



Case Report

Phenotypic Variation in Dysferlinopathy

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Abstract

Mutations in the dysferlin gene cause distinct phenotypes of muscular dystrophy known by the term “dysferlinopathy”. Nowadays, four subtypes of dysferlinopathies have been established: limb-girdle muscular dystrophy 2B (LGMD 2B), Miyoshi myopathy (MM), distal anterior compartment type and scapulo-peroneal type.

We report a girl with dysferlinopathy with an unusual involvement of muscles in lower extremities and her brother whose symptoms started after the diagnosis of his sister.

Both of them had lower limb weakness, marked elevation of serum creatine kinase (CK) levels and myopathic patterns in electromyography (EMG). Muscle biopsy of the girl who was diagnosed as having dysferlinopathy disclosed dystrophic changes and an absence of dysferlin. She had both proximal and distal weakness of the lower limbs presented in a 5-year-period. However her brother had difficulty only in foot dorsiflexion at the beginning of the symptoms.

In conclusion, phenotypic variability, particularly at onset is one of the features of dysferlinopathies. To recognize and distinguish them from polymyositis is important to protect the patients from unnecessary treatment modalities. Recent imaging studies indicate that the pattern of muscular involvement is essentially uniform when both symptomatic and presymptomatic involvement is considered.

Keywords: Dysferlin; dysferlinopathy; distal myopathy; limb-girdle muscular dystrophy; distal anterior compartment myopathy

Disferlinopatide Fenotipik Varyasyonlar

Özet

Disferlin genindeki mutasyonlar, 'disferlinopati' adı altında bilinen musküler distrofide ayrı fenotipler olmasına sebep olmaktadır. Bugüne kadar, disferlinopatilerin dört alt tipi bildirilmiştir: limb-girdle musküler distrofi 2B (LGMD 2B), Miyoshi Miyopatisi (MM), distal anterior kompartman tipi ve skapulo-peroneal tip. Biz, alt ekstremitelerinde alışılmadık kas tutulumu olan disferlinopati bir kadın hasta ile semptomları onun tanı almasından sonra ortaya çıkan erkek kardeşini bildirmekteyiz. Her ikisinin de alt ekstremitelerde güçsüzlüğü, serum kreatin kinaz (CK) seviyesinde belirgin yükseklik ve elektromiyografilerinde (EMG) miyopatik tutulum bulguları mevcuttu. Disferlinopati tanısı alan kadın hastanın kas biyopsisi, distrofik değişiklikleri ve disferlin yokluğunu göstermekteydi. Alt ekstremitelerinde, beş yıllık dönem içinde ortaya çıkan, hem proksimal hem de distal kas güçsüzlüğü vardı. Buna rağmen, erkek kardeşinde semptomların başlangıcında sadece ayak dorsifleksiyonunda zayıf bulunuyordu.

Sonuç olarak, özellikle semptomların başlangıcında, fenotipik değişkenlik, disferlinopatilerin özelliklerinden biridir. Bunları farketmek ve polimiyozitten ayırmak, hastaları gereksiz tedavi yöntemlerinden korumak açısından önemlidir. Son zamanlardaki görüntüleme çalışmaları, semptomatik ve presemptomatik tutulum göz önüne alındığında, musküler tutulum paterninin aslında uzun dönemde benzer olduğunu göstermektedir.

Anahtar Kelimeler: Disferlin, disferlinopati, distal miyopati, limb-girdle musküler distrofi, distal anterior kompartman miyopati

INTRODUCTION

Limb-girdle muscular dystrophy (LGMD) encompasses a genetically and clinically heterogeneous group of disorders characterized by proximal muscle weakness⁽¹⁹⁾. To date, the autosomal dominant type of LGMD, designated as LGMD I, has been classified in 5 subtypes, LGMD IA to IE, and at least 9 recessively inherited forms have been identified, subtypes 2A to 2I^(19,13). Typical features of LGMD are progressive muscular weakness of limb and limb girdles, very high levels of creatine kinase (CK), myopathic pattern in needle electromyography (EMG) and dystrophic changes in muscle biopsy^(1,9).

However, there are rare group of myopathies clinically characterized by primary involvement of distal muscles and by myopathic features in the muscle biopsy. One of them, Miyoshi myopathy (MM), shows histological features compatible with muscular dystrophy^(1,2). In this myopathy, distal and posterior leg muscles, mainly gastrocnemius is the most frequently and severely affected muscle^(13,1,2,10). CK is usually high. EMG shows myopathic pattern in which motor units are usually of small amplitude at short duration and biopsy reveals dystrophic changes without presence of rimmed vacuoles⁽⁹⁾.

Recently it has been shown that dysferlin, one of the components of muscular fiber membrane, is decreased or absent in both LGMD 2B and MM^(1,2,4,7,8,12,18). Later, two different types of myopathy quite different in clinical phenotypes, distal anterior compartment myopathy and scapulo-peroneal type, which are found to

lack dysferlin are added to this group^(19,13,9). The scapulo-peroneal type is described in only one patient in Japan⁽¹⁹⁾. The term “dysferlinopathy” has been suggested^(13,9). Dysferlin is known to play an essential role in skeletal muscle fiber repair and dysferlinopathy is possibly associated with an inefficient repair and regenerative system⁽⁵⁾. The pathogenetic mechanisms and the correlation between clinical phenotype and the gene mutations is unclear suggesting the role of additional genetic and epigenetic factors in modifying clinical symptoms^(5,11,16).

We report a girl with dysferlinopathy with an unusual equal involvement of proximal as well as distal anterior and posterior group muscles in lower extremities at onset and her brother whose symptoms started after the diagnosis of his sister.

CASE PRESENTATION

Case 1: A 23-year-old female presented with weakness of lower limbs. She noticed weakness of her lower limbs at the age of 18 years with difficulty to walk and climb stairs. The motor disability progressed slowly. She was the oldest of five children in her family. There was no family history of a neuromuscular disease. In neurological examination, cranial muscles were unremarkable. Strength was normal in all muscles of the upper extremities except a questionable weakness in finger abduction. In the lower extremities, strength was found 4/5 in the proximal muscles and in dorsal and plantar flexion of the feet and toes. She couldn't stand up during Gower's test. Waddling gait with pronounced lordosis was noticed. She

couldn't walk on her heels and toes. The achilles reflex was absent on the left and diminished on the right side with flexor plantar responses. No sensory deficit was detected. Serum CK level was 5615 U/L(N:0-190 U/L). In needle EMG, myopathic changes which were short lasting motor unit potentials at short amplitude and denervation potentials such as positive waves and fibrillation potentials were detected primarily in the proximal muscles of both the upper and lower extremities. Sensory and motor nerve

conduction studies were normal. Muscle biopsy performed because of suspected polymyositis disclosed dysferlinopathy (Figure 1 and 2). Muscle biopsy showed fiber-size variability, minimal core centralization, rare images of necrosis, fibers subdivided by splitting and absence of inflammation and rimmed vacuoles. She has been followed up for 3 years and there is no significant difference in her neurological examination except for the minimal progression in the lower extremity weakness.



Figure 1: Muscle biopsy specimen of the patient with dysferlin myopathy: dysferlin (-)

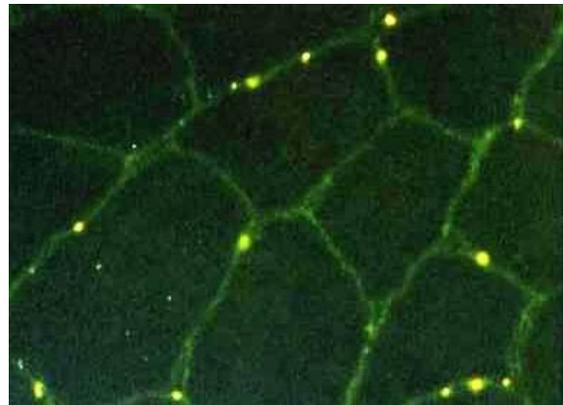


Figure 2: Control muscle: dysferlin (+)

Case 2: Nineteen-year-old brother of case 1 presented because of pain in his legs while walking. He had noticed this complaint during the last 6 months. He requested a neurological examination because of the confirmed diagnosis of dysferlinopathy in his sister 1 year ago. He is the fourth of five children. In neurological examination, strength was normal in the muscles of the upper extremities. In the lower extremities, only minimal weakness in foot dorsiflexion was present. He had minimal difficulty to walk on his heels. Deep tendon reflexes were normoactive in all extremities. He had flexor plantar

responses. Sensory deficit was absent. Serum CK level was 110 times the upper limit of normal(CK: 21040 U/L ; N: 0-190). Needle MG showed short lasting motor unit potentials at short duration, fibrillation potentials and positive waves in most of the muscles of upper and lower extremities . Muscle biopsy was not performed, because his oldest sister had already been diagnosed as having dysferlinopathy. He has been followed up for 2 years in our clinic and there is no significant difference in his neurological examination.

DISCUSSION

Both of our cases demonstrated common clinical features of dysferlinopathy. These features indicating dysferlinopathy may be pointed out as sporadic or autosomal recessive inheritance, late teenage or early adulthood onset, weakness starting in the lower limbs, slow progression without loss of walking ability before the age of 30 years and serum CK levels more than 20 times higher than the upper limit of normal^(19,14,6). Also, electrophysiological examinations of different phenotypes of dysferlinopathies generally disclose common features⁽¹⁹⁾. Fibrillation potentials and positive waves are detected as well as myopathic changes⁽¹⁹⁾. Due to electrophysiological examination findings together with early adult onset and high CK levels, a muscle biopsy was performed in our patient to exclude polymyositis, even if muscle involvement was not typical of it. As dysferlinopathies might have late onset and proximal muscles might be involved, they might be incorrectly diagnosed as polymyositis⁽⁶⁾. This has critical importance in differential diagnosis and final diagnosis should be made by muscle biopsy or genetic analysis of dysferlin gene^(9,2).

Our first case had to some extent different clinical presentation from the types of dysferlinopathies that have been described earlier. Upper extremities were spared in her, whereas proximal as well as distal anterior and posterior group muscles were equally affected in the lower extremities. This patient seemed to lack the distinct involvement of muscle groups, which define the different phenotypes of patients with dysferlin mutations. On the contrary, muscle groups which are selectively involved in the MM, LGMD 2B and distal anterior compartment myopathy, seemed all equally weak in her lower extremities. Among these phenotypes, difference between involvements of the muscle groups gradually disappears as the disease progresses and at advanced stages all muscles become weak⁽²⁾. However, we

believe that the stage of our patient cannot be considered being advanced as her strength was still 4/5 in the lower extremities with normal strength in upper extremities when she presented at 5 years of her complaints. Dysferlinopathies seemed to have wider clinical spectrum than previously thought⁽¹⁷⁾. LGMD 2B and Miyoshi myopathy had been initially reported as separate clinical entities, but about 16% of patients with Miyoshi myopathy develop proximal muscle involvement relatively early, followed by a rapid progression, so the name of “distal-limb-girdle” type muscular dystrophy has been suggested⁽¹⁹⁾. However, slow progression had been reported in many types of dysferlinopathies^(19,1).

Our second case presented with distal anterior compartment type muscle involvement seeming different from his sister. Muscle involvement of our both patients did not significantly changed during the three years follow-up period. Variable clinical phenotypes in the same family are one of the features of dysferlinopathies^(2,17). As heterogeneity is observed even within the same family, some additional factors distinct from dysferlin may be involved^(19,1,9,2). There seems to be an unknown factor causing this clinical heterogeneity which still remains to be solved⁽²⁰⁾. However, phenotypic differences which are prominent at onset become difficult to recognize as the disease progresses⁽²⁾. New diagnostic approaches using magnetic resonance imaging in presymptomatic carriers of dysferlin gene mutations demonstrated that muscle involvement progressed from distal to proximal posterior leg muscles^(15,3). In the early stages of disease patients may clinically show only proximal lower limb-girdle muscle weakness; however, muscle imaging in these patients show also distal lower limb muscle involvement, so that the pattern of muscle involvement found in dysferlin deficiency may not strictly conform to the definition of limb-girdle muscular dystrophy or Miyoshi

Myopathy^(14,3). Recent long-term clinical and magnetic imaging studies indicated that the pattern of muscular involvement is essentially uniform when both symptomatic and presymptomatic involvement is considered^(14,3).

In conclusion, phenotypic variability, particularly prominent at the onset, is one of the main features of dysferlinopathies. Dysferlinopathies have a wider clinical spectrum than previously thought. To recognize and distinguish them from polymyositis is important to protect the patients from unnecessary treatment modalities. Recent long-term clinical and magnetic imaging studies indicated that the pattern of muscular involvement is essentially uniform when both symptomatic and presymptomatic involvement is considered.

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REFERENCES

1. Aoki M, Liu J, Richard I, Bashir R, Britton S, Keers SM, Oeltjen S, Brown HEV, Marchand S, Bourg N, Beley C, McKenna-Yasek D, Arahata K, Bohlega S, Cupler E, Illa I, Majneh I, Barohn RJ, Urtizberea JA, Fardeau M, Amato A, Angelini C, Bushby K, Beckmann JS, Brown RH. Genomic organization of the dysferlin gene and novel mutations in Miyoshi myopathy. *Neurology* 2001;57:271-278
2. Argov Z, Sadeh M, Mazor K, Soffer D, Kahana E, Eisenberg I, Mitrani-Rosenbaum S, Richard I, Beckmann J, Keers S, Bashir R, Bushby K, Rosenmann H. Muscular dystrophy due to dysferlin deficiency in Libyan Jews. Clinical and genetic features. *Brain* 2000;123:1229-1237.
3. Brummer D, Walter MC, Palmbach M, Knirsch U, Karitzky J, Tomczak R, Braun C, Grundhoff N, Bornemann A, Muller CR, Lochmuller H, Schreiber H. Long-term MRI and clinical follow-up of symptomatic and presymptomatic carriers of dysferlin gene mutations. *Acta Myol* 2005;24:6-16.
4. Cagliani R, Fortunato F, Giorda R, Rodolico C, Bonaglia MC, Sironi M, D'Angelo MG, Prella A, Locatelli F, Toscano A, Bresolin N, Comi GP. Molecular analysis of LGMD-2B and MM patients: identification of novel DYSF mutations and possible founder effect in the Italian population. *Neuromuscul Disord* 2003;13:788-795.
5. Cenacchi G, Fanin M, De Giorgi LB, Angelini C. Ultrastructural changes in dysferlinopathy support defective membrane repair mechanism. *J Clin Pathol* 2005;58:190-195.
6. Cheema Z, Saperstein D, Jackson C, Newman D. Neuromuscular Highlights—AAN 2005 *J Clin Neuromusc Dis* 2006;7:206–209.
7. Fanin M, Pegoraro E, Matsuda-Asada C, Brown RH, Angelini C. Calpain-3 and dysferlin protein screening in patients with limb-girdle dystrophy and myopathy. *Neurology* 2001;56:660-665.
8. Ho M, Gallardo E, McKenna-Yasek D, De Luna N, Illa I, Brown RH. A Novel, Blood-Based Diagnostic Assay for Limb Girdle Muscular Dystrophy 2B and Miyoshi Myopathy. *Ann Neurol* 2002;51:129-133.
9. Illa I, Serrano-Munuera C, Gallardo E, Lasa A, Rojas-Garcia R, Palmer J, Gallano P, Baiget M, Matsuda C, Brown RH. Distal Anterior Compartment Myopathy: A Dysferlin Mutation Causing a New Muscular Dystrophy Phenotype. *Ann Neurol* 2001;49:130-134.
10. Katz JS, Rando TA, Barohn RJ, Saperstein DS, Jackson CE, Wicklund M, Amato AA. Late-onset distal muscular dystrophy affecting the posterior calves. *Muscle Nerve* 2003;28:443-448.
11. Kawabe K, Goto K, Nishino I, Angelini C, Hayashi YK. Dysferlin mutation analysis in a group of Italian patients with limb-girdle muscular dystrophy and Miyoshi myopathy. *Eur J Neurol*. 2004;11:657-661.
12. Kirschner J, Bönnemann CG. The Congenital and Limb-Girdle Muscular Dystrophies. *Arch Neurol*.2004;61:189-199.

13. Kurihara T. Different Phenotypes in Dysferlinopathy. *Intern Med* 2002;41:505-506.
14. Mahjneh I, Marconi G, Bushby K, Anderson LV, Tolvanen-Mahjneh H, Somer H. Dysferlinopathy (LGMD2B): a 23-year follow-up study of 10 patients homozygous for the same frameshifting dysferlin mutations. *Neuromuscul Disord* 2001;11:20-26.
15. Mastaglia FL, Lamont PJ, Laing NG. Distal myopathies. *Curr Opin Neurol*;2005;18:504-510.
16. Selva-O'Callaghan A, Labrador-Horrillo M, Gallardo E, Herruzo A, Grau-Junyent JM, Vilardell-Tarres M. Muscle inflammation, autoimmune Addison's disease and sarcoidosis in a patient with dysferlin deficiency. *Neuromuscul Disord* 2006;16:208-209.
17. Sinnreich M, Therrien C, Karpati G. Lariat branch point mutation in the dysferlin gene with mild limb-girdle muscular dystrophy. *Neurology* 2006;66:1114-1116.
18. Takahashi T, Aoki M, Tateyama M, Kondo E, Mizuno T, Onodera Y, Takano R, Kawai H, Kamakura K, Mochizuki H, Shizuka-Ikeda M, Nakagawa M, Yoshida Y, Akanuma J, Hoshino K, Saito H, Nishizawa M, Kato S, Saito K, Miyachi T, Yamashita H, Kawai M, Matsumura T, Kuzuhara S, Ibi T, Sahashi K, Nakai H, Kohnosu T, Nonaka I, Arahata K, Brown RH, Saito H, Itoyama Y. Dysferlin mutations in Japanese Miyoshi myopathy. *Neurology* 2003;60:1799-1804.
19. Ueyama H, Kumamoto T, Horinouchi H, Fujimoto S, Aono H, Tsuda T. Clinical Heterogeneity in Dysferlinopathy. *Internal Medicine* 2002;41:532-536.
20. Vilchez JJ, Gallano P, Gallardo E, Lasa A, Rojas-Garcia R, Freixas A, De Luna N, Calafell F, Sevilla T, Mayordomo F, Baiget M, Illa I. Identification of a novel founder mutation in the DYSF gene causing clinical variability in the Spanish population. *Arch Neurol* 2005;62:1256-1259.