1257.
7. Matsuda C, Aoki M, Hayashi YK, Ho MF, Arahata K, Brown RH Jr. Dysferlin is a surface membrane associated protein that is absent in Miyoshi myopathy. Neurology 1999;53:1119-1122.
8. Miyoshi K, Kawai H, Iwasa M, Kukasa K, Nishino H. Autosomal recessive distal muscular dystrophy as a new type of progressive muscular dystrophy. Brain 1986;109:31-54.
9. Mengfatt H, Gallardo E, McKenna-Yasek, De Luna N, Illa I, Brown RH Jr. A novel blood based assay for limb girdle muscular dystrophy 2B and Miyoshi myopathy. Ann Neurol 2002;51:129-133.
10. Illarioshkin SN, Ivanova- Smolensaya IA, Greenberg CR, et al. Identical dysferlin mutation in limb girdle muscular dystrophy type 2B and distal myopathy. Neurology 2000;55:1931-1933.
11. Barohn RJ, Miller RG, Griggs RC. Autosomal recessive distal dystrophy. Neurology 1991;41:1365-1370.
12. Nonaka I, Murakami N, Suzuki Y, Kawai M. Distal myopathy with rimmed vacuoles. Neuromusc Disord 1998;8:333-337.
13. Cupler EJ, Bohlega S, Hessler R, Mc Leau D, Stigsby B, Ahmad J. Miyoshi myopathy in Saudi Arabian: clinical, eletrophysiological, histopatological and radiologic features. Neuromusc Disord 1998;8:321-326.
14. Barohn RJ, Amato AA, Griggs RC. Overview of distal myopathies : from the clinical to the molecular. Neuromusc disord 1998;8:309-316.
15. Borg K, Ahlberg G, Anvret M, Edstrom L. Welander distal myopathy: an overview. Neuromusc Disord 1998;8:115-118.
16. Udd B, Haravuore H Kalimo H, et al. Tibial muscular dystrophy- from clinical description to linkage on chromosome 2q3l. Neuromusc Disord 1997;7:256-260.
17. Zimprich F, Djamshidian A, Hainfellner JA, Budka H, Zeitlhofer J. An autosomal dominant early adult onset distal muscular dystrophy. Muscle Nerve 2000;23:1876-1879.