LETTER TO THE EDITORS

Amyloid myopathy: a therapeutic trial for the rare and underdiagnosed myopathy with bortezomib

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Dear Sirs,

A 69-year-old woman was referred to our clinic because of a 6-month history of progressive muscle weakness. Five years previously, when she was diagnosed as having nephrotic syndrome, the renal biopsy showed deposition of AL-amyloid. Subsequent investigations revealed multiple myeloma with λ-type Bence-Jones protein at stage 3 according to the international staging system. A course of vincristine, doxorubicin and dexamethasone (VAD) and an additional course of cyclophosphamide were administered, followed by another course of melphalan (L-PAM) at age 67. The proteinuria slightly improved but persisted for 5 years, when proximal weakness developed.

Neurological examination revealed proximally dominant weakness with MRC scale 4 in the deltoid and 3 in the iliopsoas muscles and she was unable to stand up from a full squat. Serum creatine kinase (CK) elevated to 3,399 U/L. Electromyography showed a myogenic pattern with small motor unit potentials, fibrillation potentials and early recruitment pattern. Muscle biopsy revealed a variation of fiber size, little infiltration of inflammatory cells, and homogeneous accumulations beneath the muscle membrane (Fig. 1a). Congo red-positive materials were noted both in vessel walls and in muscle fibers

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(Fig. 1b, c, d) with fluorescence for rhodamine, consistent with amyloid deposition, the hallmark of amyloid myopathy. We were not able to identify whether the deposits were located beneath the basal lamina or the plasmalemma due to lack of electron microscopic preparation.

Five years ago, the serum CK value was 110 U/L (Fig. 2). Two years later, when her nephrotic syndrome deteriorated, the CK elevated to 2,336 IU/L without overt weakness. Interestingly, after she received L-PAM, the CK decreased to 120 U/L just 1 month after the treatment. When girdle weakness developed 6 months ago, the CK again soared to 3,378 U/L. The fluctuation of CK and the amyloid deposition in the muscle led us to the diagnosis of amyloid myopathy due to multiple myeloma. We then administered two consecutive courses of bortezomib (1.3 mg/m² on days 1, 4, 8, and 11 for the first course and 1.0 mg/m² on days 1, 4, 8, and 11 for the second course). The treatment reduced the proportion of myeloma cells from 16.8 to 1.2%. The CK started to fall a few weeks after the first course and eventually fell to 187 U/L 1 month after the second course, when she was able to rise from a sitting position more easily. However, multiple myeloma deteriorated in the following months and the CK again elevated to 694 U/L. She was not able to receive additional treatment because of her poor general status.

Amyloid myopathy, a progressive myopathy in a proximally dominant fashion, is caused by a variety of primary amyloidoses, such as familial amyloidosis, AL-amyloidosis and multiple myeloma [1–3]. Postulated mechanisms include impaired muscle metabolism or failed electrical conduction by amyloid deposition beneath the muscle membrane [4, 5]. Therapeutic trials have included plasmapheresis, administration of corticosteroid, and high-dose

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Fig. 1 Biopsied specimen of the left deltoid muscle. **a** Hematoxylin and eosin staining section revealed a small artery with thickened wall and muscle fibers with sarcoplasmic accumulations (*inset*). **b** Congo red staining section of the formalin-fixed tissue showed marked amyloid deposition in a perimysial vessel. **c, d** Congo red staining of the fresh frozen section was examined with rhodamine red. **d** Rhodamine red image overlaid on the transparent image, showing amyloid deposition in the muscle parenchyma (*arrowheads*) and the perimysial vessels (*arrow*). The figures **a, c,** and **d** are serial sections of the same part of the frozen sample. *Scale bar* 50 μm
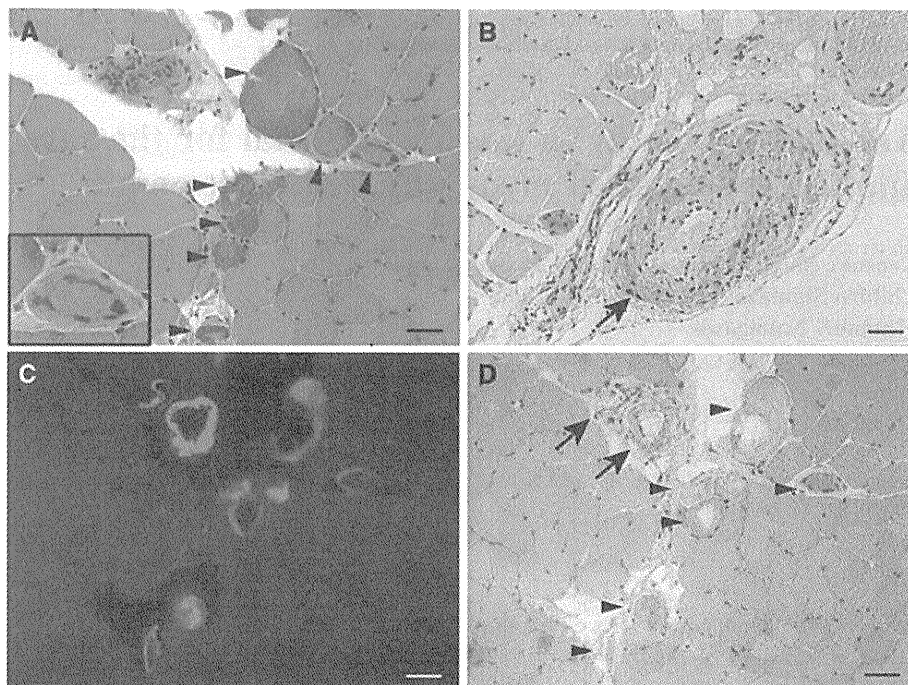

Fig. 2 The time course of serum creatine kinase and daily excretion of protein. Letters on top show administered medications. *VAD* vincristine, doxorubicin, and dexamethasone; *CPA* cyclophosphamide; *L-PAM* melphalan. The percentage on the bottom indicates the proportion of myeloma cells in bone marrow preparation. The CK value decreased in response to two different treatments, L-PAM and bortezomib. With administration of bortezomib, the daily excretion of urinary protein also decreased, another indicator of renal amyloidosis
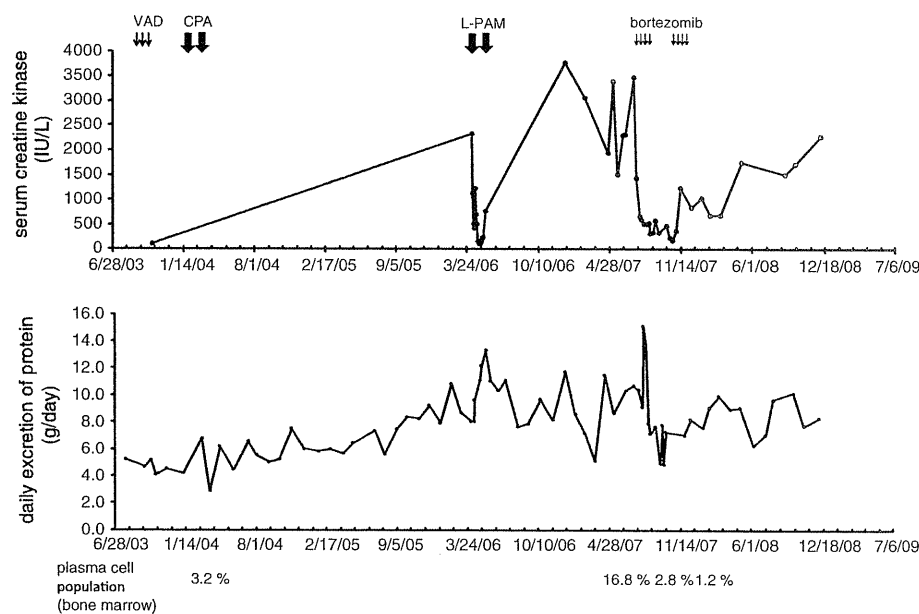
chemotherapy; however, approximately 60% of these patients were non-responders [3]. Bortezomib can decrease the production of amyloid in 35% of patients with refractory multiple myeloma and AL-amyloidosis [6, 7], thus being a feasible treatment for amyloid myopathy. It is hypothesized that circulating amyloid and amyloid oligomers are in dynamic equilibrium between deposition and clearance [8]. By inhibiting production of amyloid, bortezomib can alleviate muscle injury from still undeposited amyloid or amyloid oligomers. We surmised that the decrease of CK following the administration of bortezomib in this patient reflected alleviation of muscle injury by reducing circulating amyloid. The incomplete recovery may suggest that relatively short courses of bortezomib were not sufficient or that bortezomib should have been administered earlier. We believe bortezomib remains a potential treatment for amyloid myopathy; however, a multicenter trial is mandatory.

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構音障害をともなった封入体筋炎の1例

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要旨：構音障害を呈した封入体筋炎（IBM）の1例を経験した．症例は71歳男性で，3年前から徐々に握力の低下，しゃべりにくさ，下肢筋力低下が進行するため受診した．舌・前腕屈側・大腿内側の筋萎縮，深指屈筋・大腿四頭筋の筋力低下と構音障害をみとめた．嚥下障害は明らかでなかった．外側広筋の筋生検で，筋線維の大小不同と炎症細胞浸潤，縁取り空胞をともなう筋線維をみとめ，IBMと診断した．舌筋の針筋電図で，低振幅の運動単位電位，安静時の線維自発電位をみとめ，本症例の構音障害の原因として舌筋の障害が推測された．IBMでも，まれではあるが構音障害が合併することがあり，今後注目すべき症候と考え報告する．
（臨床神経 2010;50:695-699）
Key words：封入体筋炎，構音障害，嚥下障害，舌筋

はじめに

封入体筋炎(IBM)は，筋細胞質内に縁取り空胞をともない電子顕微鏡では核内にフィラメント様封入体をみとめる炎症性筋疾患であり，高齢者の筋炎の中ではもっとも多いとされている．一般的にステロイドに抵抗性で，慢性進行性の経過をとることが特徴である[1]．IBM患者の約10～92%に嚥下障害をともなうとされているが[2]~[15]，構音障害についてはこれまで注目されてこなかった．今回，われわれは病理学的に診断が確実なIBM症例で嚥下障害をともなわず構音障害をともなった1例を経験した．IBMにもまれではあるが構音障害が合併しうると考えられるため報告する．

症　例

患者：71歳，男性，右きき
主訴：四肢筋力低下，しゃべりにくさ
既往歴：高血圧症．
内服歴：塩酸マニジピン（10mg）1錠，カンデサルタン（8mg）1錠．
家族歴：父親が心筋梗塞，姉が認知症．類似疾患なし．
生活歴：喫煙1日13本を50年間，飲酒1日2～3合．
現病歴：68歳頃から長い釣り竿を握ることや，缶の蓋を右手指で開けることが徐々に困難となってきた．69歳頃よりしゃべりにくさを自覚し，家人にもろれつが回っていないことを指摘されるようになった．70歳頃より前腕や大腿のやせに気づき，重い箱を持ちあげることやしゃがみ立ちが困難と

なり，71歳時当科入院となった．これまで食事の際，喉のつかえや咳こみ，鼻への逆流などは自覚したことはなかった．
現症：身長160cm，体重62kg，血圧120/68mmHg，脈拍70/分，体温36.3℃．一般身体所見に異常はみとめなかった．
神経学的所見：脳神経系では，舌筋はわずかに萎縮していたが硬度に異常なく，挺舌時の軽度筋力低下をみとめた．線維束性収縮はみとめず，咽頭挙上に問題はなかった．発話速度は正常であるが，舌を小刻みに左右に動かすことはやや困難で，舌音を中心とした構音障害をみとめた．しかし，口唇音・咽頭音は保たれていた．
握力は右16kg，左21kg，右棘上筋・両側前腕屈筋群・両側大腿内側広筋に筋萎縮をみとめたが，線維束性収縮はみとめなかった．徒手筋力テストでは，MRCスケールで手根屈筋は右4，左4，浅指屈筋は右3，左5，深指屈筋は右2，左4，総指伸筋は右5，左5，大腿四頭筋は右4，左4であった．Gowers徴候は陽性，下顎反射は陰性で膝蓋腱反射が低下し，Babinski徴候は陰性であった．
嚥下評価：飲水テストでは，口唇からの水の流出，飲水後の咳嗽や湿性嗄声など嚥下障害を示唆する所見はみとめなかった．
検査所見：血算は正常，血液生化学では，CK 294IU/*l*，Aldolase 6.5U/*l*と筋酵素の軽度高値をみとめた．抗核抗体，抗dsDNA抗体，抗Jo-1抗体は陰性であった．
電気生理学的検査：神経伝導検査は正常であった．右総指伸筋（MRCスケールで5）で施行した針筋電図では，低振幅の多相性運動単位電位（MUP）と高振幅のMUPが混在し，安静時には線維自発電位と陽性棘波を多数みとめ，干渉波はearly recruitment patternであった（Fig. 1A（a）～（c））．舌
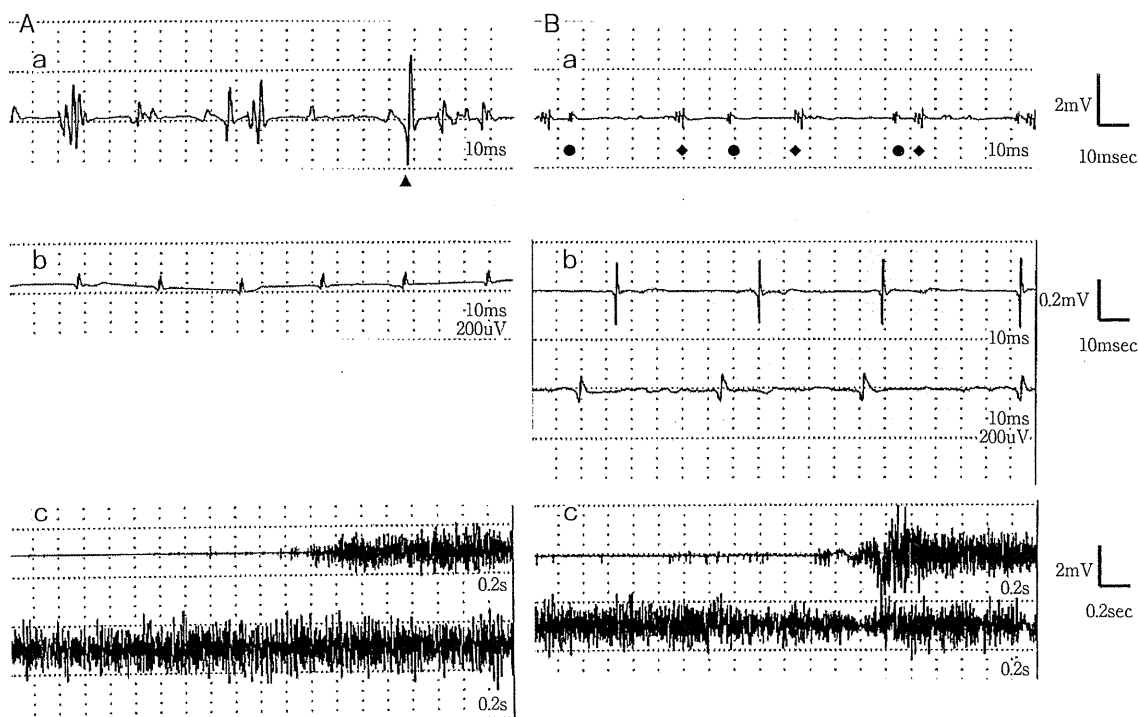
Fig. 1　EMG findings in the right extensor digitorum communis muscle (A) and tongue muscle (B).
A (a) and B (a) showed typical motor unit potentials during a voluntary contraction in each muscle.
In A (a), MUPs with relatively high amplitude were noted. In B (a), two distinct small MUPs were
seen. A (b) and B (b) revealed abundant spontaneous discharges at rest. In A (c) and B (c), interfer-
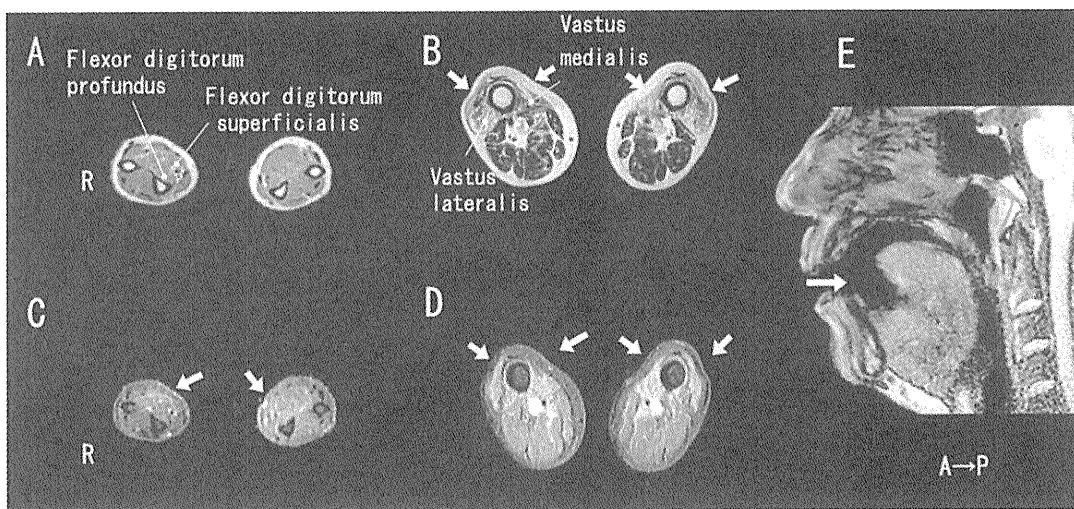ence pattern was well preserved.

Fig. 2　Muscle magnetic resonance imaging (MRI) of the forearms, the thighs, and the tongue
(T2-weighted images of the forearms (A) and the thighs (B). Short T1 inversion recovery images
(STIR) of the forearms (C) and the thighs (D). T1-weighted image of the tongue (E)).
In Fig. 2 (B), bilateral quadriceps muscles demonstrated marked atrophy. High intensity was noted
in the flexor digitorum profundus muscles (Fig. 2 (C)), vastus medialis and vastus lateralis muscles
(Fig. 2 (D)). In Fig. 2 (E), The tongue appeared to be atrophic, aparting from the soft palate above.
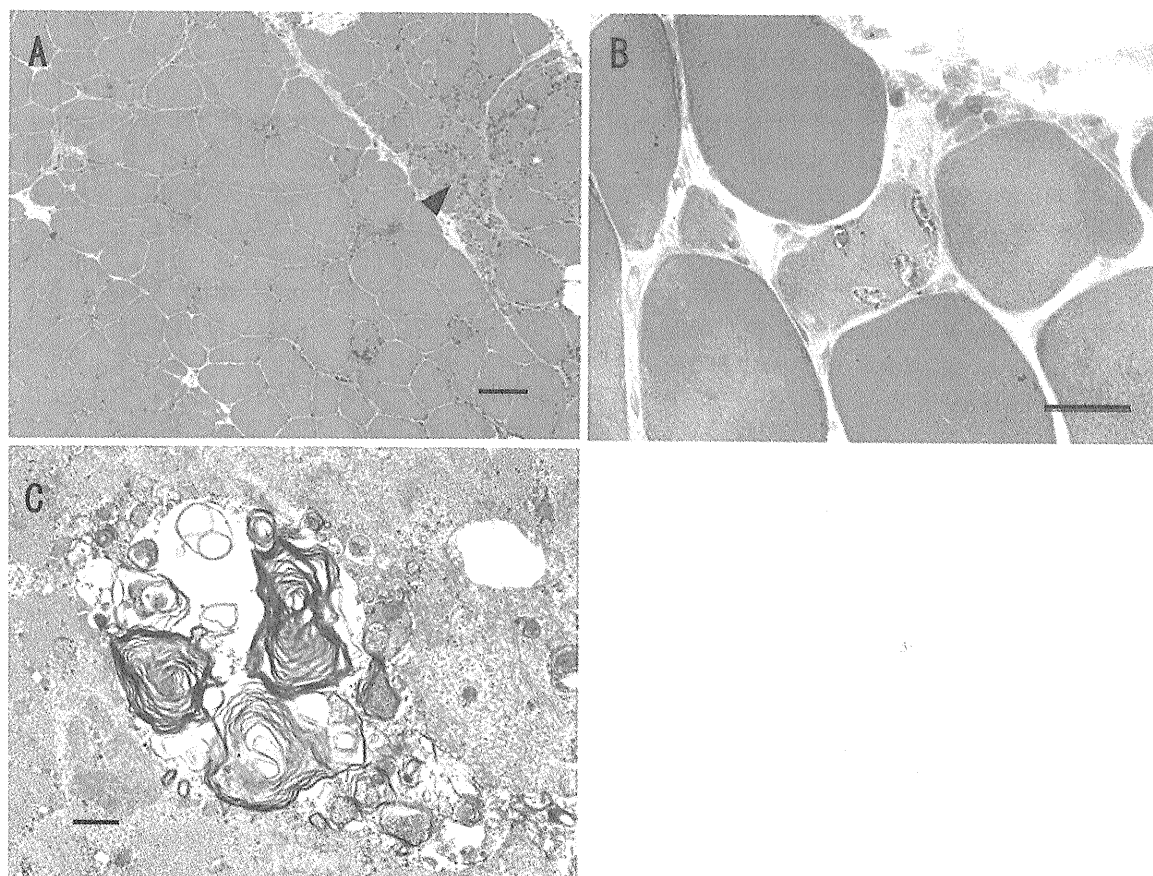
Fig. 3 Muscle biopsy from the right vastus lateralis muscle, (A: hematoxylin and eosin staining, ×100. Bar=100μm, B: Gomori trichrome staining, ×200. Bar=50μm, C: electron micrograph. Bar=500nm). There was a marked variation in fiber size (Fig. 3A). Perimysial infiltration of mononuclear cells was designated with an arrowhead (Fig. 3A). A fiber with rimmed vacuoles was shown (Fig. 3B). An electron micrograph showed tubulofilamentous inclusion-like structures with 15 to 20 nm in diameter in the cytoplasm. Myeloid bodies were also noted in a vacuole (Fig. 3C).

Table 1 The summary of the percentages of dysphagia and dysarthria among inclusion body myositis patients.

	Number of patients	Dysphagia (%)	Dysarthria (%)
Needham et. al. (2007)	57	58	—
Badrising et. al. (2005)	64	9-66	—
Hauser et. al. (1998)	19	80	—
Lotz et. al. (1989)	40	40	—
Sunohara et. al. (1989)	40	12.5	—
Dabby et. al. (2001)	9	45	—
Felice et. al. (2001)	35	54	—
Byenberg et. al. (1993)	36	14	—
Sayers et. al. (1992)	32	38	—
Lindberg et. al. (1994)	18	73	—
Ringel et. al. (1987)	19	31.5	—
Wintzen et. al. (1989)	6	66.6	—

筋の針筋電図では，随意収縮時に低振幅多相性の MUP を，安静時に線維自発電位を多数みとめた（Fig. 1B（a）～（c））．

　画像所見：前腕・大腿の骨格筋 MRI では深指屈筋・外側広筋・内側広筋の一部が T_2 強調画像，STIR 画像でともに高信号を呈していた（Fig. 2A～D）．頭部 MRI では，T_2 強調画像・FLAIR 画像で深部白質に軽度の慢性虚血性変化をみとめた．矢状断で舌筋は軟口蓋に接しておらず，舌筋の軽度萎縮を反映していると考えられた（Fig. 2E）．FLAIR 画像で舌筋の信号変化は明らかではなかった．

　筋病理所見（右外側広筋）：HE 染色にて，筋線維径は 10～120μm と大小不同をみとめ，筋内鞘への炎症細胞浸潤をみとめた（Fig. 3A）．Gomori トリクローム変法では，多くの筋線維内に縁取り空胞をみとめ（Fig. 3B），電顕では細胞質内に約 15～20nm の tubulofilaments 様構造物をみとめ，空胞内にミエリン様小体をみとめた（Fig. 3C）．

考　　察

　European Neuromuscular Centre（ENMC）diagnostic criteria の診断では，1）筋力低下の存在，2）前腕の筋力低下，とくに伸筋と比較して屈筋群の筋力低下，3）緩徐進行性，4）弧発性の発症といった 4 点の臨床症状がそろっているばあい，病理学的に 5）非壊死性筋線維への炎症細胞の浸潤と 6）縁取り空胞の存在をみとめれば，definite IBM となる[16]．本症例では，4 つの上記臨床症状と 2 つの光顕上の病理所見を備えており，definite IBM と診断した．

　本症例の特徴は，嚥下障害をともなわなかったが発症早期から構音障害を合併していた点である．

　嚥下障害は，IBM 患者の約 10～92％ の患者にみとめることが報告されており，IBM において比較的典型的な症状である[2]～[15]．本症例では，病歴上嚥下障害を示唆する症状の存在はなく，嚥下障害のベッドサイド簡易スクリーニング検査[17]でも問題はなかったため，嚥下障害は明らかでないと判断した．

　一方，本症例の構音障害は神経学的診察から主として舌音を中心とした障害と考えられた．また舌筋の筋力低下をみとめた点や下顎反射をみとめなかった点，失調症状をみとめなかった点から，失調性や偽性球麻痺性の構音障害ではなく，舌筋の障害にともなう球麻痺による構音障害と考えた．舌筋の針筋電図で活動性のミオパチーを示唆する所見をみとめた点からも，本症例の構音障害の原因として舌筋の障害がかかわっていることが推測された．

　IBM において典型的な症状である嚥下障害をともなうことは一般的に知られているが[2]～[15]，その一方で，封入体筋炎における構音障害の存在に関してはこれまで注目されてこなかった（Table 1）．しかし IBM 患者 22 人に電話によるインタビューで，8 人の患者が以前と比較し喋り方が変化したと回答したとする報告がある[8]．本症例では，発症早期に自分があるいは家族がしゃべりにくさに気づき，神経学的・電気生理学的にも舌筋の異常が確認されており，IBM における構音障害を考える上で重要な症例と考えた．

　IBM でみとめられる嚥下障害に関しては，咽頭筋の障害により咽頭壁運動不良・喉頭挙上の不良や輪状咽頭筋のアカラシアが生じ，また筋組織の繊維化により輪状咽頭筋が肥大するなどの要因が関与していると考えられている[3]．IBM で構音障害が生じる機序に関しては明らかではないが，IBM で舌筋萎縮をみとめたとする症例報告や[16]，嚥下障害をともなった IBM 患者の 74％ の症例で嚥下造影検査での舌後方筋力が低下しているとの報告があり[3]，IBM で舌筋が形態的・機能的に障害されうる可能性が示唆される．さらに Dabby らは，針筋電図で舌筋に線維自発電位をみとめた症例を報告している[6]．本症例においても，舌萎縮をみとめ，舌筋の線維自発電位が示されていることから，舌筋の障害が構音障害に関与している可能性が高いと考えた．

　IBM 患者の構音障害に関して，とくに嚥下障害は明らかでないにもかかわらず構音障害をともなう IBM の報告例はきわめて少なく，今後，本疾患において構音障害の存在にも注目していく必要があると考えられた．

ま と め

　発症早期から構音障害をともなった IBM の 1 例を報告した．本症例では，IBM に多い嚥下障害は明らかでないのにもかかわらず，構音障害をともなっていた点が特徴的であった．構音障害の原因としては，舌筋の障害が推測された．

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Abstract

A rare complication of dysarthria in a patient with inclusion body myositis: A case report

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We reported a 71-year-old man with inclusion body myositis with clinically overt dysarthria. He had been suffering from gradual progression of weakness in the hand muscles and lower extremities as well as dysarthria three years before admission. His neurological examination revealed muscle atrophy and weakness in the tongue, the forearm flexors, and the vastus medialis muscles. He had dysarthria to a moderate degree, while he denied any dysphasia. A biopsy from vastus lateralis muscle showed variation in fiber size, infiltration of mononucleated cells, and numerous fibers with rimmed vacuoles, leading to the diagnosis of definite inclusion body myositis. The EMG findings of the tongue demonstrated low amplitude motor unit potentials during voluntary contraction, abundant fibrillation potentials at rest, and preserved interference pattern at maximal contraction, implying myogenic changes. We surmised the dysarthria seen in this patient, an atypical clinical feature in IBM, presumably caused by muscle involvement in the tongue muscle. Dysphasia is common symptom in IBM patient and has been much reported previously. But dysarthria in IBM patient has not been aware, for this reason this report should be the rare case.

(Clin Neurol 2010;50:695-699)

Key words: inclusion body myositis, dysarthria, dysphagia, tongue

（会）

シャルコー―マリー―トゥース病患者診療の現況
全国1次アンケート調査報告 *

滋賀　健介, 中川　正法

目　的

　シャルコー・マリー・トゥース病（CMT）は進行性の遺伝性ニューロパチーであるが、現在特定疾患に認定されていないため、わが国での診療実態についてのまとまった報告は少ない。その一方で、医療施設で診療されない患者も存在し、患者の実情把握はきわめて重要である。今回、われわれは全国医療機関へアンケート調査を行い、患者の分布・ADL・装具療法など診療実態の把握を試みたので報告する。

対象・方法

　医療機関アンケート：全国の神経内科・小児科・リハビリテーション科（リハ科）の教育関連施設と足の外科学会関連施設あわせて計1,841施設に手紙によるアンケート調査を行い、診療されているCMT患者の数・男女比・ADL・装具療法・手術療法・リハビリテーションなどを受けている患者数・外来診療間隔などを記入形式で回答していただいた（2009年10月実施）。

結　果

　全国879施設（47.7%）から回答があり、うち244施設で計509名のCMT患者が診療されていた。1施設で診療されている患者数は1人～22人と幅があったが、3人以上診療している施設は73施設であった。性別では、男性284人、女性225人。年齢別では、10歳未満35人、11歳～20歳：74人、21歳～30歳：54人、31歳～40歳：64人、41歳～50歳：67人、51歳～60歳：91人、60歳以上：124人と11歳～20歳に小さいピークがある以外は、高齢者ほど患者数が多かった（図1A）。整形外科関連施設を除くと11歳～20歳に見られたピークは消失した。患者のADLレベルでは、杖なし歩行が58.5%、杖歩行が21.2%、車椅子が19.3%、寝たきりが1%であった（図1B）。医療処置に関しては、短下肢装具使用が31.6%、長下肢装
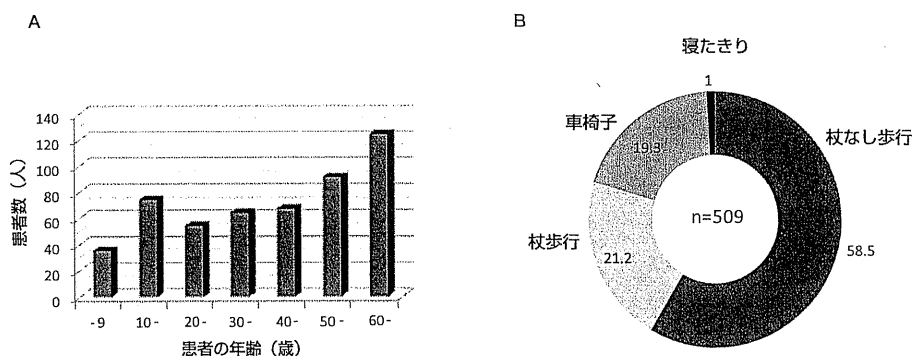

図1　A．医療機関アンケートによるCMT患者の年齢分布（n = 509）.
　　　B．医療機関アンケートによるCMT患者のADLレベル（n = 509）. 数は%をしめす.

* A nationwide survey on actual conditions in patients with Charcot Maie-Tooth disease: a preliminary report.
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具使用が1.4%、車椅子使用が12.6%、手術療法を受けている患者が8.3%、リハビリテーションを受けている患者が12.4%、気管切開を受けている患者が1.0%であった。診療間隔は0.5カ月毎〜24カ月毎と広く分布していたが、平均値3.69カ月、中央値は3カ月であった。

考　察

CMT患者の年齢分布では、10歳代で小さなピークがある以外は加齢とともに患者数は増えており、CMTは一般的には生命予後がよい疾患であることを示していると同時に、高齢化社会を反映したものと推測される。10歳代に見られる小さなピークは整形外科関連施設を除くと消失し、このピークは成長時期に施行される外科手術のために整形外科で診療された患者数を反映したものと思われた。

患者の約8割の患者は何らかの手段で歩行できている一方で、約2割の患者は車椅子を使用しており、また寝たきりの患者が1%であった。欧米の報告では、脱髄型CMT患者の26%がRankin grade 3以上[1]、あるいは約20%が「重度の身体障害を有する」としており[2]、ほぼ同等の結果と考えられた。CMT自体は生命予後がよい一方で、ADLの低下が本疾患の治療や診療・ケアを考える上で重要と考えられた。

約3割の患者が短下肢装具の装具処置を受けている一方で、長下肢装具をしている患者は1.3%と少数であり、多くの患者は短下肢装具や杖で歩行が確保できない場合、車椅子を使用している実態（12.4%）が浮かび上がってきた。そのなかでリハビリテーションを受けている患者は12.2%と少なくないことが示されたが、その多くはリハ科で診療されている患者であり、リハ科以外に通院されている患者のリハビリテーションの適応判断が今後重要になると思われた。

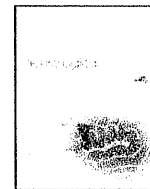## 文　献

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Distal motor axonal dysfunction in amyotrophic lateral sclerosis

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ARTICLE INFO

ABSTRACT

Nerve conduction slowing in amyotrophic lateral sclerosis (ALS) is usually caused by loss of fast motor axons. We studied the frequency, extent, and distribution of prominently prolonged distal motor latencies in ALS. We reviewed results of median, ulnar, and tibial nerve conduction studies in 91 patients with ALS, 24 with lower motor neuron disorders, and 36 with axonal neuropathy. Coincidental carpal tunnel syndrome was found for 4 (4.4%) of the ALS patients who were excluded from analyses. Markedly prolonged distal latencies (>125% of the upper limit of normal) were found only in the median nerve of ALS patients (9%), and in none of the disease controls. Excitability studies suggested membrane depolarization in some ALS patients. Our results show that approximately 10% of ALS patients shows prominently prolonged median distal latency, which cannot be explained by axonal loss and carpal tunnel lesion. The distal nerve conduction slowing may partly be caused by membrane depolarization possibly due to motor neuronal degeneration in ALS. We suggest that recognition of the pattern of distal motor axonal dysfunction predominant in the median nerve is clinically important, and could provide additional insights into the pathophysiology of ALS.

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive fatal neurological disease. The pathological hallmarks of ALS are the degeneration and the loss of motor neurons with astrocytic gliosis in the motor cortex and the secondary corticospinal tract degeneration, as well as the loss the spinal anterior horn cells and motor nuclei of the lower brainstem. Histological studies of the phrenic nerves have shown selective loss of large fibers in ALS patients [1]. In nerve conduction studies, ALS patients sometimes show mild motor nerve conduction slowing that is usually explained by loss of the fastest motor units [2]. Previous studies have shown that prolongation of distal motor latency was found in 34% of upper limb nerves in ALS patients [3]. However, distal latency very rarely exceeded 125% of the upper limit of normal [4]. Moreover, the frequency and the extent of prolongation of distal latency in each motor nerve have never been systematically investigated.

Nerve excitability studies using computerized threshold tracking have suggested axonal dysfunction in ALS [5-7]. The technique can provide an indirect insight into sodium or potassium channel functions, and membrane potential. Previous reports have shown

altered axonal excitability properties that depend on voltage-dependent potassium channels [5] and persistent sodium channels [8] in ALS patients, and the ion channel dysfunction is more prominent in distal axons than in the nerve trunk [9].We therefore studied the frequency, extent, and inter-nerve differences of prolonged distal motor latency and their relation with axonal excitability indices in ALS patients.

2. Methods

2.1. Subjects

A total of 91 consecutive patients with sporadic ALS, seen at Chiba University Hospital between 2001 and 2009, were studied. All patients fulfilled the revised El Escorial and Awaji criteria [10,11] for definite (n = 26) or probable (n = 65) ALS. The mean disease duration was 17 months. Of these, four (4.4%) patients had coincidental carpal tunnel syndrome (CTS) by clinical examination and sensory nerve conduction studies, four suffered diabetes, and four showed respiratory acidosis. These patients were excluded from analyses. CTS was diagnosed when patients had sensory symptoms/signs in the median nerve territory, or slowed median sensory nerve conduction velocity (<42 m/s; the cut-off value was defined as the mean-2SD value of 53 age-matched normal controls) with normal ulnar sensory nerve conduction study results. Patients with respiratory acidosis were excluded because axonal excitability and nerve conduction can be

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affected by tissue acidosis. Therefore, the remaining 79 patients with ALS were included in the study. There were 44 men and 35 women with age ranging from 37 to 84 years (mean, 66 years) with the mean disease duration of 17 months. All the patients included did not have slowed median sensory nerve conduction velocity.

Twelve patients with spinal muscular atrophy (SMA; 6 men; mean age, 64 years), 12 with spinal and bulbar muscular atrophy (SBMA; 12 men; mean age, 56 years), and 36 patients with axonal neuropathy due to systemic vasculitis (9 men; mean age, 54 years) served as disease controls. For neuropathy patients, only those with clinical median nerve involvement were included. The reason why we selected patient with axonal neuropathy due to systemic vasculitis as disease controls of length-dependent axonal neuropathy was that vasculitic neuropathy did not preferentially affect nerve conduction across the carpal tunnel, and that the number of patients with other axonal neuropathy due to vitamin deficiency, drug-induced or alcoholism was too small to include.

Normal nerve conduction data were obtained from 53 age-matched normal subjects (27 men; mean age, 68 years). Normal data for nerve excitability studies were obtained from 30 age-matched normal subjects (13 men; mean age, 61 years). All normal subjects and patients gave informed consent to the procedures, which were approved by the Ethics Committee of Chiba University School of Medicine.

2.2. Nerve conduction studies

Motor nerve conduction studies were made for the median, ulnar, and tibial nerves by conventional procedures using a Nicolet Viking IV EMG machine (Nicolet Biomedical Japan, Tokyo, Japan). For median and ulnar motor nerve studies, the stimulus site was 3 cm proximal to the wrist crease. Measurements included distal latency (DL), motor nerve conduction velocity, amplitude of compound muscle action potential (CMAP), and terminal latency index (TLI). CMAP amplitude was measured between baseline and negative peak. TLI was calculated with the following formula:

$$TLI = distance\,(mm)/DL\,(ms)/nerve\ conduction\ velocity\,(m/s).$$

where the distance was measured between sites of distal simulation and recording.

Anti-dromic sensory nerve conduction studies were performed in the median, ulnar, and sural nerves. Sensory nerve action potential (SNAP) was recorded from the second digit in median nerve studies, and from the fifth digit in ulnar nerve studies. In median and ulnar sensory nerve studies, the stimulus site was 3 cm proximal to the wrist crease. Skin temperature was monitored at the mid-forearm and mid-leg, and was maintained above 32 °C using a heater or blanket if necessary.

2.3. Nerve excitability testing using threshold tracking

Multiple excitability measurements were performed by a computerized threshold tracking program (QTRAC with multiple excitability protocol TRONDXM2; copyright, Institute of Neurology, London, UK) as described elsewhere [12–14]. Briefly, CMAP was recorded from the abductor pollicis brevis with stimulation at the wrist. The protocols examining stimulus–response curves used durations of 0.2 and 1.0 ms. In the following measurements, the current required to produce a CMAP that was 40% of the maximum was tracked (threshold tracking). In the threshold electrotonus studies, the membrane potential was altered by the use of subthreshold DC polarizing currents that were 40% of the unconditioned threshold current. Depolarizing and hyperpolarizing currents were used, each lasting 100 ms, and their effects on the threshold current for the test CMAP were examined. In a further test with subthreshold conditioning, the test stimulus was delivered at the end of a polarizing current pulse lasting 200 ms. The strength of the current pulse was changed systematically from 50% depolarizing to 100% hyperpolarizing in 10% steps. This produced a current–threshold relationship, analogous to the conventional current–voltage relationship. The recovery cycle of axonal excitability after a single supramaximal stimulus was measured by delivering the test stimulus at different intervals after the conditioning stimulus. The intervals between the conditioning and test stimulation were changed systematically from 2 to 200 ms.

2.4. Statistics

For each parameter in nerve conduction studies and excitability testing, correlations were tested with Spearman test, differences with the unpaired t test, multiple comparisons with ANOVA and Bonferroni procedure and differences in proportion with the Fisher's exact test, using STATA software (Stata Corp., Texas, USA).

3. Results

3.1. Nerve conduction studies in ALS

Motor nerve conduction study results for each patient group and normal group are shown in Table 1. Compared with normal controls,

Table 1
Motor nerve conduction study results.

		Normal (n = 53)		ALS (n = 79)		SMA/SBMA (n = 36)		Axonal neuropathy (n = 24)	
Median nerve									
Distal latency	(ms)	3.7	(0.4)	4.3	(0.8)***	4.1	(0.7)*	3.7	(0.4)
Conduction velocity	(m/s)	55.5	(3.9)	53.7	(4.7)*	53.9	(4.8)	55.0	(5.1)
Amplitude	(mV)	9.9	(2.3)	5.1	(2.9)***	6.5	(3.4)***	8.5	(3.0)
Terminal latency index		0.34	(0.04)	0.31	(0.05)***	0.32	(0.04)	0.4	(0.03)
Ulnar nerve									
Distal latency	(ms)	2.9	(0.3)	3.3	(0.4)***	3.2	(0.4)***	2.9	(0.4)
Conduction velocity	(m/s)	58.9	(5.1)	56.5	(5.3)*	56.2	(4.7)*	56.0	(7.1)*
Amplitude	(mV)	8.7	(1.8)	5.7	(2.6)***	7.2	(2.3)**	7.8	(2.6)
Terminal latency index		0.41	(0.05)	0.39	(0.06)*	0.40	(0.05)	0.4	(0.12)
Tibial nerve									
Distal latency	(ms)	4.3	(0.7)	4.6	(0.9)	4.2	(0.7)	4.4	(1.1)
Conduction velocity	(m/s)	44.8	(3.4)	44.1	(4.1)	43.9	(4.4)	43.0	(6.2)
Amplitude	(mV)	12.6	(4.2)	8.5	(5.3)***	9.5	(5.3)*	6.6	(4.8)***
Terminal latency index		0.32	(0.05)	0.30	(0.06)	0.34	(0.07)	0.3	(0.06)

Data are gives as mean (SD). ALS, amyotrophic lateral sclerosis; SMA/SBMA, spinal muscular atrophy/ spinal-bulbar muscular atrophy; *P<0.05; **P<0.01; ***P<0.005, compared with normal value.

ALS patients had significantly longer DL (p<0.005), slightly reduced nerve conduction velocity (p<0.05), smaller CMAP amplitude (p<0.005), and lower TLI (p<0.05) in the median and ulnar nerves, whereas in the tibial nerves, only CMAP amplitudes significantly decreased. Focusing on median DL, prolonged DL (normal>4.5 ms; the cut-off value was defined as mean+2SD values of age-matched normal controls) was found for 22 (28%) of the 79 ALS patients without CTS. Of these, seven (9%) had DL beyond 125% of the upper limit of normal (5.7 ms). Fig. 1 shows an inverse linear relationship between CMAP amplitude and DL in median nerve studies, whereas the seven patients had disproportionally prolonged DL (>5.7 ms), and appeared to constitute a separate group (circle). Such prominent prolongation of DL (beyond 125% of the upper limit of normal) was specific for median nerve, and not found for the ulnar and tibial nerves (Fig. 1B, C).

3.2. Nerve conduction studies in SMA/SBMA and axonal neuropathy

Patients with SMA/SBMA also showed longer DL, and smaller CMAP amplitude than normal controls, but the extent of abnormalities was less prominent compared with those of ALS patients, and tibial nerve studies showed only slightly reduced CMAP amplitudes (Table 1). Patients with axonal neuropathy did not have significantly prolonged DL in all the nerves tested, and the main features included
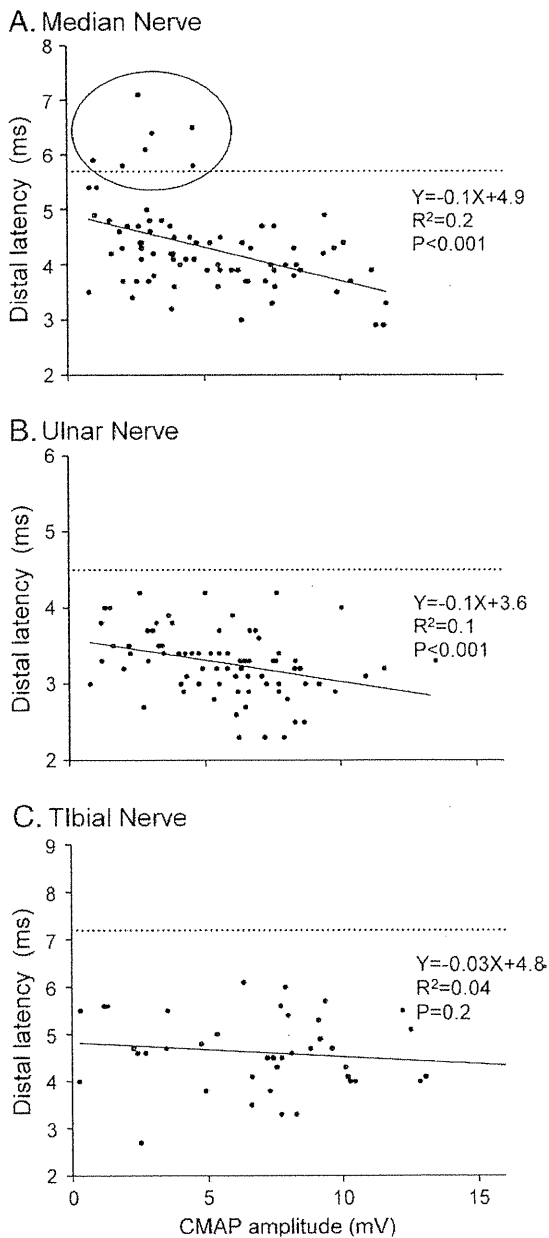

Fig. 1. Correlation between amplitude of compound muscle action potential (CMAP) and distal latency in the median (A), ulnar (B), and tibial (C) nerves of patients with amyotrophic lateral sclerosis. There are inverse linear relationships for the three nerves, but disproportionally prolonged distal latency is present only in the median nerve (circle). Dotted lines indicate 125% of the upper limits of normal.
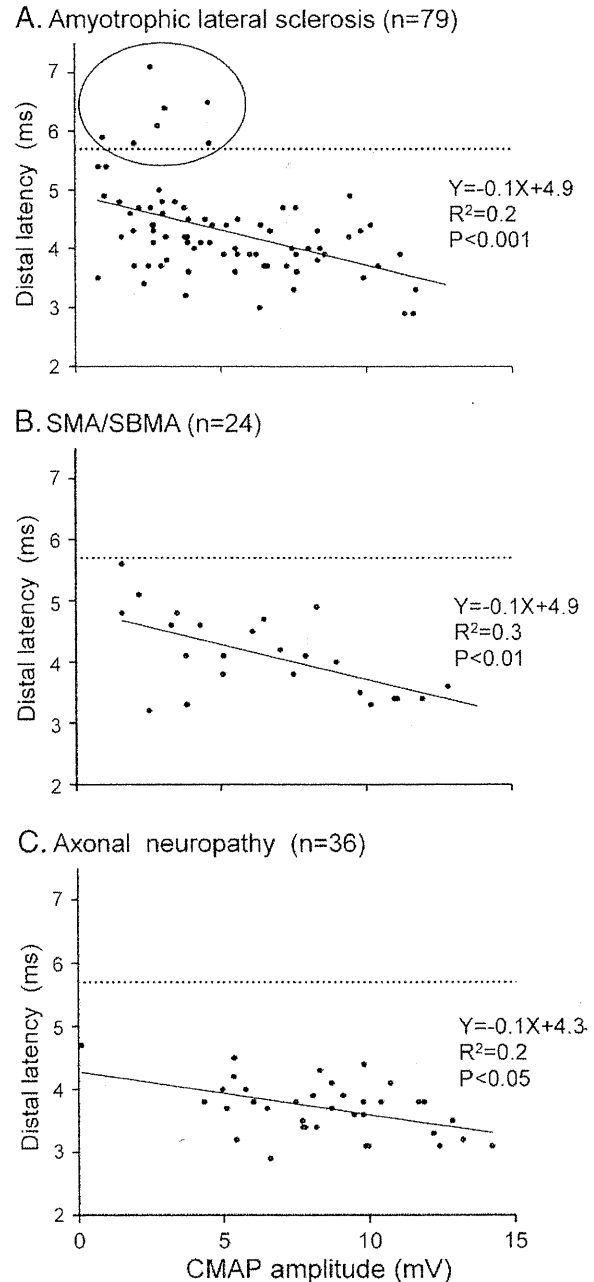
Fig. 2. Correlation between amplitude of compound muscle action potential (CMAP) and distal latency in the median nerve of patients with amyotrophic lateral sclerosis (ALS) (A), spinal muscular atrophy/spinal and bulbar muscular atrophy (SMA/SBMA) (B), or axonal neuropathy (C). There are inverse linear relationships for the three patient groups, but disproportionally prolonged distal latency is present only in the ALS group (circle). Dotted lines indicate 125% of the upper limits of normal.

decreases in tibial CMAP amplitudes, consistent with predominant involvement of lower limb nerves. Fig. 2 shows an inverse relationship in CMAP amplitude and DL in median nerve, but none of the patients with SMA/SBMA or axonal neuropathy had DL exceeding 125% of the upper limit of normal. The same pattern was seen in ulnar and tibial nerves. So, prominent prolongation of DL in median nerve was specific for ALS patients. In multiple comparison with the three patient groups, DLs in the median and ulnar nerve of ALS patients were significantly longer than those of axonal neuropathy patients (P<0.001, P<0.01, respectively).

3.3. Median nerve excitability testing in ALS patients

Table 2 shows results of excitability testing at the wrist of the median nerve in normal controls and ALS patients. Compared with normal controls, all ALS patients had significantly greater threshold changes in depolarizing threshold electrotonus (TEd [90–100 ms]), greater supernormality, and smaller threshold changes in hyperpolarizing current–threshold relationships than normal controls, consistent with results in previous studies [6].

According to DL in median nerve studies, we divided patients into three subgroups; (i) Group A, DL≤4.5 ms (normal), (ii) Group B, 4.6 ms–5.6 ms, and (iii) Group C, ≥5.7 ms (125% of the upper limit of normal). Among the three patient subgroups, the mean values were similar (Table 2). However, in individual patients, up to 29% of Group C showed either smaller threshold changes in depolarizing threshold electrotonus (fanning-in), reduced supernormality, or steep current–threshold relationships outside the 95% confidence interval of normal subjects, suggestive of membrane depolarization [12], whereas the frequency of these findings was lower in Group A (11%) and Group B (13%) patients.

4. Discussion

Our results show that in patients with motor axonal loss, prominently prolonged DL is found only for the median nerve of ALS patients (9% of the patients). Our findings also confirmed that decreased CMAP amplitudes largely affect distal latencies, but such prominent prolongation of DL cannot be explained merely by loss of the fast-conducting motor axons. In addition, axonal excitability testing showed that up to 29% of ALS patients with prominently prolonged DL showed either fanning-in in threshold electrotonus, reduced supernormality or steep current–threshold relationships suggestive of membrane depolarization [12]. The findings raise the possibility that axonal depolarization and resulting sodium channel inactivation partly contribute to the marked prolongation of DL in ALS, although we did not perform axonal excitability testing in nerves

other than median nerves. Finally, our findings show that the disproportionally prolonged DL is both ALS-specific and median nerve-specific; the prominently prolonged DL was observed only in the median nerve, and this is consistent with a clinical observation that the thenar muscles are more severely affected than the hypothenar or foot muscles in ALS, suggesting preferential involvement of distal median motor axons.

Previous studies have shown that entrapment neuropathies are not uncommon in ALS. Kothari et al. found median nerve abnormalities at wrist in 12% of their ALS series [15]. In this study, 4.4% of the 91 ALS patients had CTS. Nevertheless, 9% of the remaining ALS patients without CTS showed prominent prolongation of distal latency in median nerve studies.

Electromyography is an essential part of neurophysiologic assessments for a diagnosis of ALS, whereas motor nerve conduction studies are also important for distinguishing ALS from other lower motor neuron syndromes and peripheral neuropathies. Therefore it should be recognized that there is a subgroup of ALS patients with marked prolongation of DL in the median nerve.

A previous study by Cornblath et al. noted that DL was rarely greater than 125% of the upper limit of normal, and the values greater than that occurred in only 4% of measurements [4]. However, they analyzed the pooled data of median, ulnar and peroneal nerve studies, and findings of each nerve were not provided. Furthermore, in generally accepted criteria of diagnosis for ALS, for example revised El Escorial criteria [10] and Awaji criteria [11], the range of acceptable prolongation of DL in each nerve has not been defined. Our results indicate that the markedly prolonged DL in ALS patients is highly selective for the median nerves, suggesting that median motor axons are more vulnerable to the pathophysiology of the disease than ulnar and tibial motor axons.

The differences in vulnerability among the nerves may be interpreted by differences in excitability properties of axons innervating different muscles. A peculiar pattern of dissociated atrophy of the intrinsic hand muscles in ALS has been reported as the "split hand" syndrome [16,17]. The split hand is characterized by muscle wasting predominantly the "thenar complex" including the abductor pollicis brevis (APB) innervated by the median nerve and the first dorsal interosseus muscle (FDI) innervated by the ulnar nerve, with relative sparing of the hypothenar complex innervated by the ulnar nerve. A previous excitability study in normal subjects has shown that nodal persistent sodium conductance is more prominent in median axons than in ulnar axons innervating the hypothenar, and therefore excitability is physiologically higher in median motor axons [18]. The findings indicated that membrane properties of motor axons differ significantly, and their axonal/neuronal responses to disease may also differ. Our study lacked of the data of axonal excitability

Table 2
Excitability properties in the median nerve at the wrist.

		Normal		Amyotrophic lateral sclerosis							
				All		Group A (DL≤4.5 ms)		Group B (DL 4.6–5.6 ms)		Group C (DL≥5.7 ms)	
		(n = 30)		(n = 79)		(n = 57)		(n = 15)		(n = 7)	
CMAP amplitude	(mV)	10.8	(4.9)	5.1	(2.9)***	5.8	(2.9)***	3.4	(2.6)***	3.0	(1.3)***
TEd (10–20 ms)	(%)	69.0	(4.3)	69.2	(9.6)	68.8	(7.5)	68.8	(15.4)	73.4	(10.1)
TEd (90–100 ms)	(%)	45.8	(4.3)	48.6	(7.1)*	49.3	(7.2)**	46.2	(6.9)	48.2	(6.1)
TEh (90–100 ms)	(%)	−121.5	(18.9)	−123.3	(27)	−125.5	(23.1)	−116.8	(28.5)	−119.9	(48.9)
Refractoriness	(%)	63.6	(57)	49.1	(31.9)	49.3	(30.5)	59.4	(32.4)	18.0	(29.4)*
Supernormality	(%)	−24.7	(4.6)	−28.5	(12)*	−29.1	(10.7)**	−24.3	(16.9)	−32.6	(8.9)
Late subnormality	(%)	16.3	(5.4)	14.2	(6.3)	13.9	(6.1)	16.2	(7.7)	12.7	(4.6)
50% depolarizing current in CTR	(%)	52.3	(4.9)	53.7	(7.8)	54.0	(7.6)	52.9	(93.1)	53.9	(13.6)
100% hyprepolarizing current in CTR	(%)	−303.1	(74.9)	−278.3	(62.3)*	−285.2	(59.4)	−267.0	(56.3)*	−246.2	(93.1)

Data are gives as mean (SD). DL, distal latency; TEd, depolarizing threshold electrotonus; TEh, hyperpolarizing threshold electrotonus; CTR, current/threshold relationship. *P<0.05; **P<0.01; ***P<0.005, compared with normal value.

testing in ulnar nerve of ALS patients and this is the limitation of the present study. However, our findings may support the idea that median motor axons are preferentially affected in ALS.

Our excitability testing in median nerves of all ALS patients confirmed the results of previous studies; abnormally increased threshold changes in depolarizing threshold electrotonus and greater changes in supernormality [5–7]; these changes could result from impaired potassium channel function. A study by Kanai et al. suggested that in the advanced stage of ALS, excitability properties of motor axons somewhat change towards membrane depolarization [6]. Terminal stage axons would have metabolic failure leading to a decrease in activity of ATPase, and thereby of electrogenic Na^+/K^+ pump. A resulting membrane depolarization inactivates sodium channels, and could lead to nerve conduction slowing. Our results could not show clear differences in excitability properties in ALS patients with normal DL and those with prolonged DL, and this is presumably because the extent of fast axonal loss is the major determinant of prolonged DL. However, this study showed that there is a subgroup of ALS patients with disproportionally prolonged DL that is unexplained by merely loss of fast motor axons. Other factors such as membrane depolarization would partly contribute to prolonged DL.

Distal conduction slowing is uncommon in neurogenic amyotrophy in general, but it could reflect a part of the pathophysiology of ALS, as distal axonopathy. Rapid progression of motor neuronal dysfunction could result in significant distal motor axonal dysfunction. We suggest that it is important to recognize that prominent prolongation of DL is both ALS-specific, and median nerve-specific. This pattern of distal motor axonal impairment should be recognized, when we examine patients suspected as suffering motor neuron disease in nerve conduction studies.

Acknowledgement

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Charcot-Marie-Tooth 病の治療*

中川　正法**　　　　滋賀　健介**

Key Words : hereditary neuropathies, ascorbic acid, curcumin, rehabilitation, mechanism-based therapeutic strategies

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はじめに

Charcot-Marie-Tooth 病（CMT）の治療には，理学療法，手術療法，薬物治療があり，治療薬の開発研究が最近進められている．今後はCMTの原因遺伝子の解明とその分子病態の解明に伴って，新たな治療法の開発が期待される[1,2]．本稿では，CMT治療の最近の研究とCMTの患者が手術のため麻酔を受ける際の注意点およびロボットスーツ「HAL®」の利用などについて述べる．

I．CMTに対する薬物治療研究

遺伝子診断が不十分な時代のCMT治療研究として，Cronassial筋注（ガングリオシド製剤），linoleic/γ-linoleic essential fatty acids，vitamin E，coenzyme Q10などが試みられている．CMT 46例に対するcoenzyme Q10投与試験が行われているが，MFN2異常などのミトコンドリア機能に関連したCMTに対象を絞った試験ではない．ナルコレプシーに使用されるmodafinilを4例のCMT1A患者に投与し，昼間の疲労感が改善したとの報告もある[3]．いずれの研究も十分な規模の無作為化比較対照試験 randomized controlled trial（RCT）ではない．

1．CMT1Aの薬物治療

CMT1AはPMP22の重複によって引き起こされる病態であり，PMP22はミエリン形成におけるSchwann細胞の分化制御に重要であり，その軸索-髄鞘相互作用に関与している．動物モデルでは，PMP22の過剰発現はユビキチン化PMP22凝集体を形成し，その蛋白分解系を障害することが示唆されている．したがって，Schwann細胞におけるPMP22発現レベルの是正がCMT1Aの末梢神経障害の改善につながる合理的な治療戦略と考えられる．

2．アスコルビン酸臨床試験

アスコルビン酸は，後根神経節 - Schwann細胞の培養系におけるmyelinationに必須であり，アスコルビン酸欠乏が大腿神経障害を引き起こすことが報告されている[4]．cAMPはCREBによるPMP22プロモーターへの結合を促進し，PMP22の発現を増加させるが，アスコルビン酸はこの結合を競合的に阻害することによって，PMP22 mRNA発現量を低下させる可能性がある．また，アスコルビン酸はadenylate cyclase活性の減少を介して細胞内cAMPレベルを低下させ，PMP22 mRNAの発現を用量依存的に抑制することが報告されている[5]．アスコルビン酸がCMT1Aモデルマウスに有効であるとの報告があり[6]，国内外で臨床試験が行われた．

厚生労働省精神神経疾患研究委託費「難治性ニューロパチーの病態に基づく新規治療法の開発」研究班のもとで，「Charcot-Marie-Tooth病1Aに対するアスコルビン酸の安全性・有効性に関する臨床試験」（UMIN試験ID：UMIN 000001535）が行われた[7]．臨床試験プロトコールに従い，投与群にはアスコルビン酸 20mg/kg/日を12週間経口投与し，非投与群との比較検討を行った．CMT患者会（http://j-cmt.org/）の協力も得て2009年11月30日時点で，40例が本試験に登録された．残念ながら，プライマリーエンドポイントであるCharcot-Marie-Tooth Neuropathy Score（CMT-NS）に有意な改善はなくアスコルビン酸の有効性は確認できなかった（**Fig. 1**）．海外でのアスコルビン酸投与試験でもアスコルビン酸の有効性は証明されなかった（**Table 1**）[8]．アルコルビン酸がCMT1Aに無効なのか，アスコルビン酸の
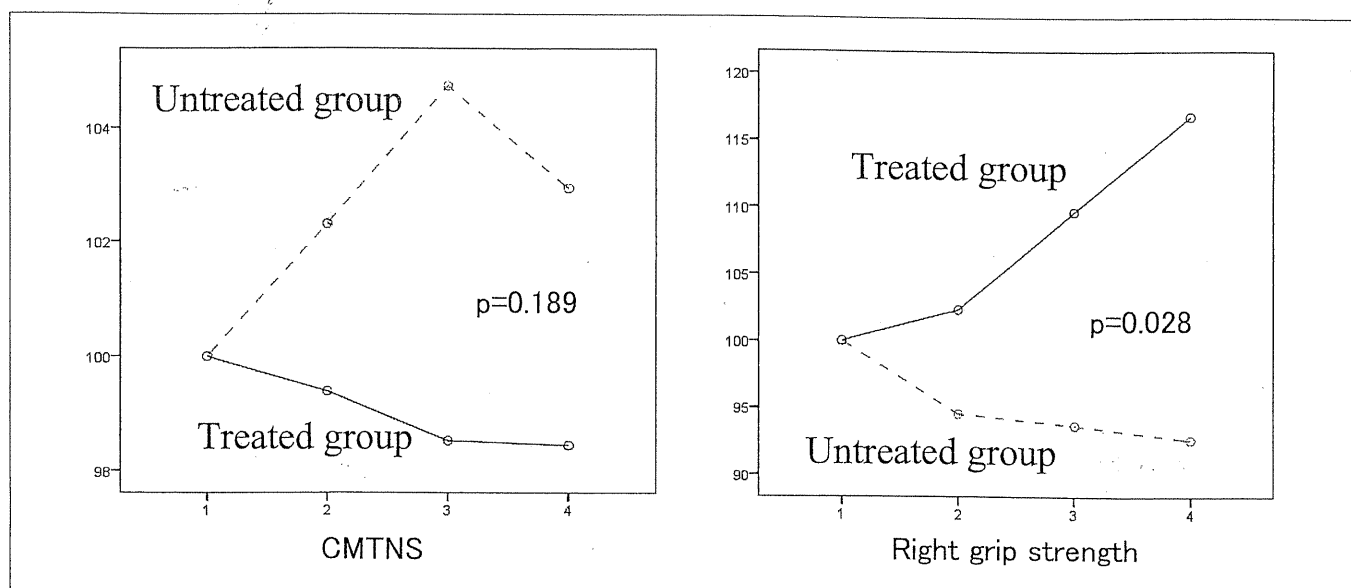

Fig. 1 Results of the clinical trial of ascorbic acid for 40 patients with CMT1A.
The vertical line is indicating the relative value of CMT neuropathy score (CMTNS) compared to the starting point of the trial. The lowering of CMTNS indicates clinical improvements. Solid line : treated group, Dotted line : untreated group. CMTNS : Charcot-Marie-Tooth neuropathy score.

Table 1 Results of clinical trials of ascorbic acid for CMT1A patients.

Authors	Micallef J et al.	Verhamme C et al.	Burns J et al.	Toth C.	Research group study in Japan
Nation	France	Netherlands	Australia	Canada	Japan
References	Lancet Neurol 8 : 1103–1110, 2009	BMC Med 7 : 70, 2009	Lancet Neurol. 8 : 537–544, 2009	Acta Neurol Scand 120 : 134–138, 2009	in preparation
Methods	a multicentre, randomised, double-blind, placebo-controlled trial	a randomised, double-blind, place-bo-controlled phase II trial	a randomised, double-blind, place-bo-controlled, safety and efficacy trial	An open-label cohort-controlled pilot study	An open-label cohort-controlled pilot study
Primary outcome measure	CMTNS	Motor nerve conduction velocity of median nerve	Motor nerve conduction velocity of median nerve	tolerability	CMTNS
Results	Not effective/safe	Not effective/safe	Not effective/safe	Intolerable	Not effective/safe
Ascorbic acid / day	1g/3g/placebo	Adults : 2 g/day, children (14 to 18 years) : 1.8 g/day, Children (9 to 13 Years) : 1.2 g/day	30mg/kg	5g/2.5g	20mg/kg/day
Number of patients	Ascorbic acid 3g for 61, 1g for 56	Ascorbic acid 6	Ascorbic acid 42	Ascorbic acid 12	Ascorbic acid 21
	Placebo 62	Placebo 7	Placebo 39	No treatment 10	No treatment 19
Dropout cases	16	2	1	5	1
Age (year) (range)	38 (36–56)	< 25	2–16	36 ± 5	51 ± 15
Duration of therapy (month)	12	12	12	24	3

CMTNS : Charcot-Marie-Tooth Neuropathy Score

投与期間・量の問題なのかに関する検討が必要である. わが国の研究班で行った臨床試験では, 右握力は有意に改善しており, ある程度の効果はあるのではないかと考えられる. 現在, 軸索興奮性を測定するQtracプログラム（ミユキ技研）を用いて非利き手正中神経において運動神経の軸索興奮性を測定し, アスコルビン酸（20mg/kg/日）投与前後での変化を検討中である.

3. Neurotrophin-3（NT-3）

Sahenkらは, CMT1A患者末梢神経をヌードマウスに直接異種移植し, 神経栄養因子であるNT-3を皮下注射し, Schwann細胞増加と軸索再生が観察されることに基づいて, NT-3を4例のCMT患者に150μg/kg/週3回, 24週またはプラセボ投与を行った. その結果, NT-3投与群では末梢神経障害スコア（NIS）が改善し, 再生軸索が増加したことを報告した[9]. この研究は, RCTで効果が示されている現時点で唯一の臨床研究であるが, CMT1A症例4例, 対照例4例と少数例の検討であること, その後この結果を再現する報告がなく, エビデンスレベルとしてはIbに留まっていること, NT-3の改善効果は, 感覚スコアの改善が主体であって運動機能の改善はなかったことなどの問題点がある.

4. プロゲステロン拮抗薬

プロゲステロンはSchwann細胞や神経細胞で産生され, PMP22, MPZなどの発現を促進し, CMT1A動物モデルの症状を悪化させること, プロゲステロン拮抗薬であるonapristoneがCMT1A動物モデルに有効であることが報告されている[10]. しかし, onapristoneは肝毒性のためヒトに使用することは出来ない. ミフェプリストンはプロゲステロン拮抗作用と部分的な刺激作用を持っているが, その安全性は確立されており, 髄膜腫, 子宮筋腫などの治療やAlzheimer病の治験に使用されている. 今後, CMT1A動物モデルを用いたmifepristoneの検討も含めて, 安全なプロゲステロン拮抗薬の開発が望まれる. 一方, プロゲステロン受容体作動薬はPMP22, MPZのmRNA発現を増加させる作用があり, ハプロ不全を示すhereditary neuropathy with liability to pressure palsies（HNPP）やnonsense-mediated mRNA decay関連MPZ変異CMTに有効であるかもしれない. この点に関する細胞レベルでの研究が必要である.

5. 点変異によるCMTの薬物療法
a. クルクミン

クルクミンは秋ウコンやカレー粉に多く含まれている自然の黄色色素である. PMP22点変異によるDejerine-Sottas syndromeやcongenital hypomyelinating neuropathyなどでは, dominant negative effectが推定されている. その分子病態として, 変異pmp22をもつtrembler Jマウスの研究から, 変異PMP22蛋白が小胞体（endoplasmic reticulum：ER）に停留し細胞膜に局在できず, ERストレス誘発性アポトーシスを来すと考えられている. Khajaviらは, クルクミンが変異PMP22蛋白を細胞膜へ解放し, 変異PMP22発現によるアポトーシスを減少させることを報告した[11]. 動物レベルにおいてもクルクミンは用量依存的に運動機能を改善させている. 病理学的にも, クルクミンは坐骨神経の軸索径を増加させ, Schwann細胞におけるアポトーシスを減少させている. 以上の検討からクルクミンがpmp22点変異マウスに有効であることが示された[12]. 同様の病態がMPZ点変異によるCMTの場合にも指摘されており, ヒトのPMP22点変異やMPZ点変異によるCMTにもクルクミンの有効性が期待される.

6. 期待されるCMT治療戦略

RNA干渉やdeoxyribozymesなどは変異アレルの発現を抑制する機序があり, toxic gain of functionを示すCMTの治療に有効性が期待される. Antisense oligonucleotides（ASO）は, 短い一本鎖RNAまたはDNA配列であり, ターゲット配列を抑制する. そのひとつであるMorpholino phosporodiamidate ASOs（morpholinos）は, 筋強直性ジストロフィー, Duchenne型筋ジストロフィーにて有用性が示唆されている[13]. RNA trans-splicingアプローチは, pre-mRNAの段階で変異配列を取り除き導入した正常の配列に置き換えることが可能であり, CMTにおいても試みられるべき方法であろう. PMP22変異やMPZ変異の中で凝集体を形成するCMTでは, Alzheimer病と同様に凝集体形成や蛋白折りたたみ異常機序の解明とその阻害が治療法になる可能性もある.

患者数が少ないCMTの場合, 臨床試験デザインについても検討する必要がある. 最近のRCTでは, 皮膚生検による末梢神経の形態およびmRNA発現の評価が行われているが, 今後, 新しいサロゲートマーカーの開発も必要である.

Ⅱ. 装具, 外科治療, リハビリテーション, 生活上の工夫

1. 装具・ロボットスーツ「HAL®」

肢位の改善, 関節の変形防止, 疼痛改善などの目的で下肢装具が有効なことが多い. 初期の段階では, ブーツやハイカット靴, 足アーチサポートをつけた特注靴, 中敷き（足底板）などで歩行の安定性が増加する. 進行に応じて, 足関節サポーター, 短下肢装具, 長下肢装具, ロフストランド杖の使用を検討する. ある程度長い距離を移動するには車椅子も考慮する方が関節の負担や筋疲労の軽減のためによい場合もある. 骨折による廃用性障害が筋力低下を進めることになるので, 転倒への注意と安定したフットウェアや装具を選ぶことが日常生活上重要である.

上肢装具では, 屈筋群の緊張が高まり指の変形が進行することを予防し, 残っている指運動の実用上の巧緻性を維持するために手関節装具を装着することが有効な場合がある.

最近, ロボットスーツ「HAL®」の利用が可能になった. 数名のCMT患者に「HAL®」を装着し, その有用性の検討をはじめている. 今後, 「HAL®」のプログラム改良などを行いCMT患者に適応したロボットスーツを作成し, CMT

患者のquality of life（QOL）の改善と就労能力の向上を図りたい.

2．外科治療

関節変形が進行し，装具を用いても足を適切な位置に保てず歩行に支障が出てきた場合，関節の安定性を図るために腱延長術や骨切り術などの整形外科手術が適応となる場合がある．外科治療が一般的に長期的な効果を有するかどうかについては現時点では十分なエビデンスはない．外科手術の長所と短所をCMT患者，家族と十分に検討した上で施行することが重要である.

3．ダイエット

CMTに特異的に効果的なダイエットとして科学的に証明されたものはないが，大切なことは「現在の体重を維持する」よう心がけられることである．体重増加はすでに負担がかかっている足・膝関節や筋肉に対して，さらに負担をかけ，疼痛，疲労の増加に加えて，転倒や骨折のリスクが高まるからである．更に，CMTでは筋力低下から運動量が限られているため，一旦増えてしまった体重を運動により減量することが極めて困難である.

4．リハビリテーション

CMTのリハビリテーションに関する研究はRCTレベルでは不十分である．一般的に，翌日に疲労を残さない程度の軽い運動療法は，筋力維持に役立つ可能性がある．週3回24週のリハビリテーションプログラムに参加することにより，膝関節伸展筋力の改善と大腿筋力の自覚症状の改善がみとめられたとの報告がある[14]．日々の生活に運動療法を組み込むことで，疾患の自然経過による進行以上の悪化を抑える効果が期待できる.

5．投与に注意した方がよい薬物

CMT患者が他の内科疾患等に罹患した場合，必要に応じて使用される薬剤が末梢神経障害を悪化させる場合がある．特に抗腫瘍薬であるvincristineやcisplatin・taxol・thalidomide・bortezomib，抗不整脈薬のamiodarone，HIV治療薬のdidanosine・zalcitabine・sanilvudin，Hansen病治療薬dapsoneなどがCMTの症状を悪化させる可能性のある薬剤として有名である（http://www.charcot-marie-tooth.org/med_alert.php）．このデータベースに記載されていない薬剤でもCMTの症状を悪化させる可能性はあり，CMT患者に投薬を行う際には「何らかの異常を自覚した場合は直ちに連絡するように」注意を喚起する必要がある.

6．CMTと麻酔

CMT患者が手術や出産などのために麻酔を受ける際にも注意が必要である．一般的に，末梢神経障害を増悪させないために脊椎麻酔（脊髄くも膜下麻酔）や硬膜外麻酔は避けるべきであると言われている．高カリウム血症をおこす可能性があるので脱分極性筋弛緩薬（suxamethonium chloride）は避けた方が良い．全身麻酔時の入眠剤，静脈麻酔薬，非脱分極性筋弛緩薬（例，vecronium）に対する感受性が高い場合があるので尺骨神経刺激による母指内転筋の反応をモニターしながら用いた方よいとする報告もある．CMTの重症例では，脳神経障害による嚥下反射の減弱・声帯麻痺・胸鎖乳突筋の筋力低下，自律神経障害による不整脈・低血圧，側彎症による拘束性換気障害，悪性高熱症，術後呼吸不全などの合併に注意すべきである.

一方，脊髄くも膜下麻酔や硬膜外麻酔で良好な結果が得られた帝王切開の例，吸入麻酔のみで骨折の観血的整復固定術を行った例，全静脈麻酔と閉鎖神経ブロックを併用した膀胱腫瘍手術例なども報告されている．局所麻酔薬による神経毒の問題もあり出来るだけ低濃度の局所麻酔薬を使用した方がよいと考えられる．今後，CMTに対する適切な麻酔法に関する再検討・再評価が必要である.

おわりに

CMTの早期診断，早期治療を考える場合，着床前診断，発症前診断などの遺伝子診断の倫理的問題は避けられない．CMTに関する遺伝カウンセリングの充実も必要である．欧米に比べるとわが国では，CMTに対する医療従事者および一般社会の認知が十分ではないと考えられる．平成21年度から厚生労働省科学研究費難治性疾患克服事業として「シャルコー・マリー・トゥース病の診断，治療，ケアに関する研究」班（研究代表者中川正法）が編成され，「シャルコー・マリー・トゥース病診療マニュアル」の発刊[15]，ホームページの開設（http://www.cmt-japan.com/index.html），CMTに関する市民公開講座の開催などが行われている．今後，CMT患者会とも協力して新たな治療法の開発に取り組んでいきたい.

文　献

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Therapies for Charcot-Marie-Tooth Disease

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Charcot-Marie-Tooth disease (CMT) is the most common inherited neuropathy. There have been substantial advances in elucidating the molecular bases of this genetically heterogeneous neuropathy and molecular diagnosis is now possible in most cases. In the premolecular era, Linoleic/γ-linoleic essential fatty acids, vitamin E and coenzyme Q10 were evaluated by non-randomized controlled trials for patients with CMT without genetic diagnosis. For the last decade, neurotrophic factors, progesterone antagonists, ascorbic acid, and curcumin have been shown to be promising in experimental models of CMT, leading to several pilot trials in human. However, randomized controlled trials of ascorbic acid for CMT1A unfortunately did not prove clinical benefit. In an open-label clinical trial of ascorbic acid for CMT1A conducted by Japanese researchers, the right hand grip strength was increased in the group treated with ascorbic acid (20mg/kg/day for 12 weeks), while CMT neuropathy score, the primary outcome measure in the trial, did not improved. It needs to be elucidated whether these negative results in human are due to the lack of efficacy of ascorbic acid or to the lack of statistical power in those studies which had been conducted for a relatively shorter period of time with a smaller number of patients.

Rehabilitation and surgical therapies are currently available treatments for CMT. Recently, robot suit HAL (Hybrid Assistive Limb®) has been developed and a pilot study for patients with CMT using HAL has been started by the Research Committee of CMT Disease supported by Grants-in-Aid from the Ministry of Health, Labour and Welfare of Japan. As the best approaches to rehabilitative therapy and foot surgery still have to be defined, prospective studies will be important.

Patients with CMT should avoid taking drugs that can cause peripheral nerve toxicity. In the case of surgery and delivery, best practice of local and general anesthesia for patients with CMT has not been defined. Proper information and genetic counseling is also important for patients with CMT and their families. Careful discussion for prenatal and preimplantation genetic diagnosis should be needed, taking ethical concerns and the national regulations and laws into account. The advances in mechanism-based strategies will provide realistic hope that therapies will emerge to slow or partly reverse several forms of CMT.