Ⅲ. 研 究 班 名 簿

平成 23 年度厚生労働科学研究費補助金
難治性疾患克服研究事業　研究奨励分野

自己貪食空胞性ミオパチーの診断基準確立と治療法開発に関する研究班
（H22－難治－一般－119）

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Ⅳ．　研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

書籍

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Ⅴ．　研究成果の刊行物・別刷

INTERNAL MEDICINE

□ CASE REPORT □

Characterization of Dermatomyositis with Coexistence of Anti-Jo-1 and Anti-SRP Antibodies

Kazuma Sugie, Yasuyo Tonomura and Satoshi Ueno

Abstract

We describe a patient with dermatomyositis who presented with rapidly developing severe muscle weakness complicated by massive pleural effusion with interstitial lung disease. Myopathological analysis was suggestive of dermatomyositis. This patient showed both anti-Jo-1 and anti-SRP antibodies in serum. To our knowledge, the coexistence of these two myositis-specific autoantibodies (MSA) is considered extremely rare and is clearly an exception to the rule of having only one MSA. Our findings provide compelling evidence that the coexistence of these two MSAs may lead to more severe clinical symptoms, interacting in a complex fashion, thus expanding the clinical spectrum of idiopathic inflammatory myopathy.

Key words: idiopathic inflammatory myopathy, dermatomyositis, pleural effusion, myositis-specific autoantibody, anti-Jo-1 antibody, anti-SRP antibody

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Introduction

Idiopathic inflammatory myopathies such as polymyositis (PM) and dermatomyositis (DM) are systemic autoimmune connective tissue diseases characterized by chronic muscle inflammation with involvement of various organs (1). The pathogenesis of PM/DM is unknown, but autoantibodies directed against various cellular constituents have been identified in patients with PM/DM. Some autoantibodies found almost exclusively in PM/DM are known as myositis-specific autoantibodies (MSA), including anti-Jo-1 (histidyl tRNA synthetase) antibody, anti-PL-7 antibody, anti-signal recognition particle (SRP) antibody, anti-Mi-2 antibody, and anti-CADM-140 antibody. Each MSA is associated with a set of unique clinical features (2, 3).

We describe a 61-year-old man with DM who presented with severe muscle involvement characterized by rapidly developing proximal weakness, culminating in severe disability. He also showed massive pleural effusion with interstitial lung disease (ILD). Interestingly, both anti-Jo-1 and anti-SRP antibodies were positive in his serum. To our knowledge, the coexistence of these two types of MSA is considered extremely rare. Only one other case of idiopathic inflammatory myopathy with these two MSAs has been described in a recent report (4). Our findings suggest that coexistence of these two MSAs is associated with specific clinicopathological features.

Case Report

A 61-year-old man was admitted in June because of a 1-month history of rapidly progressive severe weakness of all four extremities. His skin was discolored, and he had dyspnea. The past history was noncontributory to the present illness. On admission, he presented with difficulty in getting up from bed and lifting his arms above his head. Physiological examination showed severe symmetric proximal weakness (less than grade 3 according to the Medical Research Council scale) of all four extremities. There were no other motor deficits. Sensory and stretch reflexes were normal. Erythematous rashes were present on the arms, trunk, legs, and face, including a typical heliotrope rash and Gottron's papules.

Laboratory examinations showed very high levels of creatine kinase (CK) (5,685 IU/L; normal: <160) in serum. The erythrocyte sedimentation rate and C-reactive protein were slightly elevated (80 mm/hr, <10; 2.6 IU/L, <0.1). Serum

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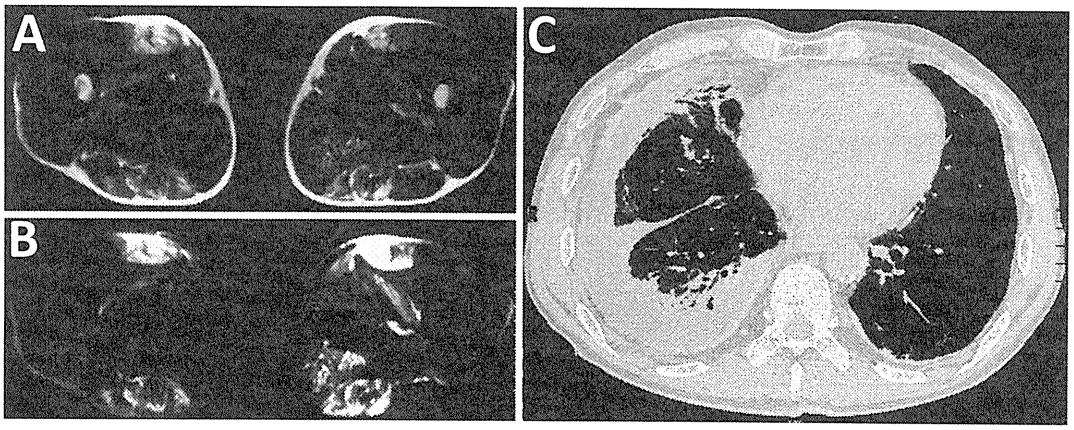

Figure 1. Magnetic resonance images of the thighs (A, B) and computed tomographic scans of the chest (C). T2-weighted (A) and T2-short-tau inversion recovery (STIR) images (B) showed diffuse high intensity in the frontal and dorsal aspects of both thigh muscles, suggesting intramuscular inflammation and edema. Chest images showed massive pleural effusion with interstitial lung disease (C).

antinuclear antibody was detected, accompanied by positivity for both anti-Jo-1 and anti-SRP antibodies, but negativity for other MSA, such as anti-PL-7 antibody. Among myositis-associated autoantibodies, anti-SS-A, anti-SS-B, anti-U1-RNP, and anti-Scl-70 antibodies were not detected. Electromyography showed short duration, small amplitude, polyphagic motor unit potentials with fibrillation potentials in the upper and lower limb muscles. Magnetic resonance images of the skeletal muscle showed diffuse inflammation and edema, most prominent in the proximal muscles of all four extremities (Fig. 1A, 1B). Computed tomography of the lung showed severe changes characteristic of ILD, with massive pleural effusion (Fig. 1C). The pleural fluid revealed exudate with no evidence of malignancy. A biopsy of the femoral muscle showed many necrotic and regenerative fibers with marked perimysial cell infiltration (Fig. 2). The infiltrating CD4+/CD8+ T cell ratio at perimysial sites (mean ± SD) was 1.58±0.28. Characteristic perifascicular muscle fiber atrophy was seen. Strong major histocompatibility complex class I (MHC-I) expression, especially in perifascicular atrophic fibers, was positive in cytoplasm. There was no expression of CD8/MHC-I complex, which suggested that CD8+ T cells invaded non-necrotic fibers that express MHC-I antigen. Expression of membrane attack complex (MAC) was present on endomysial capillaries, but not on necrotic fibers. These pathological findings of muscle suggested DM rather than PM.

The patient was given a diagnosis of DM with ILD. He initially received oral prednisone (1 mg/kg/day) for a month, with tapering to 20 mg/day over the course of the next three months. His muscle strength gradually improved, but he was still unable to move independently. Respiratory difficulties and pleural effusion were mildly decreased. The erythematous rashes decreased, but persisted slightly. Four months after the start of treatment, a progressive gastric cancer (papillary adenocarcinoma, stage IIIA) was diagnosed. A gastrectomy was thus performed. Subsequently, the muscle weakness and respiratory difficulties worsened despite an increase in the dose of steroids. One year after gastrectomy, the patient died of progressive ILD with massive pleural effusion and multiple liver metastases from gastric cancer.

Discussion

We described a patient with idiopathic inflammatory myopathy accompanied by ILD with massive pleural effusion, who presented with rapidly developing severe proximal weakness and respiratory difficulty. His skin lesions were suggestive of DM. Histopathological examination of a muscle specimen revealed many necrotic and regenerative fibers with marked perimysial cell infiltration, predominantly involving CD4+ T cells. Strong MHC-I expression by perifascicular atrophic fibers was consistent with DM (5). In addition, expression of MAC on endomysial capillaries, but not on necrotic fibers in our patient distinguished DM from paraneoplastic necrotizing myopathy (6). Collectively, these histopathological findings of muscle, including no expression of CD8/MHC-I complex, suggested DM rather than PM.

Interestingly, the present patient showed both anti-Jo-1 and anti-SRP antibody in his serum. The presence of these two MSAs is considered extremely rare and is clearly an exception to the rule of having only one MSA in association with PM/DM (7). To our knowledge, the coexistence of these MSAs has only been documented one time previously (4). That patient had severe muscle weakness and ILD, characterized by the presence of both anti-Jo-1 and anti-SRP antibody. Although the reason for this association and the pathogenic roles of these two MSAs are unclear, MSA may play a key, yet indirect part in the etiology of PM/DM.

Each MSA is associated with a set of unique clinical features (2, 3). Anti-Jo-1 antibody, one of the aminoacyl tRNA synthetases antibodies, is closely related to PM/DM, which

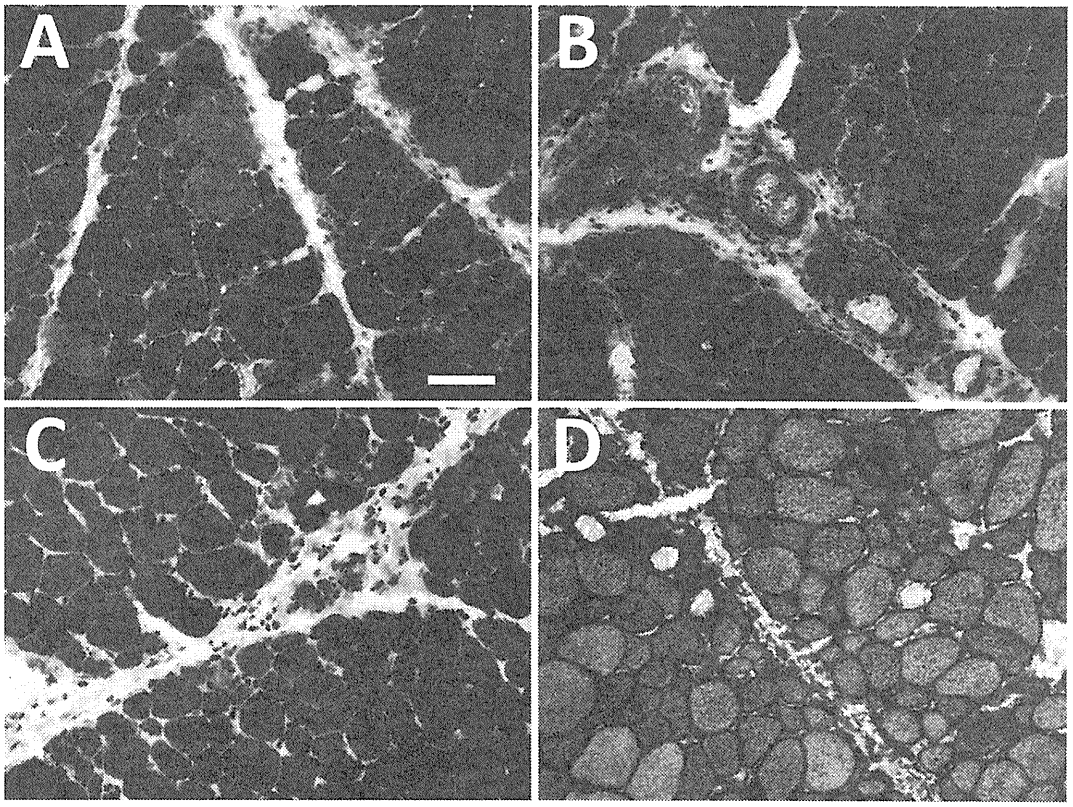

Figure 2. Light microscopic findings of femoral muscle specimens (A-D). A biopsy of the femoral muscle showed many necrotic and regenerative fibers (A). Marked perivascular lymphocytic inflammations were found in perimysial tissue (B). Perifascicular muscle fiber atrophy was seen (C). Immunohistochemical staining for MHC class I antigens showed intense labeling of the sarcolemma of all fibers and internal labeling of perifascicular atrophic fibers (D). *Bars* A-D 100 μm. A-C, Hematoxylin and Eosin staining; D, immunohistochemical staining for MHC class I antigens.

is frequently associated with ILD (2). Anti-Jo-1 antibody was reported in 20-30% of patients with PM/DM. ILD was more common than myositis in the early phase of disease and seemed to be one predictor of outcomes. The onset of weakness in patients with anti-Jo-1 antibody frequently occurs between the months of February and July (8). In contrast, anti-SRP antibody is clinically associated with pure PM and is found in 4-6% of patients with PM/DM (1, 3), although three patients with DM were reported among 23 Japanese patients with myositis associated with anti-SRP antibody (9). Patients with anti-SRP antibody most often present with severe muscle involvement characterized by rapidly developing proximal weakness, culminating in severe disability; the response to steroid therapy is often poor. Peculiar histopathological features include prominent muscle fiber necrosis without clinically significant inflammatory cell infiltration.

The present patient's condition was characterized by the coexistence of anti-Jo-1 antibody and anti-SRP antibody. Because the coexistence of these MSAs is associated with the clinical features of both antibodies, interacting in a complex fashion, affected patients may show more severe signs and symptoms. Another characteristic of our patient was the presence of massive pleural effusion associated with ILD. Although lung involvement is often found in patients with PM/DM, massive pleural effusion is very rare (10). The pathomechanism of the massive pleural effusion is unknown, but in this case it may have involved the exacerbation of pleural inflammation in association with pleural microvasculopathy in DM.

In conclusion, our findings strongly suggest that the coexistence of anti-Jo-1 and anti-SRP antibodies may lead to more severe clinical symptoms, including massive pleural effusion, thus expanding the clinical spectrum of idiopathic inflammatory myopathy. However, further clinical and pathological studies of similar cases are needed to establish firm conclusions.

The authors state that they have no Conflict of Interest (COI).

Contributions: K. Sugie was responsible for the overall study design, participated in the organization, planning, and coordination of the study, and wrote the manuscript. Y Tonomura and S Ueno contributed to running the study and analyzed and interpreted the data.

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顔面肩甲上腕型筋ジストロフィーの骨格筋障害の分布

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〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜

顔面肩甲上腕型筋ジストロフィー（facioscapulohumeral muscular dystrophy；以下 FSHD）は、その名のとおり、顔面、肩甲、上腕部の筋萎縮と筋力低下をきたす緩徐進行性の筋疾患である。しかし、症状が進行すると、前腕や下肢にも筋障害がおよぶことがある。また、左右差のある筋障害を呈することが本疾患の特徴的な所見である。ただ、障害の分布は、患者の年齢や患者個々によっても大きく異なる。

本稿では、自験例５例の検討をふまえて、FSHD患者の骨格筋障害の分布について、全身の骨格筋のCT／MRI画像所見を用いて紹介する。

〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜〜

顔面肩甲上腕型筋ジストロフィー（FSHD）とは

顔面肩甲上腕型筋ジストロフィー（FSHD; facioscapulohumeral muscular dystrophy）は、常染色体優性遺伝形式の緩徐進行性の筋疾患である[1)-8)]。遺伝性筋疾患としては、デュシェンヌ型／ベッカー型筋ジストロフィー、筋緊張性ジストロフィーに次いで頻度が高く、罹患率は人口10万人あたり約５人である。FSHDは、その名のとおり、顔面、肩甲、上腕部の筋萎縮と筋力低下をきたす。しかし、症状が進行すると、前腕や大腿、下腿にも筋障害がおよぶことがある。また、左右差のある筋障害を呈することが、本疾患の特徴的な所見である。ただ、障害の分布は、患者の年齢や患者個々によっても大きく異なる。同一家系内であっても臨床症状や重症度に差がある。

現在、提唱されているFSHDの臨床診断基準の主な点は、① 顔面または肩甲帯の筋障害を初発症状とし、外眼筋、咽頭筋、舌筋、心筋の障害を認めない、② 家系内発症者の半分以上に顔面筋罹患を認める、③ 常染色体優性遺伝形式を示す、④ 筋電図または筋生検にて筋原性変化の存在を確認することである[2)-4)]。発症年齢は０～65歳と非常に幅が広いが、95%以上の患者が20歳頃までに発症する。筋症状は緩徐進行性であり生命予後は良好で、通常は天寿を全うする。筋症状のほかに、神経性難聴や網膜症の合併も多く、約50%の患者に認められる。また、心伝導障害などの不整脈を呈する例や、精神遅滞やてんかん、呼吸不全を合併する若年発症例もある。

一般検査所見では、FSHDに特徴的なものはない。血清クレアチンキナーゼ（CK）値は上昇しても正常値の５倍程度で、半数近くは正常範囲内である。筋病理所見にもFSHDに特徴的な変化はなく、ほぼ正常な所見を示す例から、非特異的な筋原性変化を示す例まである。個体差や採取部位での差は著しく、中には、筋ジストロフィーの特徴である筋線維の壊死や再生所見とともに、血管周囲の炎症細胞浸潤がみられることがある。

FSHDの遺伝子座は、1990年に第４番染色体長腕テロメア領域（4q35-qter）に同定された[5)]。この領域には、制限酵素*Kpn*Iで切断される長さ3.3kbの繰り返し配列（D4Z4リピート）が存在する。サザンブロット解析を行うと、制限酵素*Eco*RIによる断片が、健常者では50～300kb以上検出されるが、FSHD患者のほとんどが28kb以下の短い断片を有している。D4Z4リピートの数と臨床症状とは相関することが多い。リピート数が少なく同部位の欠失が大きいほど、臨床症状が重症となり発症も早くなる傾向がある。ただし、この領域には原因遺伝子はなく、未知の分子メカニズムによって発症する可能性が示唆されている。

自験例の提示

表1　FSHD患者5例の臨床的特徴

症例	年齢（歳）	性別	発症年齢（歳）	罹病期間（年）	利き手	職業	主症状	血清 CK（IU/l）	4q35での*Eco*RI断片（正常＞35 kb）	備考
1	74	男	17	57	右	無職（元農業）	上肢挙上困難 歩行困難	180	23 kb	
2	63	男	10	53	右	会社員	右片麻痺 歩行困難	192	20 kb	文献1）
3	43	男	25	18	右	無職（元会社員）	上肢挙上困難 歩行困難	412	20 kb	
4	38	男	37	1	右	会社員	上肢挙上困難	151	23 kb	症例1の息子
5	19	男	16	3	右	学生	上肢挙上困難	430	23 kb	

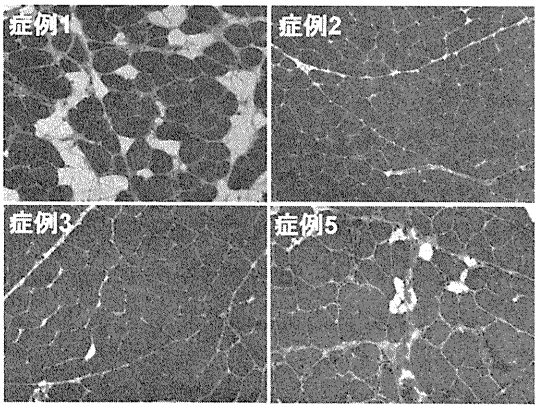

図1　FSHD患者4例の筋病理写真

FSHDの筋障害は、主に顔面、肩甲、上腕部で認めるが、症状が進行すると、前腕や大腿、下腿にも筋障害がおよぶことがある。また、特徴的な所見は左右差のある筋障害を呈することである。今回、私たちは、FSHD患者の筋障害の分布を明らかにするために、自験例5例の放射線画像を用いて検討した。

対象は、FSHD患者5例で、全例が右利きの男性で、年齢は19歳から74歳である（表1）。症例1と4は親子例である。発症年齢は10代から30代で、罹病期間は1年から57年である。FSHDに伴う症状は、主に上肢挙上困難と歩行困難で、症例2では右上下肢の筋力低下および筋萎縮であった。血清CK値は正常値の3倍以下であった。FSHDの遺伝子解析では、全例で4q35領域に欠失を確認し、4q35での*Eco*RI断片（正常＞35 kb）は23 kbが3例、20 kbが2例であった。また、4例で上腕二頭筋での筋生検を施行した。筋病理所見では、4例全例で筋原性変化を認め、軽度の筋線維の大小不同のみの症例から、壊死線維や再生線維が散在してジストロフィー変化をきたす症例までみられた（図1）。

この5例について、四肢と体幹の骨格筋をMRIあるいはCT画像を用いて評価した。各症例の画像（図2）と結果のまとめ（表2）を示す。症例1は、両肩甲帯と両下肢の高度の筋障害を示した。症例2は、上下肢と体幹で右半身の高度の萎縮を示し、左半身の筋障害はほとんどみられなかった[1]。症例3では、右優位の肩甲帯と左優位の下腿の障害を認めた。症例4、5では、左右差のある肩甲帯のみの軽度の障害を認めた。

今回の検討では、罹病期間が長いほど広範囲の筋障害を示した。また、利き手側の筋障害が強い症例が多くみられたが例外もあり、他の要因の関与も考えられた。骨格筋障害の分布と、患者の年齢や遺伝子解析での4q35での*Eco*RI断片のサイズとの間に明らかな関連は認めなかった。

FSHDの骨格筋障害の分布

FSHDの筋障害の分布は特徴的であり、顔面の頬部、肩、上腕部に強い筋障害を認める。また、天使の羽のように、肩甲骨が突出する「翼状肩甲」とよばれる徴候がみられる（図3）。翼状肩甲は、主に前鋸筋や僧帽筋の筋萎縮によって起こり、上肢の重みで肩甲骨が浮き上がって生じる。初発症状は、表情が乏しい、目を開けたまま寝る、上肢の挙上困難、翼状肩甲などの、顔面筋や上肢帯筋群の筋力低下や筋萎縮が示唆される症状が主訴になる場合が多い。前述のFSHDの臨床診断基準でも記載したとおり、外眼筋、咽頭筋、舌筋、心筋の障害は通常認めない。また、顔面筋罹患は、ごく軽度あるいは目立たない例もある。

症状の進行とともに、顔面、肩、上腕のみならず、下肢の筋障害を呈することがある。特に下肢においては、大腿後面の大腿屈筋や下腿の腓腹筋・前脛骨筋が障害されやすい[6]。下肢の筋障害の初発症状は、下垂足やしゃがみ立ち困難、歩行困難である。症状の進行は緩徐であり、将来、全体のおよそ20%が車椅子移動になるとされる。過去の報告では、高度の下肢の筋障害が、小さいサイズの*Eco*RI断片（10-13 kb）や罹病期間と相関することを報告している研究がある[6),7]。今回の検討では少数例のため、臨床的重症度と、*Eco*RI断片のサイズや罹病期間との相関は明らかにできなかった。

FSHD患者で筋障害に左右差があることは、特徴的な所見であり、他のタイプの筋ジストロフィーではまず認めない。左右差の発症機序は明らかではな

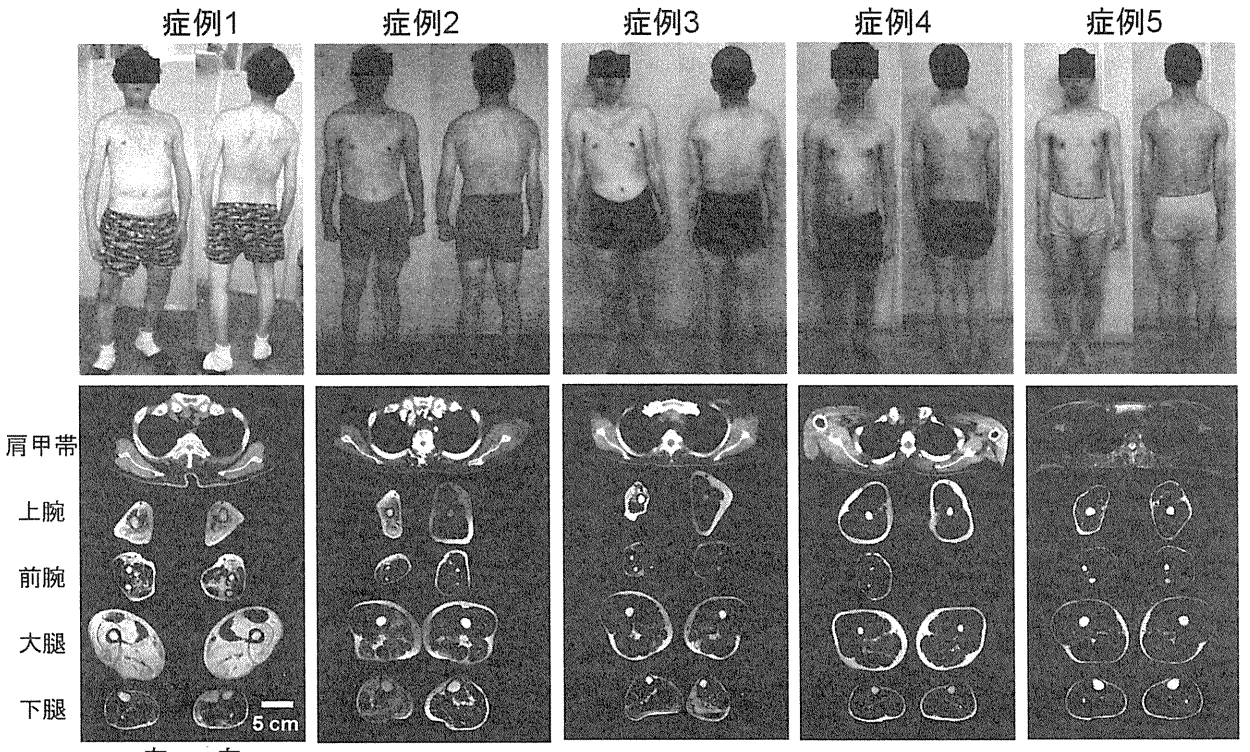

図2　FSHD患者5例の全身写真と放射線画像
症例1－4の肩甲帯：CT画像，症例5の肩甲帯と全例の上下肢：MRI T2強調画像．

表2　FSHD患者5例の画像所見のまとめ

症例	年齢（歳）	筋障害の分布
1	74	両肩甲帯と両上下肢の高度の萎縮
2	63	上下肢と体幹で右半身の高度の萎縮 （左半身の障害はほとんど認めず）
3	43	右優位の肩甲帯と左優位の下腿の萎縮
4	38	左優位の肩甲帯の萎縮
5	19	両肩甲帯と右側上肢の萎縮

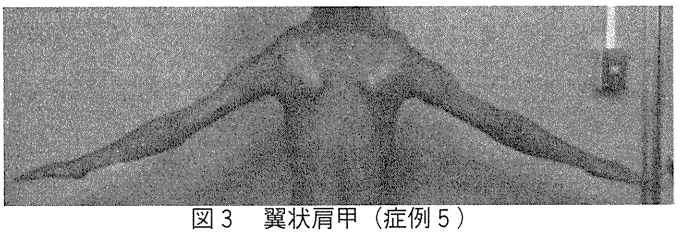

図3　翼状肩甲（症例5）

いが、遺伝性疾患であることから、遺伝的要因の関与が十分考えられる。しかし、患者個々においても、同じ家系内での患者同士でも、症状の多様性が大きいことから、エピジェネティックな変化の関与も示唆される。さらに、過去の報告では、利き手側ほど筋障害の程度が高度であることが示されていることから、FSHDでは、運動などの過重負荷による物理的な要因によっても、筋障害が進行する可能性が考えられる[8]。

結　論

FSHD患者の骨格筋障害は著明な左右差を呈することがあるが、症例ごとに筋障害の程度や部位は大きく異なる。FSHD患者の筋障害の分布には、遺伝子の異常だけではなく、エピジェネティックな変化や運動負荷などの関与の可能性が示唆された。

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ORIGINAL ARTICLE

Clinical analysis and outcomes of amyotrophic lateral sclerosis with demyelinating polyneuropathy

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Abstract

Abnormalities of both motor and sensory nerve action potentials, similar to those found in demyelinating polyneuropathy, may occur in patients with amyotrophic lateral sclerosis (ALS). We analyzed the clinical features of unusual ALS patients with demyelinating polyneuropathy (DPN) to delineate the characteristics and outcomes of this rare condition. We reviewed three ALS patients with DPN who were confirmed to meet the electrophysiological nerve conduction criteria for DPN among 157 patients with ALS. At the initial neurological examination, one patient had both subjective sensory symptoms and abnormal results of sensory examinations, and one patient had sensory symptoms. Motor weakness of the limbs was present in all patients, and fasciculation was present in two patients. Anti-GalNAc-GD1a IgG antibodies were evident in one. Sural nerve biopsy showed a moderate, marginal reduction in myelin thickness, and teased fiber analysis revealed segmental demyelination and remyelination, but axonal degeneration was found in one patient. The mean interval from disease onset to respiratory failure or death in our three patients and seven previously documented ALS patients with DPN was 43.1 ± 18.7 months. Our findings suggest that survival in ALS with DPN is similar to that in classic ALS.

Key words: *Amyotrophic lateral sclerosis, sensory symptom, demyelinating neuropathy, polyneuropathy, prognosis*

Introduction

Amyotrophic lateral sclerosis (ALS) is an untreatable, progressive disease caused by combined anterior horn and corticospinal tract degeneration; sensorial large-caliber myelinated fibers may also be affected (1). Sensory symptoms or signs are often present in patients with ALS, and electrophysiologic studies have shown abnormal sensory nerve action potentials (1). Abnormalities of motor nerve conduction, such as increased distal motor latency and mild slowing of conduction velocity, are also found in wasted muscles in ALS and are attributed to segmental demyelination secondary to distal axonal atrophy (2,3). Abnormalities of both motor and sensory nerve action potentials, similar to those found in demyelinating polyneuropathy, may occur in patients with ALS. Seven ALS patients with demyelinating polyneuropathy (DPN) have been reported on previously (4,5). We describe three unusual ALS patients with DPN and analyze their clinical features to delineate the characteristics and outcomes of this rare condition.

Materials and methods

Clinical data analysis

The subjects were two Japanese males (66 and 50 years old) and one Japanese female (53 years old) who were identified among 157 patients with clinically possible, probable, or definite ALS as diagnosed according to the El Escorial revised criteria from December 1992 through May 2011 (6). All three patients fulfilled the following criteria: 1) limb weakness and wasting developing during the disease course; 2) ultimately, respiratory function was affected or the patient died of a respiratory failure characterized by restrictive dysfunction requiring mechanical ventilation or non-invasive positive pressure ventilation in the absence of other accidental causes of respiratory dysfunction, such as pulmonary embolism or pneumonia; 3) bulbar weakness or wasting, requiring a percutaneous endoscopic gastrostomy during the disease course; 4) patients who had increased or pathologic tendon reflexes (TRs), other pathologic reflexes, or subjective sensory

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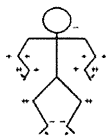
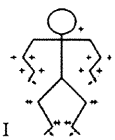
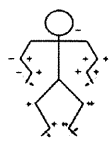
symptoms during the disease course were included; and 5) the results of electrophysiological nerve conduction studies (NCS) met the European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) (7) criteria for DPN on initial examinations. The exclusion criteria were as follows: 1) functionally significant weakness or wasting of the respiratory or bulbar musculature before involvement of the limbs; 2) the presence of bladder or bowel dysfunction, radiating pain, and other neurologic deficits, such as extrapyramidal signs, limited ocular movements, or ataxia; 3) monomelic weakness or amyotrophy at presentation; 4) a history of diabetes mellitus or increased serum levels of glucose or glycated

Figure 1. Clinical characteristics of patients with amyotrophic lateral sclerosis who had demyelinating polyneuropathy. The El Escorial category at the time of evaluation was classified according to the El Escorial revised criteria (6).

	Patient 1	Patient 2	Patient 3
Sex/age (at onset)	66/M	53/F	50/M
Total clinical course (months)	59 (dead)	49 (dead)	56 (dead)
Respiratory failure from onset (months)	59	49	not available
Gastrostomy from onset (months)	50	46	not available
Presenting complaint	numbness in all limbs	weakness in right distal upper limb	weakness in distal lower limb
Family history of suggested neurodegenerative diseases	–	–	–
Presence of past neurosurgery	Cervical hernia (C5/6), lumbar hernia (L2/3)	–	–
Initial neurologic examinations			
Neurologic evaluation from onset (months)	2 (Aug. 06)	19 (Oct. 02)	10 (Oct. 03)
Sensory symptoms	numbness in all limbs	–	numbness in distal lower limbs
Sensory examination	decreased superficial sensation in all limbs	normal	normal
Motor examination	mild weakness in all limbs, atrophy in lower limbs	moderate weakness and atrophy in distal upper limbs	moderate weakness in both lower and distal upper limbs
Fasciculation	–	forearms	both brachial muscles, femoral muscles
Tongue atrophy	–	+	–
Reflexes		 I	
El Escorial category at evaluation time	Clinically probable	Clinically probable	Clinically probable-laboratory supported
Presence of pathological reflexes during diease course	Hoffmann	Babinski	not available
Work-up			
Neurogenic changes with denervation on EMG	all limbs, thoracic paraspinal muscles	upper limbs, right lower limb	lower limbs
Signal changes of pyramidal tract on MRI	–	–	–
Compression or abnormal high lesion of spinal cord on cervical MRI	–	–	–
CMCT on magnetic stimulation (ms) (*8.3–0.7 ms)	ND	9.8↑	6.6
VC (%)	90.5**↓	95	111
FEV1 (%)	45.7**↓	82↓	91.2
ABG (PaO_2) (mmHg)	98.1**	73↓	73.1↓
ABG ($PaCO_2$) (mmHg)	40.6**↑	43.3↑	44.4↑
Anti-ganglioside antibodies	–	GalNAc-GD1a	–
Albuminocytologic dissociation	+	+	+
Treatments	IVIG, steroid pulse (no response)	IVIG (responded)	IVIG (no response)

EMG: electromyography, MRI: magnetic resonance imaging; CMCT: central motor conduction time, VC: vital capacity, FEV: forced expiratory volume; ABG: arterial blood gas; IVIG: intravenous immunoglobulin; N.D.: not done; *normal range (mean 2SD to mean + 2SD); **27 months after onset.

hemoglobin from the initial evaluation to final follow-up. Patients were also excluded if they had a mass lesion, inflammation, a syrinx, or findings suggestive of gliosis on cervical magnetic resonance imaging (MRI) or a mass lesion, inflammation, major vessel disease, or multiple infarcts on cranial MRI. All patients were admitted to our institution and evaluated by at least two experienced neurologists. One experienced analyst in our institute performed NCS according to standard methods using conventional surface electrodes, with control of surface limb temperature. Electromyography was performed at the time of neurologic evaluations, and transcranial magnetic stimulation was used to evaluate central motor conduction time (CMCT). Anti-ganglioside antibodies were measured in all patients. Vital capacity (VC), forced expiratory volume, or arterial blood gases were assessed in all patients.

Results

Clinical data

None of our three patients had a family history of motor neuron disease. The patients died 49, 59, and 56 months after disease onset, respectively (Figure 1). Two patients initially had symmetric sensory complains, and one had symmetric decreased cutaneous sensations in all limbs. Distal dominant muscle weakness of the limbs was present in all three patients (asymmetric weakness in patient 3). In one patient, weakness and atrophy were evident only in both upper limbs at initial examination, but developed in all four limbs and the bulbar region during follow-up. TRs in the four limbs were spared and partially increased in all patients. Pathologic reflexes developed during follow-up in two patients, but could not be evaluated in the other patient (patient 3) because he transferred to another hospital. Fasciculation was present in patients 2 and 3 at the initial neurologic examination, and patient 1 also showed fasciculation during the disease course. Initial NCS in all patients revealed a combination of reduced motor and sensory conduction velocities, prolonged distal latencies, and absent or prolonged F-wave latencies with reduced compound muscle action potentials (CMAP) or sensory nerve action potentials that were consistent with diffuse demyelination. These findings progressed during follow-up (Table I). In all patients, electromyography showed chronic, active denervation as defined by Brooks

Table I. Results of electrophysiologic nerve conduction studies in our three patients with amyotrophic lateral sclerosis.

			Patient 1		Patient 2		Patient 3
Sensory nerve	Variable	Normal	Aug.06	Mar.08	Oct.02	Sep.03	Oct.03
Sural	Conduction velocity (m/s)	>53.3	37.7[a]	NR[a]	48.6	48.1	34.7[a]
	Amplitude (μV)	>12.4	4.07[b]	NR[b]	14.7	11.8	2.89[b]
Median	Conduction velocity (m/s)	>59.1	55.3	48.1	45.2	44.2	40.4[a]
	Amplitude (μV)	>13.1	2.9[b]	2.15[b]	5.84[b]	4.68[b]	3.78[b]
Ulnarw	Conduction velocity (m/s)	>59.4	55.3	52.4	48.1	47.4	41.4[a]
	Amplitude (μV)	>9.4	6[b]	2.01[b]	15.3	14.5	1.7[b]
Motor nerve							
Tibial	Distal latency (ms)	<3.4	4.62[d]	7.56[c]	4.32[d]	5.64[c]	4.44[d]
	Conduction velocity (m/s)	>50	43.1	38.8[a]	44.9	37[a]	31.1[a]
	Amplitude (mV)	<22.2	2.18[b]	0.26[b]	2.63[b]	0.28[b]	3.8[b]
Median	Distal latency (ms)	<3.3	4.14[d]	5.54[c]	5.84[c]	5.86[c]	3.36
	Conduction velocity (m/s)	>59.5	46.7	42.1[a]	44.3	44.2	35.8[a]
	Amplitude (mV)	>16.4	6.15[b]	0.81[b]	0.4[b]	0.27[b]	13.1
Ulnar	Distal latency (ms)	<2.6	2.7	3.22[d]	2.96	3.88[c]	3.02
	Conduction velocity (m/s)	>58.2	54.7	49.8	45.4	47.9	34.8[a]
	Amplitude (mV)	>15.2	8.72[b]	4.58[b]	2.63[b]	0.32[b]	14.8
conduction block *1			–	–	–	–	–
temporal dispersion			TN	TN	MN	MN	–
abnormal F-wave*2			MN** UN** TN	MN** UN, TN	MN, UN	MN, UN TN	MN, UN TN

NR: not recordable; MN: median nerve; UN: ulnar nerve; TN: tibial nerve; a: below 70% of the lower limit of normal; b: below 80% of the lower limit of normal; c: above 150% of the upper limit of normal; d: above 125% of the upper limit of normal; *1: defined as a reduction in the amplitude of the compound muscle action potential by more than 50% without temporal dispersion; *2: absent or above 150% of the upper limit of normal; **: above 120% of the upper limit of normal.

et al. (6) in two or more different nerve territories. In patients 1 and 3, fasciculation potentials were present in four or more different nerve territories at initial examination. Patient 2 also showed fasciculation potentials at a later examination. CMCT was mildly prolonged in one patient (normal range, 8.3–0.7 ms (mean 2SD to mean + 2SD)). Anti-GalNAc-GD1a IgG antibodies were evident in the serum of patient 2. Other anti-ganglioside antibodies, including anti-GM1 antibodies, were not detected. Albuminocytologic dissociation was evident in all patients. VC was decreased in one patient, and carbon dioxide levels on arterial blood gas analysis were increased in all three patients. Sural nerve biopsy performed in patients 1 and 3, showed a moderate, marginal reduction in myelin thickness, with no fibrinoid necrosis, inflammatory cell infiltration, or granuloma (Figure 2). Teased fiber analysis revealed segmental demyelination and remyelination (40% in patient 1 and 18% in patient 3), but axonal degeneration was less common (none in patient 1 and 1% in patient 3). In one patient, weakness of the distal upper limbs moderately responded to initial intravenous immunoglobulin therapy (400 mg/kg/day, five days). Weakness of the digit and wrist muscles improved from a Manual Muscle Test score of 3 to 4, persisting for three weeks. The results of serum liver function tests, renal function tests, and protein electrophoresis and the levels of tri-iodothyronine and thyroid stimulating hormone were normal in all patients. The results of serologic tests were negative for human T-lymphotropic virus type 1 in patient 1; for human immunodeficiency virus in patient 3; and for syphilis, hepatitis B virus, and hepatitis C virus in all three patients. Antinuclear antibodies in all three patients, antimyelin-associated glycoprotein antibodies in patient 3, and anti-DNA, SS-A, SS-B, and antineutrophil cytoplasmic antibodies in patients 1 and 3 were not detected. Serum levels of vitamin B1 and B12, folic acid, and angiotensin 1 converting enzyme were normal in patients 1 and 3. No mutation was found in the PMP gene in patient 3. The ratios of saturated fatty acids, including C12:0–C26:0, were not increased in patient 3. Abdominal computed tomographic scans, repeated chest X-ray films, at least three tumor markers in all three patients, and Ga scintigraphy in patients 1 and 3 revealed no evidence of cancer in any patient.

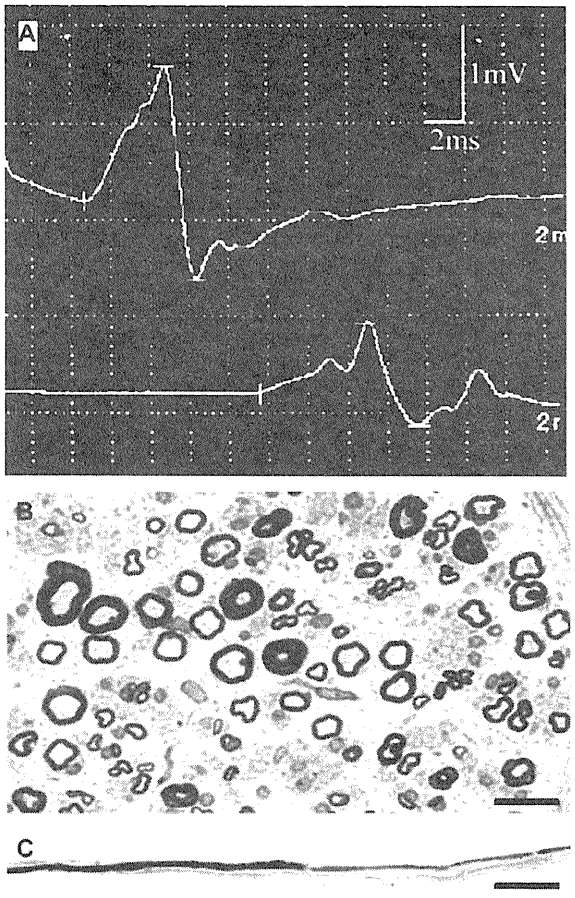


Figure 2. Electrophysiologic nerve conduction studies (patient 1) (panel A). Temporal dispersion was present in the tibial nerve. Nerve stimulation is at the knee (upper) and at the ankle (lower). Thinly myelinated axons (panel B). Biopsy of the sural nerve (patient 1) showed a moderate marginal reduction in myelin thickness. The calibration bar represents 10 μm. Teased fiber analysis (panel C). Segmental demyelination and remyelination are evident. The calibration bar represents 100 μm.

According to the revised El Escorial criteria (6), two patients (patients 1 and 2) were given a diagnosis of clinically probable ALS, and one patient (patient 3) was given a diagnosis of clinically probable-laboratory supported ALS. According to the new Awaji criteria (8), two patients (patients 1 and 2) had clinically probable ALS and one patient (patient 3) had clinically possible ALS at the initial neurologic examinations. We followed up the two patients who had a diagnosis of clinically definite ALS according to both criteria late in the course. From family discussions, one other patient (not seen by the authors) was diagnosed with ALS.

Discussion

All three of our patients showed coexistence of progressive muscular atrophy involving limb muscles as well as the bulbar and respiratory musculature with peripheral nerve demyelination on electrophysiologic and pathologic studies.

Whether our patients had demyelinating peripheral nervous disease remains an open question. TRs were not absent or decreased in our patients. A patient with hereditary motor and sensory neuropathy who had increased TRs has been documented previously (9). The increased TRs in our patient were probably attributed to primary motor neuron disease. A history of neurologic surgery for cervical and lumbar hernia, may have also promoted the increased TRs, even now ALS undertaking a laminectomy