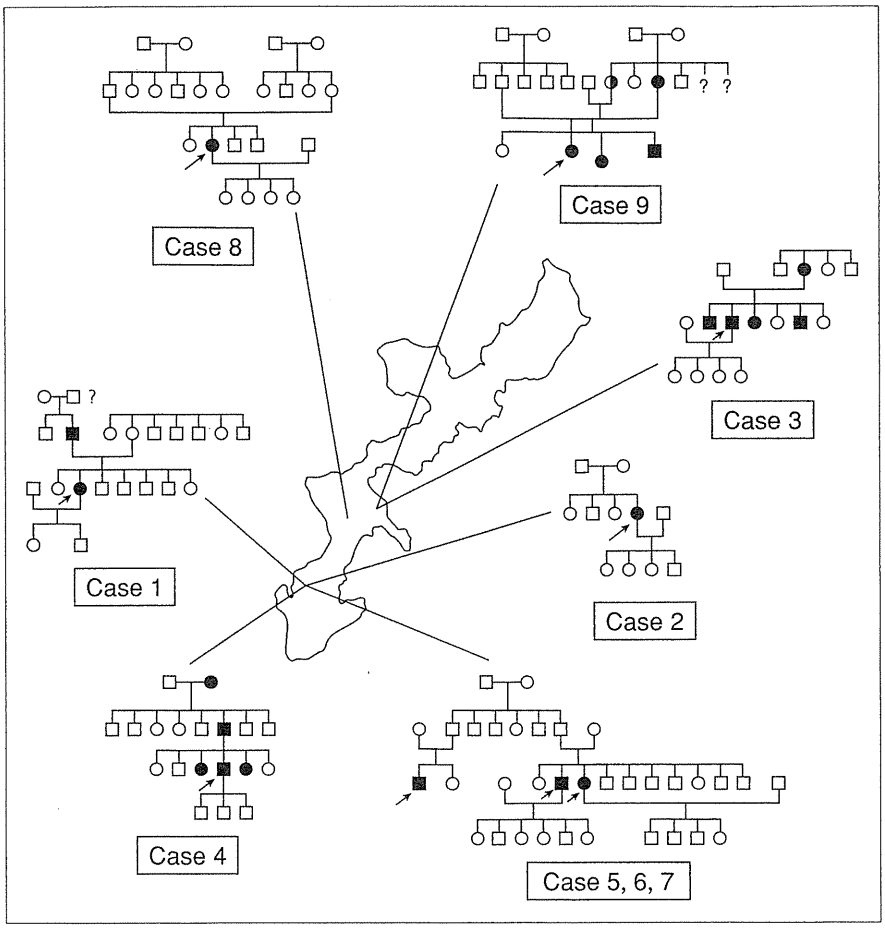

図1　1985年に厚生省(当時)研究班会議で初めてHMSN-Pが報告された
その後の調査から，HMSN-Pは沖縄県の8人/人口10万人であり，沖縄本島を中心に100名以上のHMSN-P患者がいると推定される．(文献[2]より引用)

異なる疾患である[9)10)]．これまで「琉球型」という言葉は，Kondoらによる琉球型筋萎縮症にしか用いられたことがなく，HMSN-Pに対して使用することは混同するため避けなければならないと考える．

中原らが，1985年に厚生省(現，厚生労働省)「筋ジストロフィー症の疫学，病態および治療開発に関する研究」班会議で報告し[2)]，1989年に「沖縄本島にみられる特異なHMSN」として17例中9例の臨床的特徴を記載している(図1)[11)]．この中で本症は，常染色体優性遺伝形式であり，CKの上昇を伴う近位優位の筋力低下，電気生理学的にも明確にとらえられる感覚障害，約10年で歩行不能となる特徴を持ち，進行すると人工呼吸器を必要とするほどの筋萎縮を起こし，頸部以下はほとんど動かなくなるほどに悪化することを明らかにした．また，この報告の中で，本症は，motor neuron disease(MND)，HMSN，SMAのような分類でははっきりと分けられない病型であることも述べられている．

当時，沖縄病院ではご遺族から病理解剖の承諾を頂くことはきわめて困難であったが，1994年に初めてHMSN-P例の病理解剖が行われ，1995年3月4日に沖縄病院で行われた第159回沖縄神経懇話会でCPCが行われた．その病理学的特徴は，脊髄全長にわたる後索の著明な萎縮，神経線維の脱落，脊髄前角神経細胞の著しい脱落とグリオーシス，後根神経節細胞の脱落，末梢神経有髄線維の著明な脱落であった[1)]．

HMSN-Pの遺伝子座

1997年，われわれはマイクロサテライトマーカーを用いた遺伝子連鎖解析を行い，DNAマーカーD3S3652, D3S1591, D3S1281でそれぞれ最大lod score 4.63, 3.13, 3.09(θ＝0.0, 0.043, 0.031)を得たことより，疾患遺伝子座を3q13領域

に絞り込んだ[1]．この領域の9種類のDNAマーカーを用いたDISMULTによる分析では，lod score 4.93（$p<0.00000095$）であり，この領域に強い連鎖不平衡が示された．さらに家系を超えて疾患に連鎖したハプロタイプが共通であることを見出し，創始者効果についても報告した[12]．

HMSN-P疾患単位の確立

1997年，われわれは詳細な臨床症候，電気生理検査所見，筋病理所見，剖検病理所見も含めて報告し，新しい疾患として世界的に認識されるに至った[1]．この報告により，メンデル遺伝病のデータベースであるOMIM（Online Mendelian Inheritance in Man）に登録された．本症の臨床的な特徴は，①常染色体優性遺伝形式，②成人発症，緩徐進行性の近位筋優位の筋力低下，③四肢，体幹の筋痙攣，fasciculations，④深部腱反射の低下・消失，⑤異常知覚，深部感覚障害を伴う感覚障害，⑥電気生理学的検査にて軸索優位の運動・感覚神経障害，⑦血清CK値の上昇，⑧脂質異常症，耐糖能異常の合併，⑨末梢神経有髄神経の著明な脱落である．

電気生理的検査では，針筋電図においてchronic denervation, reinnervationの所見，fasciculationの頻発，complex repetitive discharge（CRD），neuromyotonic dischargeなどを認め，神経伝導検査では病初期からF-wave後のafter-dischargeが出現し，中期以降にはCMAPの低下ないし消失がみられる．感覚障害の自覚症状に比べて感覚神経の障害が強く，上肢，下肢ともに導出不能例もしばしば経験する[1)13)]．

病理所見として，前角細胞と後根神経節，後索の強い障害を認めたため，当時の定義に当てはめると，筋萎縮性側索硬化症（ALS）やSMAなどの運動ニューロン病に分類することは考えにくく，われわれは本疾患をHMSN-Pと名づけた．OMIMでは，OMIM604484の番号を与えられ，Hereditary Motor and Sensory Neuropathy, Okinawa type（HMSNO），proximal type（HMSNP）などと命名されている．疾患の位置づけは，成人型のSMAと似るが感覚障害の合併の点でSMAには合致しない．CMT2とは，近位筋優位の障害という点で異なる．最も類似する疾患は，球脊髄性筋萎縮症（spinal and bulbar muscular atrophy：SBMA）で，muscle crampや近位優位の筋力低下の症候，CK上昇など，多くの点で類似している．SBMAはX染色体遺伝の疾患で遺伝子異常も同定されており完全に異なる疾患であるが，臨床的にはHMSN-PはSBMAに比べ，球症状が軽く，逆に感覚障害はより強い点が鑑別点となる．HMSN-Pの発症は，17～50歳で通常40歳前後にmuscle crampで始まる．経過はSBMAに比べ，筋力低下の進行が早くまた重篤で，5～20年の経過で歩行不能となり，10～25年の経過で呼吸不全に陥る．進行期には人工呼吸器管理となり，頸部以下の運動機能はALSと同様に著しく制限される重篤な疾患である．Fujitaらは，HMSN-Pの脳幹病変に着目し，運動神経にALSの原因遺伝子の一つであるoptineurinの異常を認めている[14]．その結果に基づいて，HMSN-Pは家族性ALSに分類すべきとの指摘もある[15]．今後，HMSN-Pの名称もより病態にふさわしいものに替わっていくかもしれない[16]．

現在の遺伝性神経筋疾患の分類を主導する米国ワシントン大学のNeuromuscular homepage（http://neuromuscular.wustl.edu/）によると，HMSN-Pは，常染色体優性遺伝性のCMT axonal typeに分類され，一方で，hereditary motor syndromeのSMAの特殊型としても分類されている．この疾患が発見された当時には，運動ニューロン病やHMSNの種類は数えるほどしかなかったが，現在はHMSNだけでも80種類以上，運動ニューロン病も70以上の型に分けられている．HMSN-Pはこの中間的な位置にあるが，HMSNの多様性から考えればこのような疾患が存在することも当然であり，*TFG*異常としての今後の分子遺伝学的病態解析の発展が期待される．

HMSN-Pは，後根神経節細胞の障害を中心とした後索・末梢神経障害と脊髄前角の脱落を主病変とする疾患であると考えられる．したがって，“neuropathy”ではなく，“neuronopathy”と考えるべきである．HMSN-Pは，成人発症の常染色体優性遺伝であり，本人の発症時点ですでに遺伝的リスクが次世代に広がっている可能性が高く，血縁者への適切な遺伝カウンセリングが必要とされる遺伝性神経疾患である．

表1　沖縄型と関西型HMSN-Pの比較検討

	沖縄型	関西型
遺伝形式	常染色体優性	常染色体優性
筋力低下の発症年齢(歳)	40～50歳代	40～50歳代
歩行不能年齢(歳)	50～60歳代	50～60歳代
症状・経過		
緩徐進行性*	＋	＋
四肢近位筋優位の筋力低下	＋	＋
四肢・体幹の筋痙攣，fasciculation	＋	＋
腱反射の低下・消失	＋	＋
深部感覚障害を伴う感覚障害	＋	＋
電気生理学的検査		
軸索優位の運動・感覚神経障害	＋	＋
末梢神経有髄神経の著明な脱落	＋	＋
血清CK値の上昇	＋	＋
脂質異常症，耐糖能異常の合併	＋	±
脊髄前角細胞，後索障害	＋	＋
疾患遺伝子変異	*TFG* c.854C>T	*TFG* c.854C>T
ハプロタイプ		
MS1	309	313
Ss532644308	T	C

＊数年の経過で死亡する例も報告されている．(文献[15]より引用)

HMSN-Pの世界的広がり

2007年，Maedaらは沖縄出身日系ブラジル人家系のHMSN-Pを報告した[17]．注目すべき点は，沖縄家系，後で述べる関西家系と同様に，このブラジル人家系も「家族性ALS」と診断されていたことである．したがって，HMSN-Pは，海外においても他の類似疾患と診断されている可能性が高く，沖縄県，滋賀県以外の国内のみならず，世界中に広く存在する可能性が高いと考えられた．ブラジル移民開始後，100年以上経過しているが，沖縄県からは1908年以来，ブラジルに約13万人，アメリカ合衆国に約8万人，ペルーに約4万人，アルゼンチンに約3万人，ボリビアに約1万人，カナダに1,500人，メキシコに650人，その他の国々に約7,250人が移住している．沖縄から移住した先祖をもつ日系ブラジル人のHMSN-P家系が見出されたことは[18]，HMSN-Pが単に沖縄県に限定されたものではなく，沖縄県民が移住した国々に広く存在することを示唆している．

関西型(滋賀型)HMSN-P

高橋らは，1984年滋賀県C町の検診を行い，筋萎縮症を呈する2家系を見出し，常染色体優性遺伝，近位筋優位の筋萎縮，軸索性末梢神経障害，CK値の軽度上昇などの特徴を報告している[19]．おそらく，関西型の最初の学会報告は，水田らによる報告であろう[20]．その後，高橋らは沖縄型との臨床的類似点と相違点を指摘している[21]．一方，梶らは，関西型の家系調査と連鎖解析を進め，その遺伝子座を沖縄型HMSN-Pとほぼ同じ第3染色体セントロメア近傍に遺伝子座をマッピングした[22]．以後，関西型HMSN-Pと呼ばれ，沖縄型HMSN-Pとの類似点・相違点が論議されてきた(表1)．

HMSN-P原因遺伝子*TFG*の解明

2012年，Ishiuraらによりついに HMSN-Pの原因遺伝子が TRK-fused gene(*TFG* c.854C>T, p.Pro285-Leu)変異であることが解明された[3]．ハプロタイプ解析の結果，沖縄家系と滋賀家系の*TFG*変異は独立した起源をもっていることも明らかとなった．*TFG*の解明は大きな反響を呼び諸外国から類似家系の報告が行われている[4][5]．HMSN-Pにおける変異と異なる新たな*TFG*ホモ接合変異による家族性痙性対麻痺例も報告されている[6]．われわれが当初から予想していたように，

HMSN-Pが国内のみならず世界中に広く存在すること，HMSN-Pの研究が運動ニューロン病の病態解明につながることが明らかとなった．

今後，HMSN-P家系および類似家系の国際疫学調査，HMSN-P患者の神経組織における分子病理学的検討，*TFG*の詳細な機能解明，*TFG*変異マウス・iPS細胞の作成などによる病態解明と治療法の開発が期待される．

文　献

1) Takashima H, Nakagawa M, Nakahara K, et al. A new type of hereditary motor and sensory neuropathy linked to chromosome 3. Ann Neurol 1997 ; 41 : 771-80.
2) 大城盛夫，中原啓一，末原雅人，ほか．沖縄本島に見られる感覚障害を伴う特異な神経原性筋萎縮症9例．厚生省神経疾患委託研究費「筋ジストロフィー症の疫学，病態および治療開発に関する研究」班．昭和59年度研究報告書．東京：厚生省；1985. p. 5-9.
3) Ishiura H, Sako W, Yoshida M, et al. The TRK-fused gene is mutated in hereditary motor and sensory neuropathy with proximal dominant involvement. Am J Hum Genet 2012 ; 91 : 320-9.
4) Lee SS, Lee HJ, Park JM, et al. Proximal dominant hereditary motor and sensory neuropathy with proximal dominance association with mutation in the TRK-fused gene. JAMA Neurol 2013 ; 70 : 607-15.
5) Campellone JV. Hereditary motor and sensory neuropathy with proximal predominance (HMSN-P). J Clin Neuromuscul Dis 2013 ; 14 : 180-3.
6) Beetz C, Johnson A, Schuh AL, et al. Inhibition of TFG function causes hereditary axon degeneration by impairing endoplasmic reticulum structure. Proc Natl Acad Sci USA 2013 ; 110 : 5091-6.
7) Nakagawa M, Nakahara K, Yoshidome H, et al. Epidemiology of progressive muscular dystrophy in Okinawa, Japan. Neuroepidemiology 1991 ; 10 : 185-91.
8) 川平　稔，中原啓一，末原雅人，納　光弘．沖縄県における筋萎縮症について．厚生省神経疾患研究委託費「筋ジストロフィー症の疫学，臨床および治療に関する研究」班．昭和58年度研究報告書．東京：厚生省；1983. p. 167-9.
9) Kondo K, Tsubaki T, Sakamoto F. The Ryukyuan muscular atrophy. An obscure heritable neuromuscular disease found in the islands of southern Japan. J Neurol Sci 1970 ; 11 : 359-82.
10) 中里　厚，木下真男，里吉営二郎．“琉球型筋萎縮症”の一例．臨床神経 1977；17：353-6.
11) 中原啓一，末原雅人，中島洋明，ほか．南九州における神経疫学の実態―筋萎縮性疾患を中心として．神経研究の進歩 1989；33：840-52.
12) Takashima H, Nakagawa M, Suehara M, et al. Gene for hereditary motor and sensory neuropathy (proximal dominant form) mapped to 3q13.1. Neuromuscul Disord 1999 ; 9 : 368-71.
13) 末原雅人．神経ネットワークシリーズ．沖縄型家族性神経原性筋萎縮症．医療 2001；55：101-3.
14) Fujita K, Yoshida M, Sako W, et al. Brainstem and spinal cord motor neuron involvement with optineurin inclusions in proximal dominant hereditary motor and sensory neuropathy. J Neurol Neurosurg Psychiatry 2011 ; 82 : 1402-3.
15) Maeda K. Heterogeneous prognosis for hereditary motor and sensory neuropathy with proximal dominance. J Neurol Disord Stroke 2013 ; 1 : 1006.
16) Nakagawa M. Optinurin inclusions in proximal hereditary motor and sensory neuropathy (HMSN-P): familial amyotrophic lateral sclerosis with sensory neuronopathy? J Neurol Neurosurg Psychiatry 2011 ; 82 : 1299.
17) Maeda K, Sugiura M, Kato H, et al. Hereditary motor and sensory neuropathy (proximal dominant form, HMSN-P) among Brazilians of Japanese ancestry. Clin Neurol Neurosurg 2007 ; 109 : 830-2.
18) Patroclo CB, Lino AM, Marchiori PE, et al. Autosomal dominant HMSN with proximal involvement : new Brazilian cases. Arq Neuropsiquiatr 2009 ; 67 : 892-6.
19) 高橋光雄．滋賀県家族性筋萎縮症の検診の思い出．末梢神経 Peripheral Nerve 2006；17：87-8.
20) 水田英二，斉田恭子，斉田隆彦，ほか．Proximal dominant weaknessを呈したhereditary motor sensory neuropathy type IIの1家系(会)．臨床神経

1988；28：1082.
21) 高橋光雄，三井良之，依藤史郎，ほか．滋賀県でみいだされた近位筋優位遺伝性運動感覚ニューロパチーの臨床報告．臨床神経 2007；47：571-6.
22) Maeda K, Kaji R, Yasuno K, et al. Refinement of a locus for autosomal dominant hereditary motor and sensory neuropathy with proximal dominancy (HMSN-P) and genetic heterogeneity. J Hum Genet 2007；52：907-14.

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Prominent fatigue in spinal muscular atrophy and spinal and bulbar muscular atrophy: Evidence of activity-dependent conduction block

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HIGHLIGHTS

- We showed that patients with chronic lower motor neuron disease [spinal muscular atrophy and spinal and bulbar muscular atrophy (SMA/SBMA)] frequently suffer disabling muscle fatigue.
- Single fiber electromyography with high-frequency stimulation revealed that SMA/SBMA patients might have activity-dependent conduction block phenomenon in distal motor axons.
- Activity-dependent conduction block is presumably produced by the reduced safety factor due to markedly increased axonal branching associated with collateral sprouting.

ABSTRACT

Objectives: To clarify whether patients with spinal muscular atrophy (SMA) or spinal and bulbar muscular atrophy (SBMA) suffer disabling muscle fatigue, and whether activity-dependent conduction block (ADCB) contributes to their fatigue. ADCB is usually caused by reduced safety factor for impulse transmission in demyelinating diseases, whereas markedly increased axonal branching associated with collateral sprouting may reduce the safety factor in chronic lower motor neuron disorders.
Methods: We assessed the fatigue severity scale (FSS) in 22 patients with SMA/SBMA, and in 100 disease controls (multiple sclerosis, myasthenia gravis, chronic inflammatory demyelinating polyneuropathy (CIDP), and axonal neuropathy). We then performed stimulated-single fibre electromyography (s-SFEMG) in the extensor digitorum communis (EDC) muscle of 21 SMA/SBMA patients, 6 CIDP patients, and 10 normal subjects.
Results: The FSS score was the highest in SMA/SBMA patients [4.9 ± 1.1 (mean ± SD)], with 81% of them complaining of disabling fatigue, compared with normal controls (3.5 ± 1.0), whereas patients with multiple sclerosis (4.3 ± 1.6), myasthenia gravis (4.0 ± 1.6) or CIDP (4.3 ± 1.4) also showed higher FSS score. When 2000 stimuli were delivered at 20 Hz in s-SFEMG, conduction block of single motor axons developed in 46% of patients with SMA/SBMA, and 40% of CIDP patients, but in none of the normal controls.
Conclusion: SMA/SBMA patients frequently suffer from disabling fatigue presumably caused by ADCB induced by voluntary activity.
Significance: ADCB could be the mechanism for muscle fatigue in chronic lower motor neuron diseases.

1. Introduction

Fatigue and weakness are common complaints of neurological disorder patients and significantly impair the quality of life. It is

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widely known that fatigue is one of the most disabling symptoms in patients with multiple sclerosis (MS) (Krupp et al., 1988) and those with chronic inflammatory demyelinating polyneuropathy (CIDP) (Boukhris et al., 2005; Bissay et al., 2008). Activity-induced fatigue and weakness were also described in not only patients with MS and CIDP but also with multifocal motor neuropathy (Cappelen-Smith et al., 2000; Kaji et al., 2000; Vucic et al., 2010; Straver et al., 2011).

In addition to demyelinating diseases, patients with a neurodegenerative motor neuron disorder often complain of fatigability. Persistent fatigue is a common complaint in patients with amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) (Piepers et al., 2008; McElhiney et al., 2009), and is associated with an impaired quality of life (Robbins et al., 2001). Straver et al. demonstrated that SMA patients had activity-induced weakness more often than normal subjects (Straver et al., 2011). Spinal and bulbar muscular atrophy (SBMA) is also a slowly progressive lower motor neuron disease, and SBMA patients may therefore show fatigability.

Activity-induced fatigue and weakness are caused by repetitive activity or exertion. It has been suggested that this phenomenon is attributable to activity-dependent conduction block (ADCB) arising in demyelinated axons. After repetitive firing, ionic concentration gradients in the axon are restored by increased Na^+/K^+ pump activity (Bostock and Grafe, 1985). Thus, with each pump-cycle, three Na^+ ions are expelled and only two K^+ ions enter (i.e., electrogenic pump), and the axons hyperpolarized by the pump (Schoepfle and Katholi, 1973), resulting in a decrease in the safety factor for impulse transmission. Nerve conduction is blocked if the safety factor is below unity due to leakage of the driving current caused by demyelination. In lower motor neuron disorders, the safety factor could also be reduced at the distal branching points due to collateral sprouting. Therefore, it is possible that ADCB could occur and may contribute to fatigue and weakness in SMA and SBMA patients.

We have developed a novel method to assess axonal activity-dependent hyperpolarization at a constant stimulus frequency using intra-muscular axonal stimulated-single fiber electromyography (s-SFEMG) (Noto et al., 2011). It was shown that tetanic stimulation at a constant rate (5, 10, and 20 Hz) resulted in a significant latency increase in single human motor axons, the extent of which depended on the stimulus frequency. This technique may detect ADCB if the safety factor is significantly reduced by demyelination or increased branching.

Given the recent interest in the mechanism of fatigue and weakness in demyelinating or chronic neurogenic diseases, the aim of this study was to assess the severity of fatigue in patients with SMA or SBMA, and to investigate whether ADCB contributes to fatigue in such patients.

2. Patients and methods

The study was conducted at Chiba University Hospital between October 2009 and March 2011. Informed consent was provided by each subject, and all experiments and the study protocol were conducted in accordance with the Declaration of Helsinki and with the approval of the Ethics Committee of Chiba University School of Medicine for Human Research Studies.

2.1. Subject

The present study included five different patient groups [SMA/SBMA, CIDP, MS, myasthenia gravis (MG), and axonal neuropathy] and normal subjects. The SMA/SBMA group ($n = 22$) consisted of 5 SMA patients and 17 SBMA patients; one of the 5 SMA patients had mutation of the SMN gene and the remaining SMA patients did not have genetic testing and were diagnosed based on the clinical/familial history and electrophysiological examination. All SBMA patients had expanded CAG repeats of the androgen receptor. Disease durations of SMA and SBMA patients were 22.6 ± 9.5 (mean ± SD) years and 10.2 ± 6.4 years, respectively. Modified Rankin Scale scores were 3.2 ± 0.8 and 2.2 ± 0.4.

The CIDP ($n = 16$), MS ($n = 31$), and MG ($n = 33$) groups consisted of consecutive patients in the study period. Neuropathy patients ($n = 20$) consisted of 13 patients with diabetic polyneuropathy, 6 with vasculitic neuropathy and 1 with vitamin B12 deficiency. This study also included 58 normal healthy subjects; none of whom had a neurological disorder, systematic disease, or was taking medication affecting the peripheral nerve function.

s-SFEMG was performed in 21 SMA/SBMA patients, 6 CIDP patients, and 10 normal subjects who consented to the examination protocol.

2.2. Assessment of fatigue

Fatigue was assessed by the Fatigue Severity Scale (FSS) (Krupp et al., 1989). The FSS was developed as a method of evaluating fatigue in patients with MS and other conditions such as systemic lupus erythematosus. The FSS questionnaire is composed of the following 9 statements related to patients' subjective perception of fatigue and its consequences for everyday activities: 1. My motivation is lower when I am fatigued, 2. Exercise brings on my fatigue, 3. I am easily fatigued, 4. Fatigue interferes with my physical functioning, 5. Fatigue causes frequent problems for me, 6. My fatigue prevents sustained physical functioning, 7. Fatigue interferes with carrying out certain duties and responsibilities, 8. Fatigue is among my three most disabling symptoms, 9. Fatigue interferes with my work, family, or social life. Patients are asked to rate their level of agreement (toward 7) or disagreement (toward 0) with the 9 statements. The final score represents the mean value of the 9 items.

2.3. Stimulated-single fiber electromyography

s-SFEMG was performed in the extensor digitorum communis muscle (EDC) using a Nicolet Viking 4 EMG machine (Nicolet Biomedical Japan, Tokyo, Japan), as described previously (Noto et al., 2011). The recordings were made intra-muscularly with a concentric needle electrode (30 G; TECA elite US53153). The high pass filter was set to 2 kHz and the low pass filter to 10 kHz. Intramuscular axonal stimulation was performed with a monopolar needle electrode (28 G; TECA U0809P02) and a reference surface electrode placed 2 cm laterally (Fig. 1). The stimulus duration was 0.1 ms. The distance between the stimulating and recording electrodes was 2 cm. The stimulus intensity was initially determined as 20% above the activation threshold of the target muscle action potential (MAP).

Before this study was performed, we predicted that blockings might occur due to slight movement of either the stimulating or recording electrodes produced by the muscle twitch. To avoid this phenomenon, the fingers of subjects and electrodes were fixed with a strap or a strut as shown in Fig. 1. In fact, during 20-Hz stimulation, the muscle twitch of the EDC muscle was not observed because 20-Hz axonal-stimulation produced persistent contraction of muscle bundles in all subjects. Therefore, the probability of blockings due to the movement of electrodes was low. We also observed the return of a previously blocked muscle action potential after rest in some recordings with blocking. However, we had to wait for over 15 min in each site in order to clear the effect of axonal hyperpolarization (Kiernan et al., 2004), and long time waiting

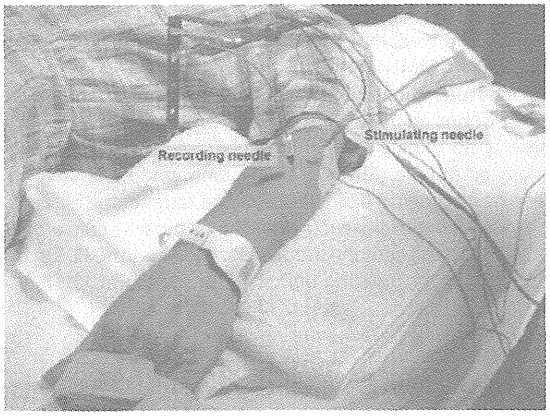

Fig. 1. The set up of stimulated-single fiber electromyography technique. To avoid slight movement of the stimulating and recording electrodes produced by the muscle twitch, fingers of the subject and electrodes were fixed with a strap or a metallic strut.

could not be tolerated for patients. For this reason, the re-stimulation after the rest was omitted.

When intermittent or persistent blockings were observed during stimulation, we increased the stimulus intensity by a further 20% of the previous intensity to secure supra-threshold stimulation. In consideration of tolerability of subjects, the extent of increasing stimulus intensity was up to 20%. A total of 2000 stimuli at 20 Hz were delivered. We examined 5 sites in the EDC in each subject and recorded the latency and shape of some MAPs, and calculated the percentage of MAPs with persistent or intermittent blockings. In this method, we defined persistent blocking as the condition whereby no MAP was evoked during the last 100 stimuli (1901–2000 times). The judgment of blocking was done by latency plotting with a special program for latency measurements (Medical Try System Co. Ltd., Tokyo, Japan).

2.4. Data analysis

The Fisher exact test was used to analyze gender ratio, the differences in proportion of subjects who have high FSS score ($\geqslant$4.0) between groups. The Wilcoxon rank-sum test was used to compare differences in FSS between genders in the normal control group. The correlation between the FSS scores and age in normal controls was tested with Spearman's rank correlation coefficient. Dunnett's multiple comparison tests were applied between normal controls and disease groups. In all comparisons, a p-value of less than 0.05 was considered to be significant. All statistical analyses were performed using STATA software (Stata Corp., Texas, USA) and R software, which is open source and freely available (see http://www.R-project.org).

3. Results

3.1. The fatigue severity scale scores

Clinical profiles and the fatigue severity scale (FSS) scores are shown in Table 1. The mean FSS score was significantly higher in the SMA/SBMA groups than in normal controls. Among the patient groups, the mean FSS score was higher in the SMA/SBMA group than in the other disease groups, although the differences were not significant. There was no significant association of the FSS scores with age or gender. When disabling fatigability was defined as an FSS score of 4.0 or above, as in previous studies (Armutlu et al., 2007; Kaynak et al., 2006), 36% of the normal subjects and 81% of the patients with SMA/SBMA had the degree of fatigue. The percentage of patients with fatigue was higher in the SMA/SBMA group than in the other disease groups.

On analyzing the correlation of the FSS scores with the age, disease duration, or modified Rankin scale score in each disease group, a positive correlation between the FSS scores and disease duration was found only in the MS group.

3.2. Blockings in stimulated-single fiber electromyography

Total numbers of MAPs examined were 41 from 10 normal controls, 85 from 21 SMA/SBMA patients (5 SMA and 16 SBMA patients), and 23 from 6 CIDP patients. The number of examined MAPs per subject ranged from 1 to 9. Table 2 shows the detection rates of intermittent/persistent blocking in normal controls, as well as SMA/SBMA and CIDP patients. Also, in this population, the mean FSS score in the SMA/SBMA group was significantly higher than in normal subjects.

In normal controls, no blocking was observed during 2000 stimuli. A representative recording and the latency scattergraph of a single MAP from a single normal subject are shown in Fig. 2A, 3A, and Supplementary Video 1. The latency prolonged linearly. Although increased jitter with intermittent blockings was found in normal subjects because of subthreshold stimulation, the jitter and blockings disappeared with an increasing stimulus intensity.

In SMA/SBMA and CIDP patients, intermittent or persistent blockings were similarly observed at the 2000th stimulus. We calculated the detection rates of persistent/intermittent blockings at the 2000th stimulus. The percentages of them in SMA/SBMA and CIDP groups were 11.8/45.8 and 13.3/40.0%, respectively (Table 2). Fig. 2B, 3B, and Supplementary Video 2 illustrate a characteristic recording and latency plot of intermittent blocking (finally leading to persistent blocking) from a single SBMA patient. Jitter and blocking were clearly visible in real-time (Supplementary Videos 2, 3). Such a phenomenon was never detected in normal controls. No significant correlation between the FSS score and percentage of intermittent/persistent blockings was demonstrated in SMA/SBMA and CIDP patients.

Table 1
Demographic, clinical findings and fatigue severity scale (FSS) score.

	Normal controls (n = 58)	SMA/SBMA (n = 22)	CIDP (n = 16)	Multiple sclerosis (n = 31)	MG (n = 33)	Neuropathy (n = 20)
Gender (M:F)	28:30	19:3**	13:3*	2:29**	16:17	9:11
Age; mean (range)	50 (20–85)	59 (37–75)	54 (23–79)	45 (20–65)	61 (24–83)**	60 (31–71)**
Disease duration (years); mean (range)	N/A	13.3 (1.5–34.0)	8.7 (0.2–22.0)	10.7 (1.3–38.0)	5.1 (2.0–6.9)	9.7 (0.2–30.0)
Modified Rankin Scale; median (range)	0	2 (2–4)**	2 (1–4)**	2 (1–4)**	1 (0–2)**	1 (1–4)**
FSS score; mean (SD)	3.5 (1.0)	4.9 (1.1)**	4.3 (1.4)	4.3 (1.6)*	4.0 (1.6)	3.6 (1.6)
FSS score $\geqslant$ 4.0 (%)	36	81**	63	65*	61*	35

*P < 0.05, **P < 0.01 vs. Normal control. SMA/SBMA, spinal muscular atrophy/spinal and bulbar muscular atrophy; CIDP, chronic inflammatory demyelinating polyneuropathy; MS, multiple sclerosis; MG, myasthenia gravis; N/A, not applicable.

Table 2
Detection rates of intermittent and persistent blockings during 2000 stimuli at 20 Hz in stimulated-single fiber electromyography and fatigue severity scale score.

	Normal controls	SMA/SBMA	CIDP
	$n = 10$	$n = 21$	$n = 6$
Gender (M:F)	6:4	18:3	5:1
FSS score; mean (SD)	3.8 (1.0)	4.9 (1.1)*	4.3 (1.5)
Intermittent blocking (%)***	0.0 (0.0)	11.8 (16.7)	13.3 (24.2)
Persistent blocking (%)***	0.0 (0.0)	45.8 (32.9)**	40.0 (23.5)*

$P < 0.05$, *$P < 0.01$ vs. Normal control, ***mean (SD); SMA/SBMA, spinal muscular atrophy/spinal and bulbar muscular atrophy; CIDP, chronic inflammatory demyelinating polyneuropathy; FSS, fatigue severity scale.

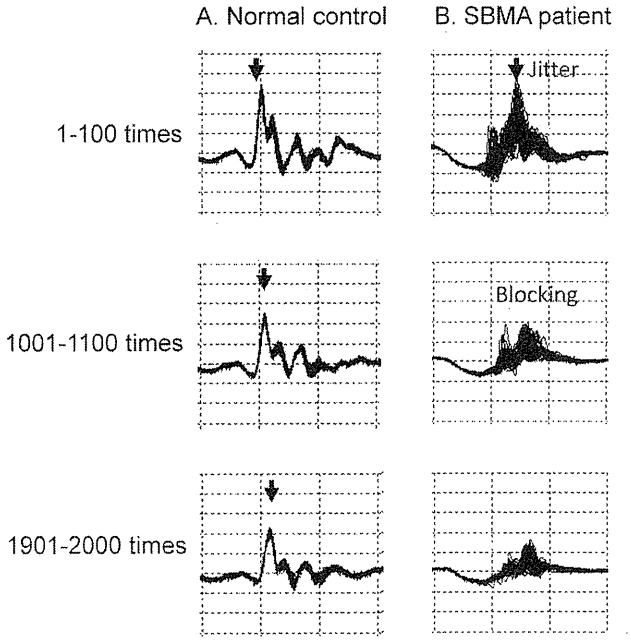

Fig. 2. Examples of superimposed single muscle action potentials during prolonged 20-Hz intramuscular microstimulation in the extensor digitorum communis muscle of a normal control (A) and a spinal and bulbar muscular muscular atrophy (SBMA) patient (B). Traces 1–100, 1001–1100, and 1901–2000 are shown separately. Note a gradual increase in latencies with no block of a muscle action potential (MAP) in a normal control (arrow in A), and jitter and subsequent blocking of a MAP in an SBMA patient (arrow in B).

4. Discussion

The present study demonstrates that patients with SMA/SBMA have prominent muscle fatigue, as well as patients with MS or CIDP. s-SFEMG studies have shown that SMA/SBMA and CIDP patients might have ADCB phenomenon induced by high-frequency axonal stimulation, and that both baseline neuromuscular transmission failure and axonal hyperpolarization could contribute to the activity-dependent changes observed in this study. The pathophysiology and mechanisms of fatigue are different among the disorders. This study firstly shows evidence that ADCB could contribute to muscle fatigue in SMA/SBMA.

4.1. Fatigue in neurodegenerative lower motor neuron disorders

In this study, "fatigue" means activity-induced muscle weakness and fatigability, not baseline muscle weakness and clinical severity. Demyelinating diseases, such as MS, MMN, and CIDP, often cause fatigability (Krupp et al., 1988; Boukhris et al., 2005; Bissay et al., 2008), and ADCB has been regarded as a mechanism of fatigue in MS and MMN (Vucic et al., 2010; Kaji et al., 2000). A recent report showed that SMA patients exhibited fatigue to the same extent as MMN and CIDP patients using FSS (Straver et al., 2011). Our study confirmed that fatigue was a frequently disabling symptom in not only SMA but also SBMA patients.

There is no widely used method to assess activity-dependent weakness or fatigue. Although FSS alone could not discriminate between psychological disinclination and fatigue due to an impairment of nerve, neuromuscular junction or muscle, some questions of FSS are to assess activity-induced fatigue, and the FSS score correlated with motor function deficits (Huisinga et al., 2011).

4.2. Mechanisms for blocking during 20-Hz stimulation

Our s-SFEMG technique detected axonal conduction failure during 20-Hz stimulation in SMA/SBMA and CIDP patients, whereas our method could not identify the site of blocking (axon, neuromuscular junction or muscle) accurately. This was a main limitation of our method. However we considered the main site of conduction failure we observed was axons. The possibility of electrode dislocation cannot be excluded as explanation of disappearance of some potentials. However we think it is possible that the change in the muscle action potential's shape is induced by hyperpolarization of the muscle fiber membrane as Bergmans (2012) emphasized in his recent commentary. This phenomenon was also consistent in this study. The change was generally observed in all subjects, and occurs not at random.

Our previous study demonstrated that tetanic stimulation at 20-Hz results in a significant latency increase in normal subjects (Noto et al., 2011). Along with previous studies, this phenomenon is believed to be induced by activation of the electrogenic Na^+/K^+ pump and resulting axonal hyperpolarization which leads to axonal conduction slowing (Vagg et al., 1998; Kuwabara et al., 2001; Kuwabara et al., 2002; Bergmans, 1970; Lin et al., 2000). Meanwhile, our previous study demonstrated the muscle action potential's shape became smaller and less sharp during stimulation. This phenomenon might be physiological, and was not due to a recording needle dislocation. Bergmans commented to this phenomenon in our previous study that the changes in waveforms and amplitudes in muscle action potentials during stimulation were caused by hyperpolarization of the muscle fiber membrane (Bergmans, 2012).

Regarding the physiological aspects of axonal firing, A 20-Hz stimulation is almost equivalent to physiological maximum voluntary contraction in EDC, and causes axonal hyperpolarization (Burke and Jankelowitz, 2009). This is the reason why we selected 20-Hz stimulation. As seen in Fig. 3B, the latency is gradually prolonged until the blocking occurs, although the dispersion of latencies (i.e., jitter) is also observed simultaneously. These findings may reflect activity-dependent hyperpolarization in the axon and the following blocking (i.e., ADCB).

This technique could not deny that blockings occur at the neuromuscular junction due to dysfunction of the synaptic terminal (e.g., the deficiency of acetylcholine in the axon). 20-Hz s-SFEMG with administration of cholinesterase inhibitor could solve this problem. However, it was difficult to perform it because of invasiveness. A further improvement in methodology is needed in future. In addition, recent studies reported that survival motor neuron protein deficiency produce neuromuscular junction dysfunction (Ling et al., 2012; Martinez et al., 2012). Although this factor might contribute to findings obtained from SMA patients, they were similar to findings in SBMA patients, and were not necessarily specific in SMA patients.

Also, our method was unable to calculate jitter values accurately. For this reason, we judged the intermittent/persistent blocking by latency plotting. Most of the blockings occurred a

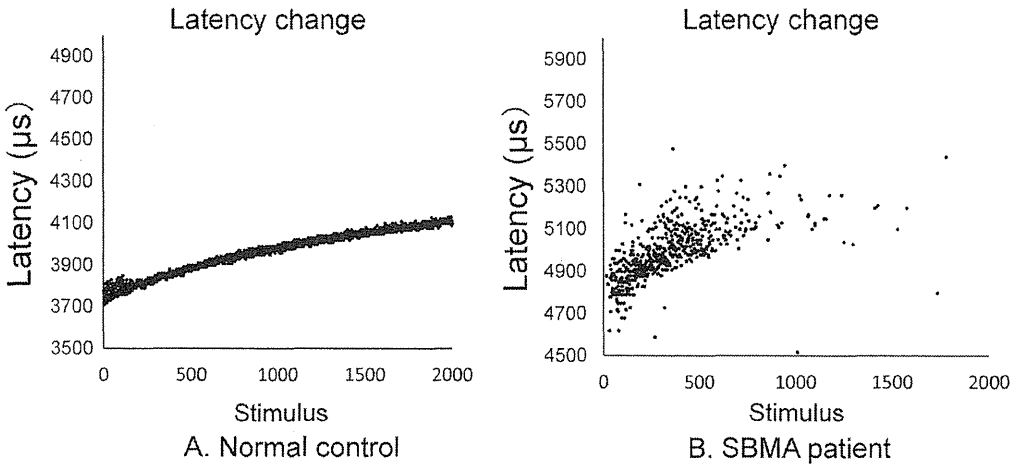

Fig. 3. Examples of the scatter plot of the latencies of single muscle action potentials during 20-Hz stimulation recorded from the extensor digitorum communis muscle of a normal control (A) and a spinal and bulbar muscular atrophy (SBMA) patient (B). The 2 subjects are the same as in Figure 2. Note a progressive increase in latencies during 2000 stimuli at 20 Hz in a normal control, and the dispersion of latencies and subsequent blocking in an SBMA patient.

few seconds after the start of stimulation, and they were judged as absolute blockings by enhancing the stimulus intensity. Enhancing level was set a further 20% of the previous intensity. Although it was difficult to ensure suprathreshold stimulation, the findings of SMA/SBMA and CIDP patients were distinctly different from that of normal controls in our method.

While there were some methodological limitations, blockings observed only during 20-Hz stimulation were likely to suggest conduction failure due to axonal hyperpolarization. Thus, these findings may reflect the existence of ADCB in physiological voluntary activity.

4.3. Activity-dependent conduction block in SMA and SBMA

The mechanism of ADCB in demyelinating neuropathy has been discussed in previous studies (Burke and Jankelowitz, 2009; Park et al., 2011). In SMA and SBMA, the main pathology is slowly progressive axonal loss. ADCB in neurodegenerative lower motor neuron disorders may be related to increased multiple axonal branches associated with collateral sprouting. Computer model by Zhou et al. simulated action potential propagation from a parent myelinated branch through a single branch point to two myelinated daughter branches (Zhou and Chiu, 2001). In the study, action potentials in daughter branches were smaller than that in the parent branch. If an axon has many sprouting branches, an axonal driving current in each nerve terminal branches will be extremely small. Thereby the safety factor could become critically lowered in the nerve terminals. This condition leads to a vulnerability to conduction failure when axons are hyperpolarized. Stålberg et al. reported that paired blocking was seen in ALS and SMA patients using a voluntary-single fiber electromyography method (Stålberg and Thiele, 1972). They proposed that this type of blocking occurred in newly formed sprouts because myelination in new branches was premature and offered a low safety factor for transmission. However, we assume that blocking could also occur in the terminals of many mature branches considering the existence of an axonal hyperpolarization mechanism induced by activity.

This reinnervation mechanism may also partly contribute to ADCB in chronic demyelinating disease, such as CIDP and MMN, because denervation and collateral sprouting are seen in the pathology of these diseases (Bouchard et al., 1999; Van Asseldonk et al., 2003). In addition to reinnervation, axons with higher firing rates might be involved in ADCB in motor neuron disorders. Vucic et al. demonstrated relatively larger increases in the threshold following activity in ALS patients than in healthy controls (Vucic et al., 2007). The central drive for higher firing rates in surviving axons would cause a greater impulse load on the axon also in SMA and SBMA. It is clinically relevant to explore the ionic mechanisms for muscle fatigue, which may provide a new treatment option by modulating the pump activity and specific ionic currents.

Disclosure

Drs. Noto, Misawa, Mori, Kawaguchi, Kanai, Shibuya, Isose, Nasu, Sekiguchi, Beppu, Ohmori, and Nakagawa report no disclosures. Dr. Kuwabara serves as an Associate Editor of *Journal of Neurology, Neurosurgery, and Psychiatry*, and as an Editorial Board Member of *Clinical Neurophysiology*.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.clinph.2012.12.053.

References

Armutlu K, Korkmaz NC, Keser I, Sumbuloglu V, Akbiyik DI, Guney Z, et al. The validity and reliability of the Fatigue Severity Scale in Turkish multiple sclerosis patients. Int J Rehabil Res 2007;30:81–5.

Bergmans J. Characteristics of post-tetanic hyperpolarisation of a bundle of myelinizated nervous fibers. C R Seances Soc Biol Fil 1970;164:1254–61.

Bergmans J. Serendipity in nerve excitability research. Clin Neurophysiol 2012;123:422–3.

Bissay V, Flamez A, Schmedding E, Ebinger G. Fatigue as the presenting symptom of chronic inflammatory demyelinating polyneuropathy. Muscle Nerve 2008;38:1653–7.

Bostock H, Grafe P. Activity-dependent excitability changes in normal and demyelinated rat spinal root axons. J Physiol 1985;365:239–57.

Bouchard C, Lacroix C, Plante V, Adams D, Chedru F, Guglielmi JM, et al. Clinicopathologic findings and prognosis of chronic inflammatory demyelinating polyneuropathy. Neurology 1999;52:498–503.
Boukhris S, Magy L, Gallouedec G, Khalil M, Couratier P, Gil J, et al. Fatigue as the main presenting symptom of chronic inflammatory demyelinating polyradiculoneuropathy: a study of 11 cases. J Peripher Nerv Syst 2005;10:329–37.
Burke D, Jankelowitz SK. Fatigue in chronic inflammatory demyelinating polyneuropathy. Muscle Nerve 2009;39:713–4.
Cappelen-Smith C, Kuwabara S, Lin CS, Mogyoros I, Burke D. Activity-dependent hyperpolarization and conduction block in chronic inflammatory demyelinating polyneuropathy. Ann Neurol 2000;48:826–32.
Huisinga JM, Filipi ML, Schmid KK, Stergiou N. Is there a relationship between fatigue questionnaires and gait mechanics in persons with multiple sclerosis? Arch Phys Med Rehabil 2011;92:1594–601.
Kaji R, Bostock H, Kohara N, Murase N, Kimura J, Shibasaki H. Activity-dependent conduction block in multifocal motor neuropathy. Brain 2000;123:1602–11.
Kaynak H, Altintas A, Kaynak D, Uyanik O, Saip S, Agaoglu J, et al. Fatigue and sleep disturbance in multiple sclerosis. Eur J Neurol 2006;13:1333–9.
Kiernan MC, Lin CS, Burke D. Differences in activity-dependent hyperpolarization in human sensory and motor axons. J Physiol 2004;558:341–9.
Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989;46:1121–3.
Krupp LB, Alvarez LA, LaRocca NG, Scheinberg LC. Fatigue in multiple sclerosis. Arch Neurol 1988;45:435–7.
Kuwabara S, Cappelen-Smith C, Lin CS, Mogyoros I, Burke D. Effects of voluntary activity on the excitability of motor axons in the peroneal nerve. Muscle Nerve 2002;25:176–84.
Kuwabara S, Lin CS, Mogyoros I, Cappelen-Smith C, Burke D. Voluntary contraction impairs the refractory period of transmission in healthy human axons. J Physiol 2001;531:265–75.
Lin CS, Mogyoros I, Kuwabara S, Cappelen-Smith C, Burke D. Accommodation to depolarizing and hyperpolarizing currents in cutaneous afferents of the human median and sural nerves. J Physiol 2000;529:483–92.
Ling KK, Gibbs RM, Feng Z, Ko CP. Severe neuromuscular denervation of clinically relevant muscles in a mouse model of spinal muscular atrophy. Hum Mol Genet 2012;21:185–95.
Martinez TL, Kong L, Wang X, Osborne MA, Crowder ME, Van Meerbeke JP, et al. Survival motor neuron protein in motor neurons determines synaptic integrity in spinal muscular atrophy. J Neurosci 2012;32:8703–15.
McElhiney MC, Rabkin JG, Gordon PH, Goetz R, Mitsumoto H. Prevalence of fatigue and depression in ALS patients and change over time. J Neurol Neurosurg Psychiatry 2009;80:1146–9.
Noto Y, Misawa S, Kanai K, Sato Y, Shibuya K, Isose S, et al. Activity-dependent changes in impulse conduction of single human motor axons: a stimulated single fiber electromyography study. Clin Neurophysiol 2011;122:2512–7.
Park SB, Lin CS, Burke D, Kiernan MC. Activity-dependent conduction failure: molecular insights. J Peripher Nerv Syst 2011;16:159–68.
Piepers S, van den Berg LH, Brugman F, Scheffer H, Ruiterkamp-Versteeg M, van Engelen BG, et al. A natural history study of late onset spinal muscular atrophy types 3b and 4. J Neurol 2008;255:1400–4.
Robbins RA, Simmons Z, Bremer BA, Walsh SM, Fischer S. Quality of life in ALS is maintained as physical function declines. Neurology 2001;56:442–4.
Schoepfle GM, Katholi CR. Posttetanic changes in membrane potential of single medullated nerve fibers. Am J Physiol 1973;225:1501–7.
Stålberg E, Thiele B. Transmission block in terminal nerve twigs: a single fibre electromyographic finding in man. J Neurol Neurosurg Psychiatry 1972;35:52–9.
Straver DC, van den Berg LH, van Doorn PA, Franssen H. Symptoms of activity-induced weakness in peripheral nervous system disorders. J Peripher Nerv Syst 2011;16:108–12.
Vagg R, Mogyoros I, Kiernan MC, Burke D. Activity-dependent hyperpolarization of human motor axons produced by natural activity. J Physiol 1998;507:919–25.
Van Asseldonk JT, Van den Berg LH, Van den Berg-Vos RM, Wieneke GH, Wokke JH, Franssen H. Demyelination and axonal loss in multifocal motor neuropathy: distribution and relation to weakness. Brain 2003;126:186–98.
Vucic S, Krishnan AV, Kiernan MC. Fatigue and activity dependent changes in axonal excitability in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 2007;78:1202–8.
Vucic S, Burke D, Kiernan MC. Fatigue in multiple sclerosis: mechanisms and management. Clin Neurophysiol 2010;121:809–17.
Zhou L, Chiu SY. Computer model for action potential propagation through branch point in myelinated nerves. J Neurophysiol 2001;85:197–210.

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RESEARCH PAPER

Neck weakness is a potent prognostic factor in sporadic amyotrophic lateral sclerosis patients

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ABSTRACT

Objective To clarify the emergence of muscle weakness in regions of the body that affect survival, and deterioration in activities of daily living (ADL) in amyotrophic lateral sclerosis (ALS) patients.

Methods We conducted a multicentre-based prospective cohort study of patients with ALS. We enrolled 401 sporadic patients with ALS. Death or the introduction of invasive ventilation was defined as the primary endpoint, and the time to five clinical markers of ADL deterioration associated with bulbar paralysis or limb weakness were defined as ADL milestones. Muscle weakness was assessed in the neck flexor muscles; the bilateral abductors of the shoulders; the bilateral wrist extensor muscles; the bilateral flexor muscles of the hips; and the bilateral ankle dorsiflexion muscles. We performed Cox proportional hazards regression analyses for the primary endpoint and the five ADL milestones, adjusting for known covariate prognostic factors for ALS.

Results The Medical Research Council (MRC) score for the neck flexors was the most significant prognostic factor for the primary endpoint (HR 0.74, p<0.001), *loss of speech* (HR 0.66, p<0.001), and *loss of swallowing function* (HR 0.73, p<0.001), and was one of the significant prognostic factors for *loss of upper limb function*, *difficulty turning in bed*, and *loss of walking ability* (p=0.001, 0.002, and 0.008, respectively). The MRC score for the neck flexors was also a significant prognostic factor for covariates of the previously reported prognostic factors.

Conclusions Neck weakness is an independent prognostic factor for survival and deterioration in ADL in Patients with ALS.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is an adult-onset neurodegenerative disease characterised by progressive upper and lower motor neuron loss, which leads to limb and bulbar paralysis and respiratory failure.[1] Symptoms develop at a progressive rate, and the median survival time from disease onset is 2–4 years.[2–4] However, patients with ALS show extensive variability in clinical courses, with durations ranging from a few months to more than 10 years. Furthermore, major symptoms that differentially affect activities of daily living (ADL) and prognosis also show variability among patients with different disease forms.[5] A better understanding of the factors influencing deterioration in ADL and prognosis would help physicians and patients determine whether and when to introduce non-invasive positive pressure ventilation, tube feeding, tracheostomy and artificial ventilation, and would lead to effective stratification strategies in clinical trials. Several studies have shown that age,[6–10] bulbar symptom onset,[6 7] respiratory function,[3 8 11 12] time from symptom onset to diagnosis,[2 6 10 13 14] functional score[2 14] and rate of disease progression[2 15–17] are predictors of survival. Muscle weakness in particular regions of the body affect the prognosis of ALS, although it has not been sufficiently determined which regions are most predictive.[18] To investigate the longitudinal course of patients with ALS and clarify the emergence of muscle weakness, which affects deterioration in ADL and ALS prognosis, we conducted a prospective, multicentre study.

METHODS

Patient registry and follow-up system

We constructed a multicentre registration and follow-up system called the Japanese Consortium for Amyotrophic Lateral Sclerosis research (JaCALS), which consists of 21 neurology facilities in Japan. Patients with ALS diagnosed in these facilities were consecutively registered with written informed consent. The ethics committees of all the participating institutions approved the study. Full clinical examinations were conducted at registration by neurologists in each of the respective institutions. Muscle strength was manually tested and scored with the scale of the Medical Research Council (six points, range: 0–5)[19] in nine muscle groups as follows: neck flexors; bilateral abductors of shoulders as representatives of proximal upper extremity muscles; wrist extensors muscles as representatives of distal upper extremity muscles; bilateral flexors of hips as representatives of proximal lower extremity muscles; and ankle dorsiflexion muscles as representatives of distal lower extremity muscles. All manual muscle testing was performed with standard positioning and procedures by certified neurologists.[20] The MRC score of the neck

flexors was determined with the patient in the supine position. We confirmed the inter-rater reliability of the manual muscle testing method employed in this study using 23 patients with neuromuscular disease. The values of the kappa statistics of each muscle ranged from 0.65 to 0.93. To standardise the procedures and the examinations, the three organising doctors (NA, RN, HaW) visited each participating facility and ascertained the evaluation methods for this study.

Disease onset was defined as when the patients became initially aware of muscle weakness or impairment of swallowing, speech, or respiration. We enrolled patients who fulfilled the revised El Escorial criteria.[21] The diagnostic accuracy of the enrolled patients was then assessed by members of the steering committee of the JaCALS. Included patients were then followed-up with telephone surveys conducted by clinical research coordinators (CRC) or with examinations by neurologists every 3 months, and the degree of deterioration in ADL was determined at each time point. We employed the Japanese version of the ALSFRS-R as a scale for ADL, which was validated by Ohashi *et al*, using a telephone survey system.[22] We confirmed the reliability of the telephone survey system for the Japanese version of the ALSFRS-R previously,[23] and the English version of the telephone survey system has been confirmed in several previous studies.[24–26] Prior to the study, we informed and trained the CRCs of the study plan, procedures for the telephone survey, ethical issues relevant to the study, and requisite considerations for patients with ALS and caregivers, and then provided them with a general knowledge of ALS.

We defined a primary endpoint and ADL milestones in the disease course of the patients with ALS and determined their occurrence by telephone survey or examinations by neurologists. The introduction of tracheostomy positive pressure ventilation (TPPV) or death of the patient was defined as the primary endpoint, and TPPV-free survival was defined as survival. *Loss of speech function*, *loss of swallowing function*, *loss of upper limb function*, *difficulty turning in bed*, and *loss of walking ability* were set as ADL milestones. The time at which each ADL milestone occurred was defined as follows: *loss of speech function* was determined to have occurred when non-vocal communication became needed; *loss of swallowing function* was determined to have occurred when parenteral or enteral feeding became needed exclusively; *loss of upper limb function* occurred when the patient needed to be fed and became unable to grip a pen; *difficulty turning in bed* occurred when the patient became unable to turn in bed alone; *loss of walking ability* occurred when the patient became unable to walk without assistance.

Patients

A total of 520 patients with ALS were initially registered in the JaCALS from January 2006 to June 2011. We excluded 26 patients with known gene mutations: 17 patients with SOD-1 mutations, two patients with TDP-43 mutations, two patients with FUS/TLS mutations, three patients with angiogenin mutations, and two patients with C9ORF72 repeat expansions. We also excluded 13 patients with family histories of ALS and 40 patients who were categorised as clinically possible or suspected according to the revised El Escorial criteria. An additional 20 patients for whom we could not obtain follow-up information to their refusal to participate in the telephone survey were also excluded. Twenty patients were excluded due to invalid data. The study finally included 401 sporadic patients with ALS diagnosed as clinically definite, probable, or probable laboratory-supported. Of these, 382 patients were followed for more than a year or died within a year of registration, and 19 patients were censored within a year from registration. Eleven patients declined the telephone survey during the course of the study, and we lost contact with eight patients during the survey.

Statistical analysis

The clinical data of the registered patients were anonymised in each participating facility of the JaCALS and assigned unique patient numbers. The data were then sent to the clinical data centre located at the Nagoya University Graduate School of Medicine and inputted into the JaCALS database.

We performed Cox proportional hazards regression analyses for the time of registration to the primary endpoint or onset of each ADL milestone to evaluate the impact of muscle weakness on the time to the primary endpoint and each decline in ADL. Specifically, for the primary endpoint and each ADL, we evaluated the HR for the MRC scores in nine muscle groups (ie, neck flexors, left and right abductors of shoulders, wrist extensor muscles, flexors of hips and ankle dorsiflexion muscles) at registration, identifying the muscles groups associated with the primary endpoint and five common ADL milestones. Additionally, we examined the HR for each muscle group after adjusting for known prognostic factors as follows: age at registration,[6–10] gender (male vs female),[6 27] disease duration,[2 6 10 13 14] percent vital capacity (%VC),[3 8 11 12] ALSFRS-R score,[14] riluzole use (yes vs no),[28] bulbar symptom,[6 7] and classification according to the revised El Escorial criteria (definite vs probable or probable laboratory-supported).[7 8 10 14] We compared the time from registration to the primary endpoint or each of the previously defined ADL milestones in the patients divided by their degree of muscle weakness using the Kaplan–Meier method. The log-rank test was used to test the null hypothesis that all the Kaplan–Meier curves were equal. A two-sided $p<0.05$ was considered statistically significant. All statistical analyses were conducted using the PASW V.18.0 program (SPSS Inc, Chicago, Illinois, USA).

RESULTS

Demographic characteristics of the registered patients

The patient sample comprised 244 men and 157 women. The median age at disease onset was 62.2 years (IQR: 53.5–68.5 years), and the mean follow-up period was 2.1±1.5 years. The follow-up rate at 1 year after registration was 95.3%. As initial symptoms, 47.4% of the patients showed upper limb weakness, 31.4% lower limb weakness, 22.9% dysarthria, 5.5% dysphagia and 2.0% cervical weakness. At registration, the median score on the ALSFRS-R was 38 (IQR: 32–42). (see online supplementary table S1).

Identification of weakened muscle groups that affect survival and progression to the ADL milestone

Cox proportional hazard regression analyses for the primary endpoint and the ADL milestones

Table 1 shows the results of Cox proportional hazard regression analyses for the primary endpoint and the five ADL milestones, including the MRC scores of the nine muscle groups. The MRC score for the neck flexors was the most significant negative prognostic factor for the primary endpoint, *loss of speech*, and *loss of swallowing function* (HR 0.74, $p<0.001$, HR 0.66, $p<0.001$, HR 0.73, $p<0.001$, respectively). For the *loss of upper limb function*, *difficulty turning in bed* and *loss of walking ability*, the MRC score for the neck flexors was a significant negative prognostic factor (HR 0.77, $p=0.001$, HR 0.77, $p=0.002$, and HR 0.80, $p=0.008$, respectively). Whereas, the MRC score for the left wrist extensors was a significant positive prognostic factor for the primary endpoint and each ADL milestone except for *difficulty turning in bed*.

Table 1 Multivariate Cox regression analyses for the primary endpoint and each activity of daily living milestone using the MRC score of each muscle group at registration

	Primary endpoint		Loss of speech		Loss of swallowing function		Loss of upper limb function		Difficulty turning in bed		Loss of walking ability	
Muscle group	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
Neck flexors	0.74 (0.65 to 0.86)	<0.001	0.66 (0.56 to 0.76)	<0.001	0.73 (0.63 to 0.85)	<0.001	0.77 (0.66 to 0.89)	0.001	0.77 (0.66 to 0.91)	0.002	0.80 (0.67 to 0.94)	0.008
Left shoulder abductors	0.87 (0.69 to 1.11)	0.266	0.89 (0.69 to 1.14)	0.363	0.89 (0.71 to 1.12)	0.309	0.62 (0.49 to 0.79)	<0.001	0.72 (0.56 to 0.93)	0.012	0.75 (0.57 to 1.00)	0.049
Right shoulder abductors	0.98 (0.77 to 1.25)	0.890	1.11 (0.87 to 1.43)	0.399	1.02 (0.81 to 1.29)	0.867	1.19 (0.94 to 1.50)	0.159	1.08 (0.85 to 1.39)	0.529	0.99 (0.75 to 1.30)	0.917
Left wrist extensors	1.29 (1.04 to 1.59)	0.018	1.28 (1.03 to 1.59)	0.026	1.24 (1.02 to 1.51)	0.034	1.42 (1.14 to 1.77)	0.002	1.24 (1.00 to 1.55)	0.054	1.39 (1.08 to 1.79)	0.010
Right wrist extensors	0.90 (0.74 to 1.08)	0.254	0.88 (0.73 to 1.07)	0.193	0.92 (0.77 to 1.11)	0.380	0.73 (0.60 to 0.88)	0.001	0.80 (0.66 to 0.98)	0.029	0.98 (0.79 to 1.22)	0.884
Left hip flexors	0.99 (0.72 to 1.36)	0.964	0.96 (0.73 to 1.28)	0.791	0.85 (0.62 to 1.15)	0.284	0.74 (0.55 to 0.99)	0.040	0.77 (0.56 to 1.06)	0.115	0.90 (0.61 to 1.32)	0.585
Right hip flexors	0.96 (0.69 to 1.34)	0.830	0.95 (0.70 to 1.28)	0.719	1.09 (0.79 to 1.50)	0.613	1.18 (0.87 to 1.62)	0.290	1.18 (0.84 to 1.66)	0.331	1.06 (0.69 to 1.64)	0.788
Left ankle extensors	1.14 (0.93 to 1.40)	0.214	1.13 (0.94 to 1.34)	0.185	1.14 (0.95 to 1.37)	0.166	1.26 (1.04 to 1.52)	0.021	1.09 (0.91 to 1.30)	0.367	0.93 (0.71 to 1.21)	0.583
Right ankle extensors	0.94 (0.76 to 1.15)	0.530	0.95 (0.79 to 1.14)	0.564	0.94 (0.77 to 1.14)	0.539	0.85 (0.70 to 1.04)	0.125	0.81 (0.68 to 0.97)	0.023	0.72 (0.57 to 0.91)	0.007

According to table 1, the MRC score for the neck flexors was commonly identified as a possible prognostic factor for the primary endpoint and the five ADL milestones. We further examined its impact after adjusting for the other established or potential risk factors, that is, age at registration, gender, disease duration from onset to registration, percent vital capacity (% VC) at registration, ALSFRS-R score at registration, classification according to revised El Escorial criteria, riluzole use and bulbar symptom at registration (table 2). As seen in table 2, the MRC score for the neck flexors was an independent and significant prognostic factor for the primary endpoint, *loss of speech*, *loss of swallowing*, *loss of upper-limb function* and *difficulty turning in bed* in patients with ALS except for *loss of walking ability*. ($p<0.001$, $p=0.001$, $p=0.003$, $p<0.001$, $p=0.027$, respectively). At registration, there were moderate and significant correlations between the MRC score for the neck flexors and the % VC or the ALSFRS-R score. Pearson's correlation coefficients were 0.367 ($p<0.001$) and 0.496 ($p<0.001$), respectively.

Differences in survival time and time to ADL milestones in patients in terms of the MRC score grade for the neck flexors

We divided the registered patients into four categories according to their MRC score for the neck flexors (ie, 5, 4, 3 and ≤2). Figure 1 shows the Kaplan–Meier curves for the four categories for the primary endpoint and each ADL milestone. All the differences between the curves were significant according to a log-rank test ($p<0.001$).

DISCUSSION

In a prospective and multicentre cohort study, we identified that weakness of the neck flexors is a potent factor for the prediction of survival and for the deterioration of ADL, such as speech, swallowing, upper limb function, turning in bed, and walking, in sporadic patients with ALS.

The neck flexors consist of the sternocleidomastoid muscle (SCM), the platysma muscle, hyoid muscle, longus capitis muscle, longus colli and scalenus. These muscles are innervated by motor neurons in the cervical cord (C1–8) and accessory nerve nuclei,[29 30] primarily the C2–4 segments. By contrast, respiratory muscles consist of the diaphragm and the internal and external intercostals muscles, which are innervated by motor neurons of the upper cervical cord (C3–5) and thoracic cord (Th1–Th12), respectively.[30] Thus, the muscles for neck flexion and those for respiration partially share spinal segments of the motor neuron column for their motor innervations. Furthermore, significant correlations are present between compound muscle action potentials of the SCM and those of the diaphragm in patients with ALS,[31] suggesting that neck muscle weakness is correlated with weakness of the diaphragm to some extent in ALS. Because the main cause of death in patients with ALS is respiratory insufficiency, it is reasonable that neck flexor weakness was associated with respiratory impairments and, eventually, survival time. The motor response amplitude of the phrenic nerve motor neurons which are located in the C3–5 segments has been shown to be a significant prognostic factor for survival in patients with ALS.[32] This supports our findings.

Why then is weakness of the neck flexors a determinant factor for the deterioration of ADL for speech, swallowing, upper limb function, truncal turning and walking ability? Recently, some studies have suggested that the degeneration of motor neurons is initially a focal process in ALS that later spreads contiguously throughout the three-dimensional anatomy of connected or neighbouring neurons.[33–36] Dysfunction of speech and swallowing involves the impairment of motor

Table 2 Multivariate Cox regression analyses with the adjustments of the covariates that we selected for the primary endpoint and each activity of daily living milestone using known predictive factors

	Primary endpoint		Loss of speech		Loss of swallowing function		Loss of upper limb function		Difficulty turning in bed		Loss of walking ability	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
MRC score of neck flexors at registration	0.72 (0.62 to 0.83)	<0.001	0.78 (0.67 to 0.90)	0.001	0.80 (0.69 to 0.93)	0.003	0.76 (0.65 to 0.88)	<0.001	0.83 (0.70 to 0.98)	0.027	0.95 (0.79 to 1.15)	0.601
Age at registration (years)	1.03 (1.02 to 1.04)	<0.001	1.02 (1.01 to 1.03)	0.002	1.03 (1.01 to 1.04)	<0.001	1.01 (0.99 to 1.02)	0.264	1.01 (0.99 to 1.02)	0.265	1.00 (0.98 to 1.01)	0.890
Gender (male vs female)	1.14 (0.85 to 1.52)	0.381	0.85 (0.65 to 1.12)	0.247	1.13 (0.85 to 1.49)	0.398	1.27 (0.97 to 1.68)	0.088	1.01 (0.76 to 1.33)	0.947	0.85 (0.61 to 1.17)	0.309
Duration from onset to registration (years)	0.64 (0.57 to 0.72)	<0.001	0.72 (0.64 to 0.80)	<0.001	0.69 (0.62 to 0.77)	<0.001	0.82 (0.75 to 0.9)	<0.001	0.74 (0.65 to 0.85)	<0.001	0.75 (0.66 to 0.87)	<0.001
%VC at registration	0.98 (0.98 to 0.99)	<0.001	0.98 (0.97 to 0.99)	<0.001	0.98 (0.98 to 0.99)	<0.001	0.99 (0.98 to 1.00)	0.001	0.99 (0.99 to 1.00)	0.007	1.00 (0.99 to 1.00)	0.491
ALSFRS-R at registration	0.97 (0.94 to 0.99)	0.008	0.99 (0.97 to 1.02)	0.483	0.96 (0.93 to 0.98)	0.001	0.96 (0.94 to 0.98)	0.001	0.89 (0.86 to 0.92)	<0.001	0.91 (0.88 to 0.94)	<0.001
El Escorial criteria (probable or probable laboratory-supported)	0.72 (0.53 to 0.99)	0.043	0.61 (0.45 to 0.82)	0.001	0.76 (0.56 to 1.04)	0.087	0.67 (0.50 to 0.90)	0.007	0.71 (0.52 to 0.97)	0.031	0.63 (0.44 to 0.88)	0.008
Riluzole administration	1.02 (0.75 to 1.37)	0.916	1.09 (0.82 to 1.44)	0.551	0.97 (0.73 to 1.29)	0.843	0.95 (0.72 to 1.25)	0.694	0.84 (0.63 to 1.13)	0.258	0.94 (0.68 to 1.31)	0.721
Bulbar symptom at registration	0.91 (0.67 to 1.22)	0.524	2.04 (1.52 to 2.73)	<0.001	1.41 (1.06 to 1.86)	0.018	0.68 (0.50 to 0.93)	0.015	0.63 (0.47 to 0.84)	0.002	0.68 (0.49 to 0.96)	0.028

%VC, percent vital capacity; ALSFRS-R, revised amyotrophic lateral sclerosis functional rating scale.

neurons relayed via the glossopharyngeal, vagus, accessory and hypoglossal nerves to the medulla oblongata.[30] The medulla oblongata and cervical cord motor neurons innervating the neck flexion muscles are anatomically different in their three-dimensional layering, while these two groups of neurons are rather contiguously located. Thus, it may be speculated that if the contiguous spreading of motor neuron degeneration occurs according to the local spreading hypothesis, neck flexion impairment may eventually affect speech and swallowing functions. Furthermore, motor neurons for the neck flexion muscles, which are located in the C1–8 segments,[29 30] are also contiguous or overlapping with those for the upper limb muscles in the C5–Th1 segments, particularly the proximal upper limb muscles.[29 30] Neck flexion and upper limb function may be correlated with disease progression through the local spreading view of motor neuron degeneration. Truncal turning and walking require not only lower limb muscle activities but also power in a broad area of the chest, abdominal and back muscles, which are innervated by the cervical to lumbar cord.[37–39] Therefore, propagation of weakness from the cervical and lumbar areas may affect truncal turning or walking. We need, however, further investigations to demonstrate the underlying mechanisms of the correlation between the neck muscles and other muscles of the body that together determine ADL.

In this study, the MRC score for the left wrist extensors shows a positive prognostic factor for the primary endpoint and some ADL milestones, the reason for which might be that the weakness of the distal muscle in the non-dominant arm was least relevant to survival, or ADL declines so that it was shown to be a positive factor in the multivariate analyses.

A number of studies have demonstrated survival curves for patients with ALS and some factors that influence these survival curves.[18] The majority of these studies have found that older age is a strong risk factor for shorter survival in patients with ALS,[6–10] and the onset of bulbar symptoms is associated with a worse prognosis than the onset of spinal symptoms.[6 7] Several studies have found that a longer diagnostic delay correlates with a better prognosis,[2 6 10 13 14] and that a lower %VC or a percent forced vital capacity (%FVC) is correlated with shorter survival for patients with ALS.[3 8 11 12] The progression rate of the ALSFRS-R at the time of diagnosis was also related to ALS prognosis.[17] Neck flexor weakness has not been listed as a prognostic factor for patients with ALS, and most of these studies evaluated survival alone as an endpoint, and did not determine the onset of loss of speech, swallowing, limb and truncal function. In this study, we showed that neck flexor weakness was not only a novel prognostic factor for survival but also a significant prognostic marker for non-survival events related to ADL decline for patients with ALS.

In the course of ALS, patients must make some difficult decisions, including the use of gastrostomy for tube feeding, the use of assisted ventilation, and end-of-life planning, which require the support of the attending physician and a multidisciplinary team. All patients with ALS should be provided with sufficient information concerning these interventions and given sufficient opportunity for the careful consideration of their decision. In the medical, nursing and social care of patients with ALS, simple and robust indicators for predicting the status of each patient for several months or a year after diagnosis are necessary for patient management. Medical staff and caregivers need to have a predictor of the patient's status in the near future, including survival prognosis and also estimates for the loss of speech, swallowing, limb and truncal function. Our findings may contribute to such prediction.

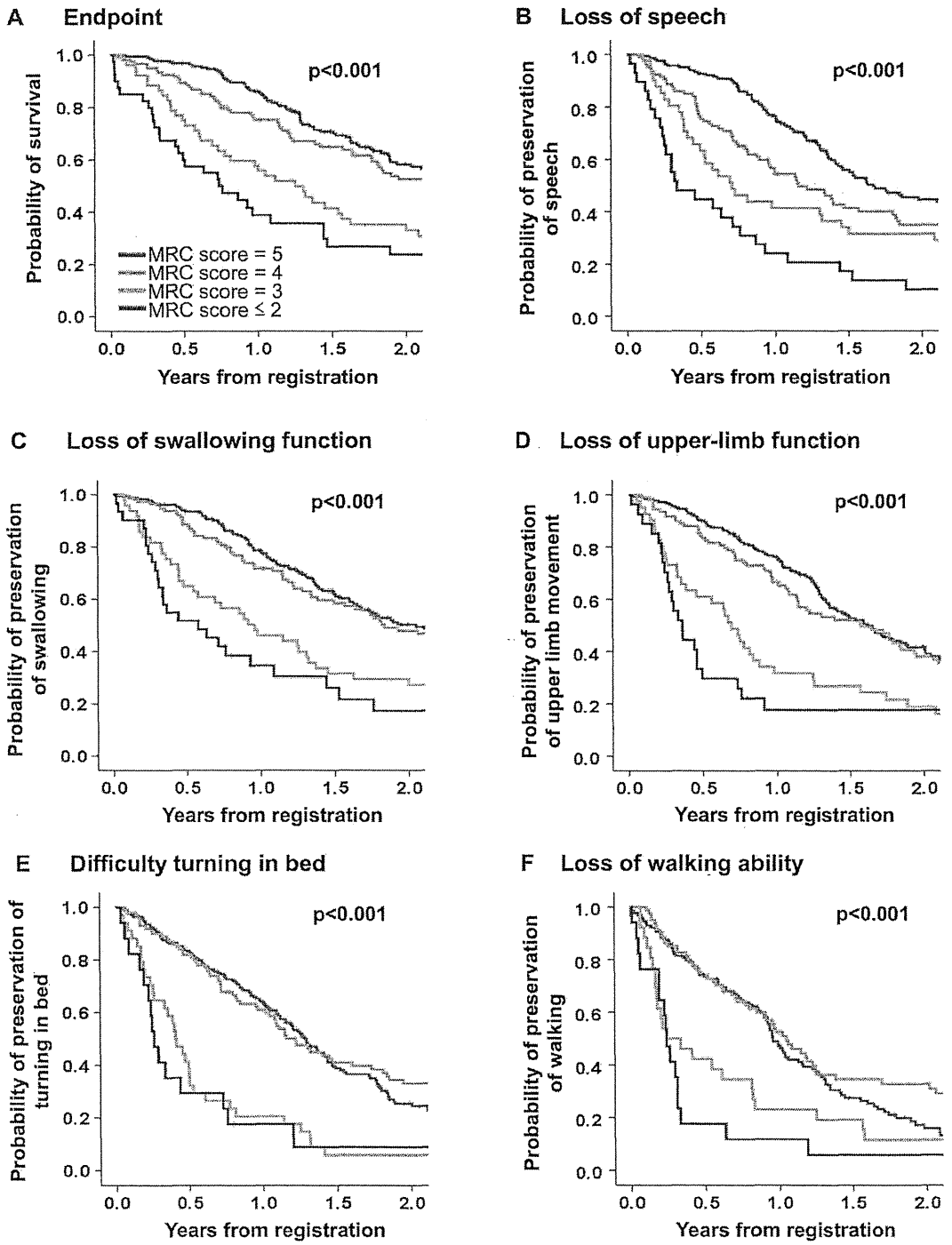

Figure 1 Kaplan–Meier curves according to the MRC score for the neck flexors. The Kaplan–Meier curves for the primary endpoint and each activity of daily living milestone among four categories divided according to the MRC score for the neck flexors were compared by the log-rank test. Curves are shown for the MRC score 5 (blue), the MRC score 4 (green), the MRC score 3 (orange), and the MRC score ≤2 (purple) groups. All the differences of the curves were significant (p<0.001).

The course of ALS is highly variable between patients,[5] which is one of the major factors limiting the power of ALS clinical trials.[40 41] Therefore, robust stratification factors that could divide ALS patient groups depending upon prognosis are needed for designing trials. Compared with known prognostic factors for patients with ALS, such as age, duration from onset to registration, ALSFRS-R at registration, and presence of bulbar symptom, weakness of the neck flexors was a potent and independent prognostic factor. Thus, the MRC score for the neck flexors might be used for stratification factor in a future clinical trial.

Neck extensor muscle weakness with head drop as an early symptom has been reported in a few patients with ALS.[42 43] However, Katz *et al*[44] wrote that neck flexor weakness is typically observed. We assert that neck flexor weakness is commonly observed in patients with ALS, and is useful for the prediction of prognosis.

The limitations of this study are as follows: registered patients were followed-up by telephone survey, and we did not examine longitudinal changes in the strength of multiple muscles. As we demonstrated, the relationship between the involved muscle groups and survival prognosis and estimates of ADL deterioration would offer insights into the modalities of progression in patients with ALS. However, to examine the pattern of spread more precisely, a cohort study that observes longitudinal changes in the strength of muscle groups and extensions of muscle weakness will be required.

This study analysed a multicentre cohort of patients with ALS in a single nation, Japan. Although the clinical profiles of ALS are broadly similar among countries in previous reports, the outcome of our study would be better confirmed in cohorts of patients with ALS in multiple countries.

In conclusion, we showed that neck weakness is an independent prognostic factor for survival and deterioration in ADL in patients with ALS. We hope that our report will be helpful for clinicians who want to provide medical, social and nursing care to patients with ALS with proper timing, and to researchers as they plan clinical trials for ALS.

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REFERENCES

1 Rowland LP, Shneider NA. Amyotrophic lateral sclerosis. *N Engl J Med* 2001;344:1688–700.
2 Haverkamp LJ, Appel V, Appel SH. Natural history of amyotrophic lateral sclerosis in a database population. Validation of a scoring system and a model for survival prediction. *Brain* 1995;118:707–19.
3 Ringel SP, Murphy JR, Alderson MK, *et al*. The natural history of amyotrophic lateral sclerosis. *Neurology* 1993;43:1316–22.
4 Norris F, Shepherd R, Denys E, *et al*. Onset, natural history and outcome in idiopathic adult motor neuron disease. *J Neurol Sci* 1993;118:48–55.
5 Chio A, Calvo A, Moglia C, *et al*. Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study. *J Neurol Neurosurg Psychiatry* 2011;82:740–6.
6 del Aguila MA, Longstreth WT Jr, McGuire V, *et al*. Prognosis in amyotrophic lateral sclerosis: a population-based study. *Neurology* 2003;60:813–19.
7 Magnus T, Beck M, Giess R, *et al*. Disease progression in amyotrophic lateral sclerosis: predictors of survival. *Muscle Nerve* 2002;25:709–14.
8 Chio A, Mora G, Leone M, *et al*. Early symptom progression rate is related to ALS outcome: a prospective population-based study. *Neurology* 2002;59:99–103.
9 Christensen PB, Hojer-Pedersen E, Jensen NB. Survival of patients with amyotrophic lateral sclerosis in 2 Danish counties. *Neurology* 1990;40:600–4.
10 Millul A, Beghi E, Logroscino G, *et al*. Survival of patients with amyotrophic lateral sclerosis in a population-based registry. *Neuroepidemiology* 2005;25:114–19.
11 Stambler N, Charatan M, Cedarbaum JM. Prognostic indicators of survival in ALS. ALS CNTF Treatment Study Group. *Neurology* 1998;50:66–72.
12 Czaplinski A, Yen AA, Appel SH. Forced vital capacity (FVC) as an indicator of survival and disease progression in an ALS clinic population. *J Neurol Neurosurg Psychiatry* 2006;77:390–2.
13 Czaplinski A, Yen AA, Appel SH. Amyotrophic lateral sclerosis: early predictors of prolonged survival. *J Neurol* 2006;253:1428–36.
14 Kaufmann P, Levy G, Thompson JL, *et al*. The ALSFRSr predicts survival time in an ALS clinic population. *Neurology* 2005;64:38–43.
15 Armon C, Graves MC, Moses D, *et al*. Linear estimates of disease progression predict survival in patients with amyotrophic lateral sclerosis. *Muscle Nerve* 2000;23:874–82.
16 Armon C, Moses D. Linear estimates of rates of disease progression as predictors of survival in patients with ALS entering clinical trials. *J Neurol Sci* 1998;160(Suppl 1): S37–41.
17 Kimura F, Fujimura C, Ishida S, *et al*. Progression rate of ALSFRS-R at time of diagnosis predicts survival time in ALS. *Neurology* 2006;66:265–7.
18 Chio A, Logroscino G, Hardiman O, *et al*. Prognostic factors in ALS: a critical review. *Amyotroph Lateral Scler* 2009;10:310–23.
19 Medical Research Council. *Aids to the examination of the peripheral nervous system*. London: Her Majesty's Stationery Office, 1976.
20 Campbell WW. *Dejong's Neurologic Examination*. Philadelphia, USA: Lippincott Williams & Wilkins, 2005.

21 Brooks BR, Miller RG, Swash M, *et al*. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2000;1:293–9.
22 Ohashi Y, Tashiro K, Itoyama Y, *et al*. Study of functional rating scale for amyotrophic lateral sclerosis: revised ALSFRS(ALSFRS-R) Japanese version. *No To Shinkei* 2001;53:346–55.
23 Atsuta N, Watanabe H, Ito M, *et al*. Development of a telephone survey system for patients with amyotrophic lateral sclerosis using the ALSFRS-R (Japanese version) and application of this system in a longitudinal multicenter study. *Brain Nerve* 2011;63:491–6.
24 Kasarskis EJ, Dempsey-Hall L, Thompson MM, *et al*. Rating the severity of ALS by caregivers over the telephone using the ALSFRS-R. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2005;6:50–4.
25 Kaufmann P, Levy G, Montes J, *et al*. Excellent inter-rater, intra-rater, and telephone-administered reliability of the ALSFRS-R in a multicenter clinical trial. *Amyotroph Lateral Scler* 2007;8:42–6.
26 Mannino M, Cellura E, Grimaldi G, *et al*. Telephone follow-up for patients with amyotrophic lateral sclerosis. *Eur J Neurol* 2007;14:79–84.
27 Chancellor AM, Slattery JM, Fraser H, *et al*. The prognosis of adult-onset motor neuron disease: a prospective study based on the Scottish Motor Neuron Disease Register. *J Neurol* 1993;240:339–46.
28 Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/ motor neuron disease (MND). *Cochrane Database Syst Rev* 2012;3:CD001447.
29 Brendler SJ. Human cervical myotomes—functional anatomy studied at operation. *J Neurosurg* 1968;28:105–11.
30 Parent A. *Carpenter's human neuroanatomy*. Quebec, Canada: Williams & Wilkins, 1996.
31 Pinto S, de Carvalho M. Motor responses of the sternocleidomastoid muscle in patients with amyotrophic lateral sclerosis. *Muscle Nerve* 2008;38:1312–17.
32 Pinto S, Pinto A, de Carvalho M. Phrenic nerve studies predict survival in amyotrophic lateral sclerosis. *Clin Neurophysiol* 2012;123:2454–9.
33 Ravits JM, La Spada AR. ALS motor phenotype heterogeneity, focality, and spread: deconstructing motor neuron degeneration. *Neurology* 2009;73:805–11.
34 Fujimura-Kiyono C, Kimura F, Ishida S, *et al*. Onset and spreading patterns of lower motor neuron involvements predict survival in sporadic amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 2011;82:1244–9.
35 Kanouchi T, Ohkubo T, Yokota T. Can regional spreading of amyotrophic lateral sclerosis motor symptoms be explained by prion-like propagation? *J Neurol Neurosurg Psychiatry* 2012;83:739–45.
36 Brettschneider J, Tredici KD, Toledo JB, *et al*. Stages of pTDP-43 pathology in amyotrophic lateral sclerosis. *Ann Neurol* Published Online First: 20 May 2013. doi:10.1002/ana.23937.
37 Kavanagh J, Barrett R, Morrison S. The role of the neck and trunk in facilitating head stability during walking. *Exp Brain Res* 2006;172:454–63.
38 Ballesteros ML, Buchthal F, Rosenfalck P. The pattern of muscular activity during the arm swing of natural walking. *Acta Physiol Scand* 1965;63:296–310.
39 Richter RR, VanSant AF, Newton RA. Description of adult rolling movements and hypothesis of developmental sequences. *Phys Ther* 1989;69:63–71.
40 Cudkowicz ME, Katz J, Moore DH, *et al*. Toward more efficient clinical trials for amyotrophic lateral sclerosis. *Amyotroph Lateral Scler* 2010;11:259–65.
41 Sorenson EJ. What is next in ALS clinical trials? *Neurology* 2007;69:719–20.
42 Gourie-Devi M, Nalini A, Sandhya S. Early or late appearance of "dropped head syndrome" in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 2003;74:683–6.
43 Uemura M, Kosaka T, Shimohata T, *et al*. *et al*. Dropped head syndrome in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Frontotemporal Degeneration* 2013;14:232–3.
44 Katz JS, Wolfe GI, Burns DK, *et al*. Isolated neck extensor myopathy: a common cause of dropped head syndrome. *Neurology* 1996;46:917–21.

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