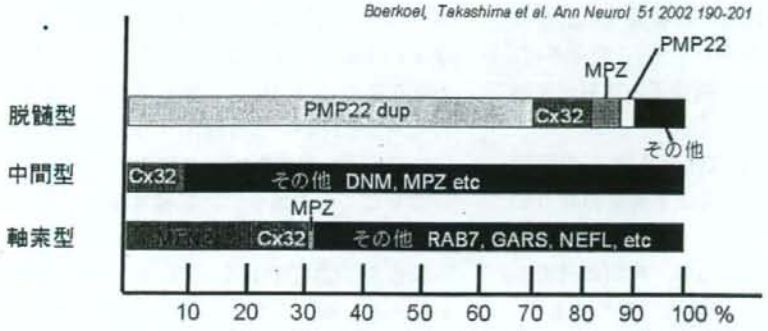
17p12 重複	79	51.6%
GJB1遺伝子異常(Cx32)	11	7.2%
MPZ遺伝子異常	5	3.3%
PMP22遺伝子異常	5	3.3%
EGR2*遺伝子異常*	1	0.65%
PRX遺伝子異常	1	0.65%
MTMR2遺伝子異常	0	0%
NEFL遺伝子異常	1	0.65%
遺伝子異常見つからず	50	32.7%

CMT1 or 2患者 計153 例

Boerkoel, Takashima et al. Ann Neurol 51 2002 190-201



Szigeti et al. NeuroMolecular Med 2006 改変

図 3　CMT病の遺伝子異常とその頻度

と呼ばれる型で常染色体優性遺伝形式(AD)であり、CMT全体の約50%、脱髄型の約70%を占めています(図 3)。

それゆえ、CMTのふたりにひとりはCMT1Aと言えます。CMT1Aの原因はミエリン構成タンパクであるPMP22 (Peripheral myelin protein 22)を含む染色体17p11.2領域の1.4Mb（メガベース；100万塩基）のゲノム（染色体の一部分）の重複により起こります。脱髄型で2番目に頻度の高いものはGJB1/Cx32の異常で、X染色体性遺伝形式のため CMTXと呼ばれます。その次にミエリン構成タンパクであるMPZ、PMP22の遺伝子異常の順に続きます。日本ではGJB1よりMPZの異常が多いとの報告もあります。中間型では、GJB1の異常が多く、その他の遺伝子は少数しか明らかになっていません。

軸索型(CMT2)では、MFN2, GJB1であり、その他は少数で、原因の同定できない場合も多いようです。他の遺伝子異常症は、頻度としてはおおよそ5%以下と推定されます（図 3)。

CMTの診断

診断方法として、CMT1Aの原因は、細胞核の染色体を直接染めるFISH法により決定されています。PMP22を含む1.4Mbのゲノムの重複により、通常 2 つのPMP22遺伝子が 3 つになるため、正常では 2 つのシグナルが 3 つに見えることで診断できます。これは、保険診療で検査することができます。ゲノムが重複するメカニズムとして、PMP22をはさんで非常に類似した配列の領域が17番染色体にあり、これが染色体の組換え（精子や卵子を作る過程で起こる）のときに、誤った組換えが起こります。

その際にPMP22の重複や欠失が起こるということであり、これは遺伝もしますが、自然発生的にも起こっています。このようにCMT1Aは、PMP22という遺伝子の発現量が1.5倍多いことで疾患が起こっているため、このPMP22の発現を抑制することで治療するという方法が考えられました。

それを証明するために、CMT1Aのモデルマウスを用いてPMP22の発現量を減らすことができないかという検討が行われました。実際、アスコルビン酸（ビタミンC）の投与によりPMP22の発現を確かに抑制でき、マウスに治療効果があることが発見されました。マウスで確認されたことが人でも確認できるのかどうかについての検討が必要なわけですが、その試験が、実際の患者にも行われております。日本では難治性ニューロパチー研究班の京都府立医大の神経内科中川教授を中心に行われています（本誌の特集 2 の第 1 部参照)。また、海外でも、実際に効果があるかの確認を行っていますが、まだ結論は出ていません。

そのほかの脱髄型CMTの原因を示しました（図 1)。原因の多くは髄鞘の主な構成タンパクやシュワン細胞で重要なものなどです。髄鞘の主構成タン

パクの20%を占めるPMP22の質的な異常も末梢神経障害を引き起こします。また、病気の原因となるMPZは、髄鞘の50%を占め、髄鞘の接着に関与しています。GJB1 (Gap junction protein, beta-1, Cx32)は髄鞘と軸索間の結合をとりもち、栄養物質の交換にも関与しています。鞘形成時に必要な転写因子であるEGR2、SOX10は、髄鞘形成に必要な蛋白の転写を誘導する働きがあります。このように、主にシュワン細胞で働く様々な遺伝子の異常が脱髄型CMTを引き起こします。

軸索型CMT(CMT2)についても示しました（図2）。軸索型にも多くの病型と遺伝子異常が有ります。CMT2の原因としては、体のエネルギーを生み出すミトコンドリアに関連したもの、軸索の構造を支える神経線維、軸索内の物質輸送に関わるもの、DNA,RNA関連および核膜タンパクなど神経細胞を支える蛋白合成と関わるもの、末梢神経の発生分化に関連するものなどがあります。軸索型では、原因としても頻度が高いのが、ミトコンドリア関連のMFN2でありますが、現在のところ原因のわかっていない例のほうが多いようです。

遺伝子異常と関連する臨床的特徴は、いくつかは非常に特徴的な症状でありますが、実際にはそれだけでは、原因遺伝子を予想することは難しいです。そこで私どもは、マイクロアレイ法のなかのリシークエンスという手法を利用し、CMTの遺伝子診断チップを作成いたしました。本チップは、既知の28のCMTの原因を一度に調べるものであります。現在はまだ、システムの構築中で結果判定に時間がかかりますが、私ども鹿児島大学神経内科で行っております。この解析では、110,000の遺伝子塩基配列を一度に決めるため、実際様々な遺伝子変異が見つかります。現在、迅速な結果判定のため、その変異が異常か正常多型かの判定するためのデータを蓄積しているところです。このような原因遺伝子の検索は、将来の治療も見据えた抜本的対策を立てるためにも、重要だとだと思っております。

臨床症状、経過、予後

CMTの臨床症状といっても、軽症から重症まで様々であります。先天性の先天性髄鞘形成不全（CHN）は、最も重症でフロッピー児（生まれたときから力が入らない）として生まれ、一般的に呼吸不全や感染症の合併により、予後不良と考えられます。しかし、ときに成長に伴って運動機能の改善が続く場合もあり、遺伝子異常のタイプによってはすべてが予後不良とはかぎりません。

デジェリン・ソッタス病（DSS）は、幼児期発症で内反足、側彎、全身性筋力低下、感覚障害、協調運動障害、反射の消失、神経肥厚などの症状があります。本症は、様々な遺伝子異常により同様の病態が起こるため、経過も一様ではありません。一般的には成長に伴い、ある程度筋力が改善することが多いのですが、青年期頃から悪化し、年齢とともに歩行できなくなる場合、呼吸障害が起こり気管切開、人工呼吸器使用となる場合もあります。

最も多いCMTであるCMT1Aが一番一般的なCMTと言えると思いますが、名古屋大学の報告では、平均発症年齢20.3歳で35%は10歳以下の発症ですが、60歳以上での発症も数%みられます。生活に介助が必要な方はごくわずかで、多くは自立した生活を営むことができます。CMT1Aの場合は寿命に関わる可能性はほとんどありません。

症状としては、下肢の運動感覚障害、感覚障害、反射の低下はほぼ全例にみられます。多くの方の障害は、下肢遠位に集中しており、凹足や、その他の足の変形により、歩行時のバランスが悪くなります。感覚低下は、自覚的にはわかりにくいのですが、振動覚や触覚、温痛覚も落ちていることが多いようです。足の冷えもよくあります。下肢をMRIなどで検査をすると、足底の筋肉には明らかな萎縮があり、また下腿の筋にも遠位部から萎縮が起こっています。足関節を固定する力が弱く、下垂足になる場合もあります。また他の検査では、髄液タンパクの上昇も半数にみられます。電気生理検査では、正中運動神経の伝導速度は平均21.1ｍ/秒（正常50m/sec以上）で通常の2～3分の1の速度でありました。

軸索型のCMTも、個人ごとに重症度に大きな開きがあります。脱髄型よりも筋萎縮の程度が強いかもしれません。ほぼ上記と同様な症状が報告されています。

遺伝的な側面では、CMTは遺伝する場合もあり、様々な遺伝相談になることがあります。たとえば最も多いCMT1Aの場合、60歳過ぎまで発症しない場合もありますし、若くして発症しても確かに足が悪いということは外見上目立ちますが、考えようによっては、多くの人が持っている高脂血症、喘息、

糖尿病、高血圧、癌など寿命を短くしうる多くの病気にも相当の遺伝性があります。それら多くの人が普通に持っている遺伝的な病気とくらべて、一概にCMTのほうが人体に有害とは言えませんので、遺伝的な面について必要以上に悩む必要は無いのかもしれません。

障害はありますが、自分自身が意志をしっかりもって、有意義な人生を歩むことが大切だと思います。

治　療

一般的には対症的に行われています。CMTの場合は足の問題が中心だと思われます。足関節（足首の関節）が重要で、前脛骨筋（足首を上げる筋肉）が障害されやすく、筋力が低下すると下垂足になります。下垂足は、歩くときに足を高く上げなければ引っかかってしまうため、転倒の原因になります。軽い場合は、サポーターや足首まで覆うような靴を履くことにより改善します。

より程度が重い場合には、短下肢装具を装着します。足が変形している場合は、足底板の利用、調節、および手術療法で足の形を整える場合があります。入浴時は、下肢の筋力低下だけでなく感覚障害もあるため滑りやすく、ぴったりとした海で使う様なゴムシューズをはくと滑り止めになります。

リハビリテーションは、アキレス腱短縮の予防やその他変形の予防、筋力の維持、歩容の改善に有効と思われます。よりハードな筋力の増強が有効かどうかについては、議論のあるところでありますが、必要な筋力は維持することは大切です。

現在までに根治的な治療は確立されていません。先ほど述べたようなCMT1Aに対して、アスコルビン酸治療の有効性の確認が行われています。この治療が効く可能性があるのは、CMT1Aだけであります。また、CMT1A患者に対し、Neurotrophin-3 (NT-3)治療のパイロット試験がアメリカで行われ、臨床効果が得られたとの報告もあります。

もともとCMTの多くは命を奪われるような重篤な疾患でないため、遺伝子治療など安全性の確立されてない治療は、試みられていません。また、実験的にはMPZ蛋白の遺伝子異常のモデルマウスにクルクミン（ウコンの黄色い色素）を投与すれば、症状が改善したという報告もあります。実際に人に効果があるかどうかはわかっていませんので、今後の研究によりあきらかにされていくと思われます。近年のiPS細胞に代表されるような、急速に進歩する医学全体の流れのなかで、近い将来、新たな治療が開発されるものと考えられます。

最後に、CMT友の会が運営されているホームページも友の会の方々の努力により立ち上がりましたので、ごらん下さい。日々の参考になることが記載されております。

CMT友の会ホームページは下記の通りです。

http://j-cmt.org/contents/aboutcmt/index.html

(会)

マイクロアレイDNAチップによるCharcot-Marie-Tooth病の遺伝子診断*

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はじめに

遺伝性ニューロパチー（特にChacot-Marie-Tooth disease; CMT）は、現在まで少なくとも30の遺伝的な原因は解明されてきたが、その遺伝子数の多さにより、正確な遺伝子診断に対する費用と労力は膨大であり、個々の患者に対する十分な遺伝子検査は困難であった。しかしながら、近年急速な進歩を遂げているマイクロアレイ技術（resequencing array）により、一度に多数の遺伝子を診断しうるシステムを開発することが可能となってきた。そこで我々は、昨年度までに同定されたほぼすべての遺伝性ニューロパチー（CMT type）の遺伝子異常診断しうる遺伝子チップを開発し、遺伝子検査システムの確立を行う。また、同時に複数の候補遺伝子についても遺伝子チップに搭載し、新しい原因遺伝子の発見をめざす。

対象・方法

検体の収集

厚生労働省のニューロパチー研究班において収集された、遺伝性ニューロパチーCharcot-Marie-Tooth病患者のDNAがすでに1000検体以上収集されている。全例において、インフォームド・コンセントを得た症例について検査を開始する。具体的には、CMTの半数を占める、CMT1A（PMP22の重複例）については保険診療の検査であるPMP22の重複同定FISH検査を行い、その陰性例においてのみ、遺伝子チップによる検査を行う。

DNA Chipの作成と解析

CMT1, CMT2, DSS（Dejerine-Sottas syndrome), CHN（congenital hypomyelinating neuropathy), Giant axonal neuropathyや小脳失調症など特徴的な症状を持つもの（SCAN1, AOA1, AOA2）などの臨床型を示す疾患に対応するべく27遺伝子を遺伝子チップに搭載した。さらに、末梢神経関連遺伝子および既知の遺伝子の関連遺伝子の中から、遺伝性ニューロパチーの原因となりうる10の候補遺伝子を選択し、遺伝子情報（配列、構造、多型など）を入手し、プライマーを設定した。

DNA Chipには、既知の遺伝子として*PMP22, MPZ, SIMPLE, EGR2, NEFL, SOX10, GDAP1, MTMR2, SBF2/MTMR13, KIAA1985, NDRG1, PRX, GJB1, MFN2, RAB7, GARS,*

Key Words：Chacot-Marie-Tooth disease（シャルコー・マリー・トゥース病), microarray（マイクロアレイ）

* Genetic diagnosis in Charcot-Marie-Tooth disease by DNA Chip

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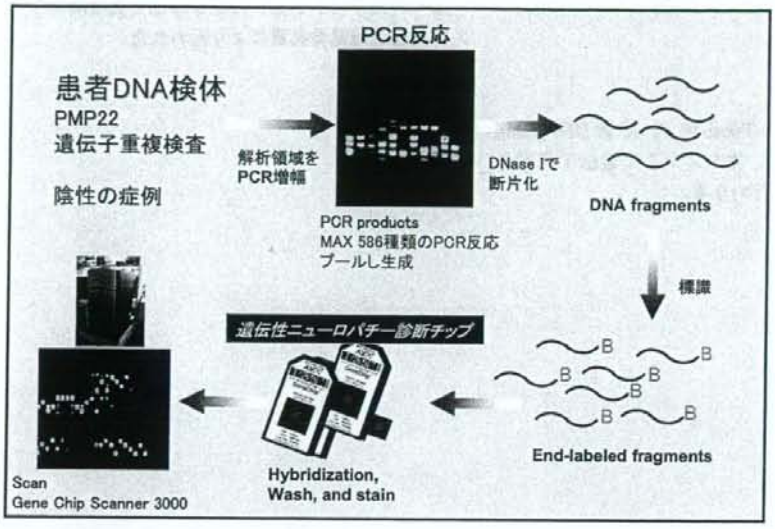
遺伝性ニューロパチー遺伝子診断システム



*HSPB1, HSPB8, LMNA, GAN1, KCC3, APTX, SETX, TDP1, DNM2, DHH, YARS*の配列、多型を決定しgene chip に搭載した。臨床報告のあるほぼすべての遺伝子をカバーした。さらに新規遺伝子候補として、10の遺伝子を搭載し、全配列で548エクソン110,938塩基であった。

患者DNAは、multiplex PCR法により必要領域が増幅され、1つのチューブで15-40の種類のPCR反応を行うため、最適化を行った。PCR反応後、プール後、DNase Iで断片化しラベル後、チップとハイブリダイゼーションし、Gene Chip Scanner 3000によりチップの情報が検出され、Gene Chip DNA Analysis Software（GDAS）により解析した。

結　果

はじめに、本アレイで実際に遺伝子配列が読めるかどうか検討し、その後PCRのステップの最適化など行い、最終的には、最適化を行うことで586のPCR反応を26本のチューブで増幅することが可能となり、増幅過程が飛躍的に簡素化された。

実際、CMT患者80例、について解析を行った。症例によっては、エクソン単位で配列がはっきりしない例も認められたが、全般的にはシークエンス解析より、遙かに精度が高いものであった。

実際、*PRX, MFN2, MPZ, SETX, MTMR13*遺伝子において、病的異常が確認された。ほとんどの遺伝子において多型または病的と考えられる変異が同定された。

考　察

アレイによる遺伝子解析は、遺伝子異常を調べるコストと時間を飛躍的に縮小させると考えられる。実際患者1例あたりのスクリーニングの費用は従来の方法では140万円かかるものが、マイクロアレイ法では約7万円にまで20分の1に軽減できる。Multiplex PCRで

も比較的よい結果が得られているが、症例によってはいくつかのエクソンでは症例によって不安定なものある。今後、さらに多数例について検討する。

結　論

Charcot-Marie-Tooth病の診断DNA Chipチップは完成し、本システムで遺伝子異常の検出を効果的に行いうる。

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Electrophysiological features of late-onset transthyretin Met30 familial amyloid polyneuropathy unrelated to endemic foci

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Abstract *Background* Through the development of gene diagnostic techniques, late-onset transthyretin Met30-associated familial amyloid polyneuropathy (FAP TTR Met30) has been shown to be more prevalent than is generally believed. *Objective* To examine the electrophysiological features of late-onset FAP TTR Met30 unrelated to endemic foci. *Methods* Nerve conduction findings in 44 cases with an onset of more than 50 years of age in a non-endemic area were assessed and compared with findings from 21 earlier-onset cases related to endemic foci. *Results* The extent of the reduction of the compound muscle action potential and, especially, the sensory nerve action potential was more profound in the late-onset group even when the decline of these indices with aging in normal control subjects was taken into account. The feature of predominant lower-limb involvement seemed to be more conspicuous in the late-onset group. Electrophysiological indices tended to be aggravated as the duration of neuropathic symptoms increased in the early-onset group, while most of these indices in the late-onset group did not show this correlation. A slowing of conduction velocity and a prolongation of distal latency, which suggests demyelination, were conspicuous in some patients. Pathologically, a predominant loss of small-fibers was not conspicuous in sural nerve biopsy specimens from late-onset patients. Large myelinated fiber density showed a negative correlation with the disease duration in early-onset cases, but not in late-onset cases. *Conclusions* Electrophysiological differences between late- and early-onset cases were present, probably reflecting the different underlying pathogenic mechanisms of neuropathy. The demyelinating feature does not exclude the possibility of this disease.

Key words familial amyloid polyeuropathy · amyloid · transthyretin

Introduction

Transthyretin Met30-associated familial amyloid polyneuropathy (FAP TTR Met30), in which methionine is substituted for valine at position 30 of transthyretin, is the most common type of familial amyloid polyneuropathy in Japan, as well as in Western countries [3, 10–12, 26, 28, 29, 35]. In Japan, these patients have been known to concentrate in two geographic areas (Arao and Ogawa) [11, 12, 26]. Although there are exceptions, typical cases of FAP TTR Met30 in these endemic foci show characteristic features including the age at onset from late 20s to early 40s, a high penetrance rate, marked autonomic dysfunction, loss of superficial sensation including nociception and thermal sensation (i.e., sensory dissocia-

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tion), atrioventricular conduction block requiring pacemaker implantation, and the presence of anticipation of age at onset [2, 11, 16, 24, 26].

In contrast to conventional FAP TTR Met30 with relatively early age at onset in the endemic foci, we have reported the presence of a late-onset type of FAP TTR Met30 unrelated to the endemic foci that is widely distributed throughout Japan [16, 18, 23]. The typical features of these cases were distinct from those related to the endemic foci. These differences include an age at onset of over 50 years, a low penetrance rate, relatively mild autonomic dysfunction, loss of all sensory modalities rather than sensory dissociation, the frequent presence of cardiomegaly, extreme male preponderance, and the absence of anticipation of age at onset [16, 18, 23, 24, 34]. Differences in geographic distribution and clinical features between early- and late-onset types of FAP TTR Met30 have also been reported in Portugal [5, 6, 35]. Previously, we reported pathologic differences between these two types that corresponded well to clinical differences [18]. The causal mechanism of the different clinical and pathologic features of the early- and late-onset types of FAP with the same mutation in the transthyretin gene has not yet been determined. The late-onset type of FAP TTR Met30 in a non-endemic area may be a prototype of FAP TTR Met30 and some environmental or genetic factors in the endemic foci induced anticipation and created the early-onset type of FAP TTR Met30. Thus, late-onset FAP TTR Met30 is considered to be more prevalent in Japan and elsewhere than is generally believed, but it is still not widely recognized. Wide geographic distribution, sporadic occurrence, and atypical clinical features still may result in missed diagnoses. Before the availability of molecular diagnosis, late-onset FAP TTR Met30 patients residing outside of endemic foci frequently were misdiagnosed with polyneuropathy of undetermined cause or CIDP [1, 28].

In the present study, we investigated electrophysiological features in patients with late-onset FAP TTR Met30 unrelated to endemic foci to provide more recognition for this type of FAP with apparently nonspecific clinicopathological features.

Patients and methods

We examined the nerve conduction findings in 44 patients (36 men, 8 women) with late-onset FAP TTR Met30 from non-endemic areas of Japan who were referred to the hospitals of Nagoya University Graduate School of Medicine, Kumamoto University School of Medicine, or Shinshu University School of Medicine. Twenty-one patients (10 men, 11 women) with early-onset cases from endemic foci were also assessed for comparison. Inclusion criteria for late-onset cases were FAP TTR Met 30 with an onset age over 50 years and no relationship to the endemic foci within the two most recent prior generations [16, 18, 23]. For early-onset cases, inclusion criteria were an onset age under 50 years and a relationship to one of the two Japanese endemic foci within the two most recent prior generations [16, 18, 23]. No patient in the study belonged to the same kindred as another. In order to confirm the diagnosis of FAP TTR Met30, DNA analyses for mutation of the transthyretin gene were performed in all patients as described previously [26, 31]. Informed consent was obtained, and all aspects of the study were approved by the ethics committees of Nagoya University Graduate School of Medicine, Kumamoto University School of Medicine, and Shinshu University School of Medicine.

Rough backgrounds and clinical characteristics of the cases are described in Table 1. The age at onset of neuropathic symptoms in the late-onset group was 64.0±6.4 (mean±SD) years, and that of the early-onset group was 34.4±6.4 years. The duration from onset of neuropathy to the examination was shorter in the late-onset group (3.1±2.8 years) than in the early-onset group (6.0±4.6 years), while the activity of daily living assessed by the modified Rankin Scale [41] was not very much different between the groups (2.0±0.8 in the late-onset group and 2.2±1.2 in the early-onset group). Clinical features of the two groups of patients included in the present study were well within accordance with previous descriptions [12, 16, 23]. Because a previous large-scale comparative study divided patients solely by their age at onset, but not their relationship to endemic foci [16], the characteristics of the two groups in the present study are more distinct.

As a routine practice for detection of peripheral neuropathy, motor and sensory conduction was measured in the median, tibial, and sural nerves, using a standard method with surface electrodes for stimulation and recording [20]. Motor conduction was investigated in the median and tibial nerves, recording from the abductor pollicis brevis and abductor hallucis brevis, respectively. Wrist to elbow for the median nerve and ankle to popliteal fossa for the tibial nerve were used for calculating motor conduction velocity (MCV). Sensory con-

Table 1 Background and clinical features of FAP TTR Met30

Features	Late-onset group in non-endemic area, n = 44	Early-onset group in endemic foci, n = 21 (10 M/11 F)
Men/women	36/8	10/11
Age of onset (years)	64.0±6.4	34.4±6.4
Age of examination (years)	67.0±6.0	40.5±7.6
Presence of family history	17 (39)	21 (100)
Initial complaint		
Neuropathic symptoms*	39 (89)	10 (48)
Autonomic symptoms**	4 (9)	11 (52)
Cardiac symptoms***	1 (2)	0 (0)
Sensory deficit		
Superficial sensation-dominant	8 (18)	19 (90)
All modality	36 (82)	2 (10)
Deep sensation-dominant	0 (0)	0 (0)
Modified Rankin Scale****	2.0±0.8	2.2±1.2

Values are expressed as numbers of patients with percentages in parentheses, or as the mean ± SD

* Numbness or weakness in distal portion of the extremities

** Orthostatic hypotension, syncope, nausea/vomiting, diarrhea/constipation, urination, or impotence

*** Dyspnea or edema in the lower extremities

**** Modified Rankin Scale [41]: 0, asymptomatic; 1, nondisabling symptoms not interfering with lifestyle; 2, minor disability from symptoms leading to some restriction of lifestyle but not interfering with patients' capacity to look after themselves; 3, moderate disability from symptoms significantly interfering with lifestyle or preventing totally independent existence; 4, moderately severe disability from symptoms clearly precluding independent existence, though not requiring 24-hour attention from a caregiver; and 5, severe disablity and total dependence, requiring constant attention day and night

duction was investigated in the median and sural nerves. These were recorded antidromically using ring electrodes at the second digit for the median nerve and bar electrodes at the ankle for the sural nerve. Sensory nerve conduction velocity (SCV) was calculated for the distal segment. Amplitudes of compound muscle action potential (CMAP) and sensory nerve action potential (SNAP) were measured from the baseline to the first negative peak. Age-matched control values for the late- and early-onset groups were obtained separately because age-associated change of electrophysiological indices may be present in normal subjects [20]. Control values were obtained from 60 normal volunteers (66.9 ± 6.9 years of age; male:female, 28:32) for the late-onset group and 50 normal volunteers (40.3 ± 7.3 years of age; male: female, 31:19) for the early-onset group.

A sural nerve biopsy was performed in 21 patients of the late-onset group and results were compared to that of 9 subjects of the early-onset group as described previously [9, 17, 32]. The duration from onset of neuropathy to biopsy was 2.8 ± 1.6 years in the late-onset group and 3.2 ± 2.0 years in the early-onset group. Pathologic findings in 11 patients of the late- and 9 patients of the early-onset groups were reported previously [18]. Specimens were fixed in 2.5% glutaraldehyde in 0.125 M cacodylate buffer (pH 7.4) and embedded in epoxy resin for light and electron microscopy. Semithin sections were stained with toluidine blue for morphometric assessment with light microscopy. The density of myelinated fibers was assessed in toluidine blue-stained semithin sections using a computer-assisted image analyzer (Luzex FS; Nikon, Tokyo, Japan), and the densities of small and large myelinated fibers were calculated as described previously [25, 27, 32]. For electron microscopy, epoxy resin-embedded specimens were cut into ultrathin transverse sections and stained with uranyl acetate and lead citrate. In order to assess the density of unmyelinated fibers, electron microscopic photographs were taken at a magnification of 4000x in a random fashion to cover the area of ultrathin sections as described previously [15, 17, 22]. The remainder of the glutaraldehyde-fixed sample was processed for the teased-fiber study as described previously [17, 32].

Quantitative data of the late-onset group were presented as the mean ± SD, and were compared with those of the early-onset group. Electrophysiological indices of the late- and early-onset groups were also compared to respective age-matched control values. Statistical analyses were performed using the Mann-Whitney *U* test or Pearson's correlation coefficient analysis as appropriate. *p* values less than 0.05 were considered to indicate significance.

Results

Nerve conduction studies are summarized in Table 2. The results indicate mainly axonal neuropathy with some slowing of conduction velocities and prolongation of distal latency (DL) in both the late- and early-onset groups. Although the duration of neuropathic symptoms was shorter in the late-onset group, electrophysiological indices were rather worse in this group. In the median nerve, a variable reduction of CMAP was observed in both groups, but were more profound in the late-onset group. The average values of respective groups were compared to age-matched control values to assess whether there is an affect from a normal decline of CMAP with aging in normal subjects. However, the extent of reduction remained more conspicuous in the late-onset group (42% and 61% of control values for the late- and early-onset groups, respectively). In the tibial

Table 2 Nerve conduction studies

	1. Late-onset FAP TTR Met30 n = 37, 44	2. Control for late-onset cases n = 60	3. Early-onset FAP TTR Met30 n = 14, 21	4. Control for early-onset cases n = 50	p values 1 vs 2	3 vs 4	1 vs 3
Median nerve							
MCV (m/s)	43.7 ± 9.6	56.5 ± 3.3	47.8 ± 7.3	58.2 ± 4.0	< 0.0001	< 0.0001	NS
DL (ms)	5.5 ± 2.0	3.5 ± 0.3	4.6 ± 1.7	3.3 ± 0.5	< 0.0001	< 0.0001	NS
CMAP (mV)	3.2 ± 2.7	7.6 ± 2.6	5.1 ± 3.9	8.3 ± 2.8	< 0.0001	< 0.01	NS
Not elicited	2/44 cases (5%)		1/21 cases (5%)				
SCV (m/s)	47.8 ± 7.7	55.0 ± 5.3	48.3 ± 8.4	57.3 ± 5.2	< 0.001	< 0.0001	NS
SNAP (μV)	2.1 ± 3.5	22.7 ± 8.8	8.8 ± 9.3	30.9 ± 12.6	< 0.0001	< 0.0001	< 0.01
Not elicited	26/41 cases (63%)		5/20 cases (25%)				
Tibial nerve							
MCV (m/s)	37.6 ± 6.9	44.8 ± 3.2	42.4 ± 7.8	47.0 ± 3.7	< 0.0001	< 0.05	NS
DL (ms)	5.8 ± 1.5	4.0 ± 0.7	5.6 ± 1.8	4.0 ± 0.6	< 0.0001	< 0.001	NS
CMAPs (mV)	0.7 ± 1.2	10.7 ± 3.3	2.6 ± 5.1	12.7 ± 3.6	< 0.0001	< 0.0001	NS
Not elicited	17/37 cases (46%)		8/18 cases (44%)				
Sural nerve							
SCV (m/s)	39.8 ± 7.1	49.1 ± 5.0	42.4 ± 5.3	49.1 ± 4.1	< 0.01	< 0.05	NS
SNAP (μV)	0.4 ± 1.4	14.9 ± 9.3	2.8 ± 5.0	18.6 ± 9.7	< 0.0001	< 0.0001	< 0.05
Not elicited	36/41 cases (88%)		9/14 cases (64%)				

MCV motor nerve conduction velocity; *DL* distal latency; *CMAP* compound muscle action potential; *SCV* sensory nerve conduction velocity; *SNAP* sensory nerve action potential; *NS* not significant. Values are expressed as the mean ± SD.
Control values were obtained in age-matched 60 normal volunteers (66.9 ± 6.9 years of age; male: female, 28: 32) for the late-onset group and 50 normal volunteers (40.3 ± 7.3 years of age; male: female, 31: 19) for the early-onset group.
Statistical analyses were performed using the Mann-Whitney U test

nerve, the reduction of CMAP was severe in both groups, except for some of the early-onset cases with a short duration of neuropathic symptoms. Similar to the median nerve results, the extent of the reduction in the tibial nerve was more profound in the late-onset group (7% and 20% of average values of the respective control groups). The reduction of SNAP was more profound compared to CMAP. As in the CMAP, the degree of the reduction was more conspicuous in the late-onset group compared to the early-onset group ($p<0.01$ for the median nerve, $p<0.05$ for the sural nerve). The average values of SNAP in the median nerve were 9% and 28% of the age-matched controls for the late- and early-onset groups, respectively. Those of the sural nerve were 3% and 15%, respectively. The degree of reduction of CMAP and SNAP was greater in the lower limbs than the upper limbs in both groups, but the feature of predominant lower-limb involvement seemed to be more conspicuous in the late-onset group judging from the respective mean values. Slowing of MCV and SCV, and a prolongation of DL were observed more or less in both groups. As for the late-onset group, MCV ranged from 14.2 to 57.4 m/s in the median nerve and 20.0 to 48.7 m/s in the tibial nerve, while SCV ranged from 34.6 to 64.0 m/s in the median nerve and 33.0 to 48.0 m/s in the sural nerve when the potentials were recorded. DL ranged from 3.3 to 10.0 ms in the median nerve and 3.2 to 9.9 ms in the tibial nerve. CMAP was correlated to MCV positively ($r=0.583$, $p<0.0001$ in the median nerve and $r=0.460$, $p<0.05$ in the tibial nerve) and to DL negatively ($r=-0.414$, $p<0.01$ in the median nerve and $r=-0.532$, $p<0.05$ in the tibial nerve) in the late-onset group.

As for the correlation between electrophysiological indices and the duration of neuropathic symptoms, the late-onset group did not show any correlation except for MCV in the tibial nerve ($r=-0.598$, $p<0.01$). In the early-onset group, however, correlations were observed for MCV ($r=-0.612$, $p<0.01$), DL ($r=0.715$, $p<0.001$), CMAP ($r=-0.553$, $p<0.01$), SCV ($r=-0.537$, $p<0.05$), and SNAP ($r=-0.621$, $p<0.01$) in the median nerve, MCV ($r=-0.685$, $p<0.05$) and CMAP ($r=-0.502$, $p<0.05$) in the tibial nerve, and SCV ($r=-0.988$, $p<0.001$) and SNAP ($r=-0.670$, $p<0.01$) in the sural nerve. The relationship between electrophysiological indices and the duration of neuropathic symptoms in the individual cases for the median nerve only are illustrated in Fig. 1, because the potentials in most cases could be recorded in the median nerve, while many potentials were not elicited in the tibial and sural nerves. These findings indicate that electrophysiological indices normally tend to be preserved in the early phase of neuropathic symptoms in the early-onset group. However, they are aggravated as the duration of neuropathic symptoms becomes longer in this group. On the other hand, they tend to be severely affected even in cases with short duration of neuropathic symptoms in the late-onset group (Fig. 1).

Sural nerve biopsy specimens showed a variable degree of myelinated fiber loss in both groups. Large myelinated fibers tended to be preserved and small-fiber predominant axon loss was obvious in early-onset cases with relatively short duration of neuropathic symptoms, as previously described [7, 18, 30]. As a whole, the densities of large myelinated fibers for late- and early-onset cases were 259 ± 311 and 914 ± 1018 fibers/mm^2, respectively, while those of small myelinated fibers were 713 ± 801 and 451 ± 608 fibers/mm^2, respectively. The densities of unmyelinated fibers were 5536 ± 4593 and 993 ± 1305 fibers/mm^2 for late- and early-onset cases, respectively, which is significantly reduced in early-onset cases ($p<0.01$). Little or no axonal sprouting of myelinated fibers was observed in early-onset cases, while it was abundant in some late-onset cases, consistent with a previous report [18]. However, small-fiber predominant loss as that observed in early-onset cases was not obvious when the presence of regenerating small myelinated fibers was taken into consideration. The density of large myelinated fibers negatively correlated with the duration of neuropathic symptoms ($r=-0.769$, $p<0.05$) in early-onset cases, while such a correlation was not found in late-onset cases (Fig. 2). In the teased-fiber study, the frequencies of axonal degeneration for late- and early-onset cases were 22.2 ± 8.1 and 19.5 ± 6.9%, respectively, while those of segmental demyelination and remyelination were 7.5 ± 6.1 and 6.5 ± 2.9%, respectively.

Discussion

In this study, we examined the electrophysiological features of late-onset FAP TTR Met30 cases unrelated to endemic foci and compared the findings to conventional early-onset cases in endemic foci. Although the activity of daily living, as assessed by the modified Rankin scale, was not very much different between the two groups, the following differences were present: (1) the extent of reduction of the CMAP and SNAP, especially the latter, was more profound in the late-onset group even when the decline of these indices with aging in normal control subjects were taken into consideration; (2) the feature of predominant lower-limb involvement tended to be more conspicuous in the late-onset group; and (3) electrophysiological indices tended to be aggravated as the duration of neuropathic symptoms become longer in the early-onset group, while most of these indices in the late-onset group did not show this correlation.

In order to verify the association between the aggravation of electrophysiological indices and disease duration, we evaluated pathologic findings in the sural nerve biopsy specimens and their correlation with the duration of neuropathic symptoms. The results were similar to those of the electrophysiological findings because the

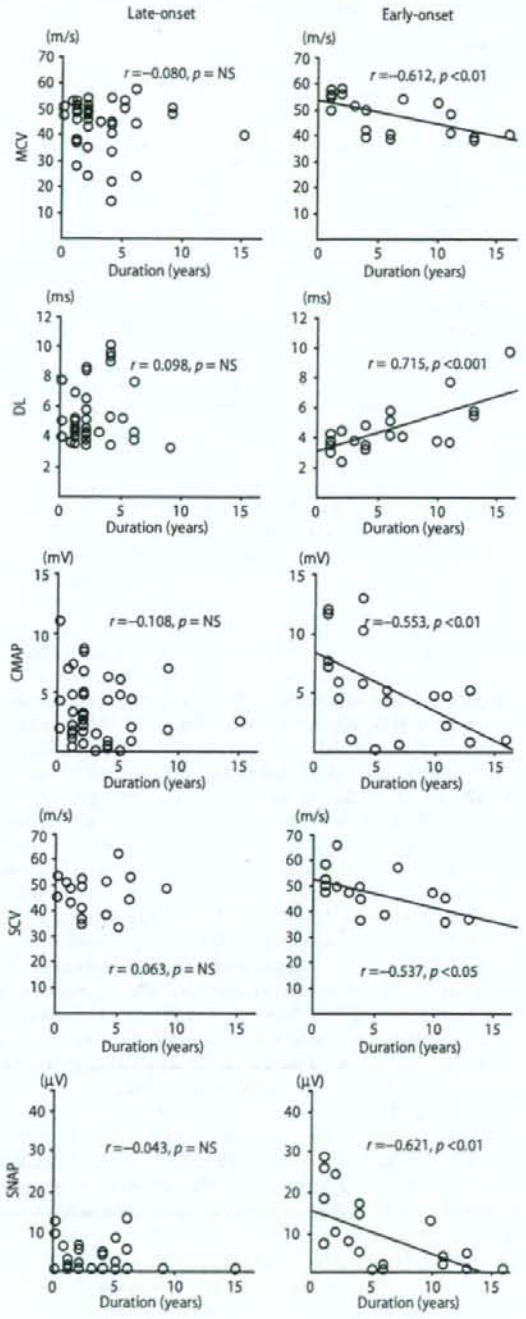

Fig. 1 Relationship between the electrophysiological indices of the median nerve and the duration of neuropathic symptoms in 44 late-onset FAP TTR Met30 cases from non-endemic areas (left panels) and 21 early-onset FAP TTR Met30 cases from endemic foci (right panels). Bold lines represent regression lines. In the early-onset cases, motor nerve conduction velocity (MCV), compound muscle action potential (CMAP), sensory nerve conduction velocity (SCV), and sensory nerve action potential (SNAP) showed a negative correlation and distal latency (DL) showed a positive correlation with the duration of neuropathic symptoms. In contrast, such correlations were not found in late-onset cases. *NS* not significant

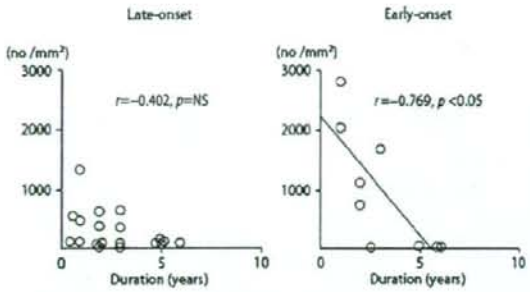

Fig. 2 Relationship between the density of large myelinated fibers in the sural nerve biopsy specimens and the duration of neuropathic symptoms in 21 late-onset FAP TTR Met30 cases from non-endemic areas (left panel) and 9 early-onset FAP TTR Met30 cases from endemic foci (right panel). Bold lines represent a regression line. In the early-onset cases, large myelinated fiber density showed a negative correlation with the duration of neuropathic symptoms. In contrast, such a correlation was not found in late-onset cases. *NS* not significant

large myelinated fiber density showed a negative correlation to the disease duration in early-onset cases, but not in late-onset cases. These findings support the view that these two forms of FAP TTR Met30 possesses different underlying mechanisms that result in neuropathy.

Through the development of the gene diagnostic techniques, transthyretin-related FAP has been shown to exist in many nations worldwide [13, 28, 29]. For example, sporadic late-onset FAP TTR Met30 is apparently not as rare in Japan as previously thought [16]. However, the classic concept of FAP is strong in the minds of many neurologists; therefore, sporadic cases are often late to receive a correct diagnosis [1, 13]. Thus, recognizing the variability in clinical, electrophysiological, and histopathological features of FAP, especially, sporadic late-onset FAP TTR Met30 in non-endemic areas, is becoming more important. Previous studies suggested that the characteristic finding of sural nerve biopsy specimens in FAP TTR Met30 in endemic foci was small-fiber predominant loss including unmyelinated fibers in association with the presence of sensory dissociation and marked autonomic dysfunction [18, 30, 33, 38]. However, this feature is not common in late-onset cases in non-endemic areas [18]. Therefore, clinicopathological features in these cases tend to be nonspecific.

Indeed, physicians did not consider FAP until amyloid became evident in sural nerve biopsy specimens in many of our late-onset cases. However, amyloid deposition may appear negative by rough examination in these cases [23], so that careful histopathological examination is needed. Therefore, recognition of the possibility for sporadic late-onset FAP TTR Met30 is needed at the time of the initial clinical and electrophysiological evaluation to avoid an incorrect diagnosis. Late-onset FAP TTR Met30 cases may be too old to undergo liver transplantation, but recent advances in therapeutic strategies, such as the prevention of amyloid fibril formation by stabilizing transthyretin tetramers or the reduction of transthyretin deposition by immunization [39, 40], render the value of early diagnosis of these patients more important. The demyelinating feature in FAP TTR Met30 is another impediment to correct diagnosis. The slowing of conduction velocity and prolongation of DL, which suggest the presence of demyelinating changes, were conspicuous in some of our patients. These demyelinating features were indicated by the presence of segmental demyelination in teased-fiber preparations [28, 30]. If a biopsy was not performed, physicians may diagnose these patients as CIDP [28]. Electrophysiological features indicating demyelination are not as conspicuous in typical axonal neuropathies, including alcoholic and beriberi neuropathies [14, 15, 17, 19], although the presence of secondary segmental demyelination due to axonal atrophy has been reported in association with these neuropathies [17, 21]. On the other hand, the electrophysiological features indicating demyelination should be taken into consideration for FAP TTR Met30. The demyelinating feature, at first glance, does not exclude the possibility of this disease.

The finding that CMAP and SNAP were reduced in the late-onset group compared to the early-onset group in spite of a similar activity of daily living may reflect the tendency of small-fiber predominant loss in early-onset cases and the loss of the entire range of nerve fibers in late-onset cases. The nerve conduction studies performed here reflect the abnormalities in large myelinated fibers, and these findings support the view that the differential modality of nerve fiber involvement is not confined to the sural nerve. However, this does not explain the difference in the mechanisms of axonal loss between early- and late-onset cases.

Although the pathogenesis of peripheral neuropathy in amyloidosis has not been clarified, the obliteration or dysfunction of small vessels [4, 8], compression or infiltration of amyloid deposition [7, 30], or toxic effect of amyloid precursors [36, 37] may be involved. According to our previous study of biopsy and autopsy cases, nerve fibers tended to be more severely reduced as a whole, while the amount of amyloid deposition tended to be milder in late-onset FAP TTR Met30 cases in non-endemic areas than in early-onset cases in endemic foci [18].

In addition, axonal sprouting was abundant in late-onset cases, even when the age at examination was taken into account [18]. This observation suggests a long history of nerve damage and repair in late-onset cases. Amorphous material, which was transthyretin-positive, but Congo-red-negative, suggesting the presence of nonfibrillar amyloid precursor, was shown to be abundant in a late-onset case [18]. Thus, amyloid may not start to deposit until the patients become elderly, but the toxicity of amyloid precursors may have a subclinical

affect during the presymptomatic stage in late-onset cases.

In this study, most of the electrophysiological indices in the early-onset group tended to remain normal during the initial phase of neuropathic symptoms and seemed to become aggravated with increased duration of neuropathic symptoms. However, most of these indices in the late-onset group were aggravated in the initial phase. The relationship between large myelinated fiber density in the sural nerve biopsy specimens and the duration of neuropathic symptoms also supports this view. Taken together, our results suggest that toxicity of non-fibrillar form of transthyretin may affect the peripheral nervous system for a long period prior to deposition of amyloid fibrils in late-onset cases. This long-standing amyloid precursor toxicity may induce the whole range of axonal damage in late-onset cases, although this issue should be further assessed. The tendency of more predominant lower limb involvement, which may be interpreted as a length-dependency of axonal damage similar to that caused by the toxicity of ethanol or its metabolites [21], is more conspicuous in late-onset cases. Therefore, toxic factors are more likely to participate in these cases. In early-onset cases, the deposition of amyloid fibrils may be severe even in the early phase of neuropathic symptoms judging from the amount of amyloid deposition compared to late-onset cases [18]. Amyloid fibrils, therefore, may cause small-fiber predominant axonal loss as previously suggested [30]. Thus, differential duration of exposure to toxic amyloid precursor may create a different mode of axonal loss.

Conflict of interest The authors declare no conflict of interest.

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References

1. Ando Y, Ueyama H, Watanabe S, Miyaji M, Tanaka Y, Ando M, Araki S (1993) Early involvement of motor nerve dysfunction in atypical cases with familial amyloidotic polyneuropathy (FAP) type I. Muscle Nerve 16:978–979
2. Ando Y, Suhr OB (1998) Autonomic dysfunction in familial amyloid polyneuropathy (FAP). Amyloid: Int J Exp Clin Invest 5:288–300
3. Benson MD, Cohen AS (1977) Generalized amyloid in a family of Swedish origin. A study of 426 family members in seven generations of a new kindship with neuropathy, nephropathy, and central nervous system involvement. Ann Intern Med 86:419–424
4. Berghoff M, Kathpal M, Khan F, Skinner M, Falk R, Freeman R (2003) Endothelial dysfunction precedes C-fiber abnormalities in primary (AL) amyloidosis. Ann Neurol 53:725–730
5. Coelho T, Sousa A, Lourenco E, Ramalheira J (1994) A study of 159 Portuguese patients with familial amyloidotic polyneuropathy (FAP) whose parents were both unaffected. J Med Genet 31:293–299
6. Conceição I, De Carvalho M (2007) Clinical variability in type I familial amyloid polyneuropathy (Val30Met): comparison between late- and early-onset cases in Portugal. Muscle Nerve 35:116–118
7. Dyck PJ, Lambert EH (1969) Dissociated sensation in amyloidosis. Compound action potential, quantitative histologic and teased-fiber, and electron microscopic studies of sural nerve biopsies. Arch Neurol 20:490–507
8. Hanyu N, Ikeda S, Nakadai A, Yanagisawa N, Powell HC (1989) Peripheral nerve pathological findings in familial amyloid polyneuropathy: a correlative study of proximal sciatic nerve and sural nerve lesions. Ann Neurol 25: 340–350
9. Hattori N, Yamamoto M, Yoshihara T, Koike H, Nakagawa M, Yoshikawa H, Ohnishi A, Hayasaka K, Onodera O, Baba M, Yasuda H, Saito T, Nakashima K, Kira J, Kaji R, Oka N, Sobue G; Study Group for Hereditary Neuropathy in Japan (2003) Demyelinating and axonal features of Charcot-Marie-Tooth disease with mutations of myelin-related proteins (PMP22, MPZ and Cx32): a clinicopathological study of 205 Japanese patients. Brain 126: 134–151
10. Holmgren G, Costa PM, Andersson C, Asplund K, Steen L, Beckman L, Nylander PO, Teixeira A, Saraiva MJ, Costa PP (1994) Geographical distribution of TTR met30 carriers in northern Sweden: discrepancy between carrier frequency and prevalence rate. J Med Genet 31:351–354
11. Ikeda S, Hanyu N, Hongo M, Yoshioka J, Oguchi H, Yanagisawa N, Kobayashi T, Tsukagoshi H, Ito N, Yokota T (1987) Hereditary generalized amyloidosis with polyneuropathy: clinicopathological study of 65 Japanese patients. Brain 110:315–337
12. Ikeda S, Nakazato M, Ando Y, Sobue G (2002) Familial transthyretin-type amyloid polyneuropathy in Japan: clinical and genetic heterogeneity. Neurology 58:1001–1007
13. Ikeda S (2007) Is familial amyloid polyneuropathy rare? DNA testing is changing the concept of this disease. Neurology 69:627–628
14. Koike H, Misu K, Hattori N, Ito S, Ichimura M, Ito H, Hirayama M, Nagamatsu M, Sasaki I, Sobue G (2001) Postgastrectomy polyneuropathy with thiamine deficiency. J Neurol Neurosurg Psychiatry 71:357–362
15. Koike H, Mori K, Misu K, Hattori N, Ito H, Hirayama M, Sobue G (2001) Painful alcoholic polyneuropathy with predominant small-fiber loss and normal thiamine status. Neurology 56:1727–1732
16. Koike H, Misu K, Ikeda S, Ando Y, Nakazato M, Ando E, Yamamoto M, Hattori N, Sobue G (2002) Type I (Transthyretin Met30) familial amyloid polyneuropathy in Japan: early- versus late-onset form. Arch Neurol 59:1771–1776

17. Koike H, Iijima M, Sugiura M, Mori K, Hattori N, Ito H, Hirayama M, Sobue G (2003) Alcoholic neuropathy is clinicopahthologically distinct form thiamine-deficiency neuropathy. Ann Neurol 54:19–29
18. Koike H, Misu K, Sugiura M, Iijima M, Mori K, Yamamoto M, Hattori N, Mukai E, Ando Y, Ikeda S, Sobue G (2004) Pathology of early- vs late-onset TTR Met30 familial amyloid polyneuropathy. Neurology 63:129–138
19. Koike H, Iijima M, Mori K, Hattori N, Ito H, Hirayama M, Sobue G (2004) Postgastrectomy polyneuropathy with thiamine deficiency is identical to beriberi neuropathy. Nutrition 20: 961–966
20. Koike H, Hirayama M, Yamamoto M, Ito H, Hattori N, Umehara F, Arimura K, Ikeda S, Ando Y, Nakazato M, Kaji R, Hayasaka K, Nakagawa M, Sakoda S, Matsumura K, Onodera O, Baba M, Yasuda H, Saito T, Kira J, Nakashima K, Oka N, Sobue G (2005) Age associated axonal features in HNPP with 17p11.2 deletion in Japan. J Neurol Neurosurg Psychiatry 76:1109–1114
21. Koike H, Sobue G (2006) Alcoholic neuropathy. Curr Opin Neurol 19: 481–486
22. Koike H, Iijima M, Mori K, Yamamoto M, Hattori N, Katsuno M, Tanaka F, Watanabe H, Doyu M, Yoshikawa H, Sobue G (2007) Nonmyelinating Schwann cell involvement with well-preserved unmyelinated axons in CMT1A. J Neuropathol Exp Neurol 66:1027–1036
23. Misu K, Hattori N, Nagamatsu M, Ikeda S, Ando Y, Nakazato M, Takei Y, Hanyu N, Usui Y, Tanaka F, Harada T, Inukai A, Hashizume Y, Sobue G (1999) Late-onset familial amyloid polyneuropathy type I (transthyretin Met 30-associated familial amyloid polyneuropathy) unrelated to endemic focus in Japan; clinicopathological and genetic features. Brain 122:1951–1962
24. Misu K, Hattori N, Ando Y, Ikeda S, Sobue G (2000) Anticipation in early- but not late-onset familial amyloid polyenuropathy (TTR Met 30) in Japan. Neurology 55:451–452
25. Mori K, Iijima M, Koike H, Hattori N, Tanaka F, Watanabe H, Katsuno M, Fujita A, Aiba I, Ogata A, Saito T, Asakura K, Yoshida M, Hirayama M, Sobue G (2005) The wide spectrum of clinical manifestations in Sjogren's syndrome-associated neuropathy. Brain 128:2518–2534
26. Nakazato M, Shiomi K, Miyazato M, Matsukura S (1992) Type 1 familial amyloidotic polyneuropathy in Japan. Intern Med 31:1335–1338
27. Oki Y, Koike H, Iijima M, Mori K, Hattori N, Katsuno M, Nakamura T, Hirayama M, Tanaka F, Shiraishi M, Yazaki S, Nokura K, Yamamoto H, Sobue G (2007) Ataxic vs painful form of paraneoplastic neuropathy. Neurology 69:564–572
28. Plante-Bordeneuve V, Ferreira A, Lalu T, Zaros C, Lacroix C, Adams D, Said G (2007) Diagnostic pitfalls in sporadic transthyretin familial amyloid polyneuropathy (TTR-FAP). Neurology 69:693–698
29. Reilly MM, Adams D, Booth DR, Davis MB, Said G, Laubriat-Bianchin M, Pepys MB, Thomas PK, Harding AE (1995) Transthyretin gene analysis in European patients with suspected familial amyloid polyneuropathy. Brain 118:849–856
30. Said G, Ropert A, Faux N (1984) Length-dependent degeneration of fibers in Portuguese amyloid polyneuropathy: a clinicopathologic study. Neurology 34:1025–1032
31. Saravia MJ, Costa PP, Goodman DS (1986) Genetic expression of a tansthyretin mutation in typical and late-onset Portuguese families with familial amyloidotic polyneuropathy. Neurology 36:1413–1417
32. Sobue G, Hashizume Y, Mukai E, Hirayama M, Mitsuma T, Takahashi A (1989) X-linked recessive bulbospinal neuronopathy, a clinicopathological study. Brain 112:209–232
33. Sobue G, Nakao N, Murakami K, Yasuda T, Sahashi K, Mitsuma T, Sasaki H, Sakaki Y, Takahashi A (1990) Type I familial amyloid polyneuropathy. a pathological study of the peripheral nervous system. Brain 113:903–919
34. Sobue G, Koike H, Misu K, Hattori N, Yamamoto M, Ikeda S, Ando Y, Nakazato M, Inukai A (2003) Clinicopathologic and genetic features of early- and late-onset FAP type I (FAP ATTR Val30Met) in Japan. Amyloid: J Protein Folding Disord 10(Suppl 1):32–38
35. Sousa A, Coelho T, Barros J, Sequeiros J (1995) Genetic epidemiology of familial amyloidotic polyneuropathy (FAP)-type I in Povoa do Varzim and Vila do Conde (north of Portugal). Am J Med Genet 60:515–521
36. Sousa MM, Cardoso I, Fernandes R, Guimaraes A, Saraiva MJ (2001) Deposition of transthyretin in early stages of familial amyloidotic polyneuropahty: evidence for toxicity of nonfibrillar aggregates. Am J Pathol 159: 1993–2000
37. Sousa MM, Fernandes R, Palha JA, Taboada A, Vieira P, Saraiva MJ (2002) Evidence for early cytotoxic aggregates in transgenic mice for human transthyretin Leu55Pro. Am J Pathol 161: 1935–1948
38. Takahashi K, Yi S, Kimura Y, Araki S (1991) Familial amyloidotic polyneuropathy type 1 in Kumamoto Japan: a clinicopathologic, histochemical, immunohistochemical, and ultrastructural study. Hum Pathol 22:519–527
39. Terazaki H, Ando Y, Fernandes R, Yamamura K, Maeda S, Saraiva MJ (2006) Immunization in familial amyloidotic polyneuropathy: counteracting deposition by immunization with a Y78F TTR mutant. Lab Invest 86:23–31
40. Tojo K, Sekijima Y, Kelly JW, Ikeda S (2006) Diflunisal stabilizes familial amyloid polyneuropathy-associated transthyretin variant tetramers in serum against dissociation required for amyloidogenesis. Neurosci Res 56:441–449
41. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJ, van Gijn J (1988) Interobserver agreement for the assessment of handicap in stroke patients. Stroke 19:604–607

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Rapidly developing weakness mimicking Guillain-Barré syndrome in beriberi neuropathy: Two case reports

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Abstract

Objective: We examined the diagnostic difficulty in thiamine deficiency.

Methods: We report on two patients with polyneuropathy associated with thiamine deficiency (i.e., beriberi neuropathy) that presented with acute motor symptoms mimicking Guillain-Barré syndrome.

Results: The cause of the thiamine deficiency was associated with gastrectomy to treat cancer in a 46-y-old man and with dietary imbalance in a 33-y-old man. The thiamine deficiency was not related to alcohol intake in either patient. In both patients, the upper and lower extremities showed a rapidly progressive weakness over the course of 1 mo. Muscle weakness in the first patient progressed even after admission to the hospital, and urinary retention, Wernicke's encephalopathy, lactic acidosis, paralytic ileus, and heart failure appeared subsequently. Clinical symptoms in both patients showed improvement after initiation of thiamine administration, although some residual deficit remained.

Conclusion: Thiamine deficiency must be actively considered as a possible cause of polyneuropathy, and variability in its clinical features should be taken into consideration.

Keywords: Thiamine; Beriberi; Neuropathy; Guillain-Barré syndrome

Introduction

Thiamine (vitamin B1) deficiency may occur in persons with a decreased intake of thiamine caused by consumption of high-carbohydrate, low-thiamine diets [1–3], chronic alcoholism [4,5], anorexia nervosa [6], or hyperemesis gravidarum [7]. In addition, it may occur in persons with increased thiamine requirements such as laborers performing heavy outdoor work [1] and pregnant or lactating women [8]. Thiamine deficiency can result in peripheral neuropathy, heart failure, and Wernicke-Korsakoff syndrome. The disorder has been largely forgotten by many physicians, especially those in developed countries, because prophylactic thiamine administration in high-risk cases and nutritional education have considerably decreased the occurrence of thiamine deficiency. However, some investigators have suggested that neuropathy associated with thiamine deficiency is not uncommon in patients with a variety of background factors including chronic alcoholism [5,9,10], prolonged parenteral nutrition [11], a postgastrectomy state to treat ulcers or neoplasms [3,5,12], and after operations to treat morbid obesity (i.e., bariatric surgery) [13]. Therefore, thiamine deficiency should still be considered in various clinical settings.

In this report, we present two cases of polyneuropathy associated with thiamine deficiency (i.e., beriberi neuropathy), one associated with gastrectomy to treat cancer and one with dietary imbalance, that presented with acute motor symptoms and posed a diagnostic difficulty by mimicking Guillain-Barré syndrome. A rough clinical profile of the

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Table 1
Nerve conduction study in patients 1 and 2

	Median nerve					Tibial nerve			Sural nerve	
	Motor			Sensory		Motor			Sensory	
	MCV (m/s)	DL (ms)	CMAP (mV)	SCV (m/s)	SNAP (μV)	MCV (m/s)	DL (ms)	CMAP (mV)	SCV (m/s)	SNAP (μV)
Patient 1	55.0	4.68	4.66	40.3	10.40	45.2	4.83	8.22	49.2	1.00
Patient 2	57.4	3.94	3.78		NE	40.0	5.58	0.13		NE
Controls (mean ± SD)*	57.8 ± 3.7	3.4 ± 0.4	10.7 ± 3.5	57.8 ± 4.7	23.5 ± 8.4	46.9 ± 3.5	4.5 ± 0.8	10.9 ± 3.8	51.0 ± 5.1	11.5 ± 4.7

CMAP, compound muscle action potential; DL, distal latency; MCV, motor nerve conduction velocity; NE, not elicited; SCV, sensory nerve conduction velocity; SNAP, sensory nerve action potential

* Control values were obtained in 191 normal volunteers (mean age ± SD 48.7 ± 16.5 y, male:female 97:94) for the median nerve, 121 (mean age ± SD 49.9 ± 15.0 y, male:female 64:57) for the tibial nerve, and 133 (mean age ± SD 50.6 ± 15.6 y, male:female 74:59) for the sural nerve [9,12].

former case was reported previously as 1 of 17 cases with postgastrectomy polyneuropathy in thiamine deficiency [12], and the latter is a new case. We believe that these case studies provide further insights into the current knowledge of this classic but occasionally forgotten disease.

Case reports

Patient 1

A 46-y-old man noted weakness in his lower extremities at 10 d before admission to the hospital. He reported no preceding episode of upper respiratory or gastrointestinal infection. Numbness in the distal portions of the lower extremities followed the initial weakness. The weakness gradually progressed over 10 d until the patient had great difficulty in walking by himself. The patient had undergone a total gastrectomy for adenocarcinoma of the stomach 3 y previously, with reconstruction using a jejunal pouch interposition. His condition had been good without complications. The patient and his wife took particular care with nutritional balance since the operation, and he completely abstained from alcohol. Neurologic examination revealed distal-dominant weakness in the lower extremities. A mild sensory deficit involving all modalities was present in the legs. Patellar and Achilles tendon reflexes were absent. Examination of the upper extremities was normal except for hypoactive deep tendon reflexes. Plantar responses were flexor on both sides. Cerebrospinal fluid examination revealed no abnormalities in protein content or cell count. A nerve conduction study, performed on the day of admission, revealed a reduction in sensory nerve action potential in the sural nerve, indicative of axonal neuropathy (Table 1). After admission to the hospital, the weakness rapidly worsened, ascending from the lower to the upper extremities to render the patient bedridden after 3 d. Urinary retention developed at 17 d after the first symptom, and, at 21 d from onset, ocular movements had become affected. A sural nerve biopsy specimen, obtained at 22 d from onset, revealed axonal degeneration, with a predominant loss of large myelinated fibers (Fig. 1). Severe edema in the subperineurial space also was observed. Decreases in the level of consciousness and the occurrence of lactic acidosis appeared on day 27. Retention of gas in the gastrointestinal tract with a decrease of bowel sounds also was noted. On day 28, severe heart failure that was unresponsive to diuretic agents appeared. A 100-mg intravenous dose of fursultiamine was given to initiate therapy on that day. The total thiamine concentration in the whole blood at this time was 15 ng/mL (normal 20–50 ng/mL, representing a mean ± 2 SD for 100 normal control subjects [5,9,12]). The patient recovered from heart failure and from the disturbance of consciousness in several days. His neurologic symptoms also showed gradual improvement beginning from that day. Six months later, he was just able to walk by himself.

Patient 2

A 33-y-old man noted numbness in his distal lower limbs at 2 wk before admission. Weakness in the lower limbs

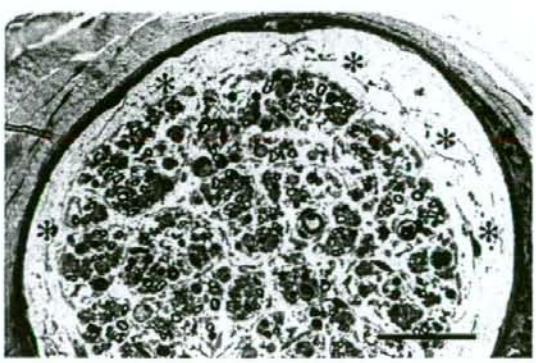

Fig. 1. Transverse section of a sural nerve biopsy specimen in patient 1. Loss of predominantly large myelinated fibers is observed. Extensive endoneurial edema with enlargement of the subperineurial space is indicated by asterisks. Scale bar = 50 μm.

appeared at 5 d before admission and subsequently progressed rapidly in the lower limbs and the upper limbs. The patient was bedridden at the time of admission to the hospital. He did not have any preceding infectious episode. He did not like to eat meat or vegetables, preferring milled white rice and noodles with no side dishes. He took these meals at very irregular intervals. The patient reported only occasional intake of alcohol, which did not exceed 20 g/d of ethanol consumption. He had maintained these dietary patterns for 6 y. Once he was engaged in heavy outdoor work, but he then lost his job. He had no history of surgical procedures including gastrectomy. Neurologic examination revealed severe distal-dominant weakness in the lower and upper extremities. The grasping power of both hands was 0 kg. Plantarflexion and dorsiflexion of the foot could not be performed bilaterally. Severe sensory deficits involving all modalities were present in the legs, whereas sensory loss was mild in the hands. Deep tendon reflexes were moderately decreased in the upper limbs and were absent in the lower limbs. Plantar responses were flexor on both sides. Consciousness was intact, and cranial nerve function was normal. Cramping pain was present in the muscles of the lower limbs. Edema was not noted in the limbs. Chest radiographs and echocardiogram revealed no signs of heart failure. Cerebrospinal fluid examination revealed no abnormalities. Nerve conduction study showed reductions in compound muscle action potentials that were mild in the upper limbs and severe in the lower limbs (Table 1). Sensory nerve action potentials could not be evoked in the upper and lower limbs. A diagnosis of Guillain-Barré syndrome was considered initially, but predominant axonal features and a history of dietary imbalance led us to consider beriberi neuropathy. A 100-mg intravenous dose of fursultiamine was administered to begin treatment. Total thiamine concentration in the whole blood at that time was 7 ng/mL. Symptoms showed gradual improvement from that day. He was able to walk with a cane 1 mo later.

Discussion

Beriberi neuropathy, caused by dietary imbalance without associated alcohol intake, is currently considered rare in developed countries. Therefore, clinicians are relatively unaware of thiamine deficiency as a possible cause of polyneuropathy, especially in patients without Wernicke's encephalopathy or heart failure at the initial phase, as in the present cases. Moreover, thiamine deficiency is not widely recognized to be related to various background factors. Previous studies of neuropathy associated with thiamine deficiency have suggested that the major causes of thiamine deficiency in Japan are heavy alcohol intake, gastrectomy to treat cancers or ulcers, and dietary imbalance [3,5,12]. In Western countries, where morbid obesity is prevalent, bariatric surgery has become a risk factor [13]. Gastrectomy to treat cancers or ulcers, and not associated with the treatment of obesity, is not widely appreciated as a possible cause of thiamine deficiency, especially when a patient's clinical condition is favorable without complications for a long period after surgery. The varied symptoms of polyneuropathy are another impediment to correct diagnosis. Previous studies have indicated the presence of variable clinical features of beriberi neuropathy, including the progression and relative predominance of motor and sensory deficits [3,5,10,12]. Some patients, especially those with rapid progression mimicking Guillain-Barré syndrome, as in the present cases, may become worse when intravenous thiamine is not administered soon after admission. Because the pathologic characteristic of beriberi neuropathy is considered to be a length-dependent dying-back axonal neuropathy, patients with thiamine deficiency, without exception, manifest symmetric polyneuropathy with more involvement in the lower than upper limbs, showing a centripetal pattern of progression [3,5,12]. In contrast, weakness that is predominant in the proximal portions of the limbs, which may be caused by simultaneous involvement of skeletal muscles due to thiamine deficiency [14], may amplify the variability of clinical features of beriberi neuropathy in some patients.

Similar to variable neuropathic features, the combination of other symptoms associated with thiamine deficiency such as Wernicke's encephalopathy and heart failure varies among individual patients [3,5,12]. If thiamine deficiency is exacerbated without treatment due to delayed reference or diagnosis, as occurred in patient 1 in the present report, this combination of symptoms may tend to worsen. However, the presence of interindividual differences in susceptibility to the development of thiamine deficiency–related disorders and differential vulnerabilities to thiamine deficiency of certain tissues and cell types has been suggested [12,15]. The cause of these variations has not been determined. Genetic factors may cause susceptibility to thiamine deficiency for individual organs [15]. For example, genetic variability of transketolase may relate to susceptibility to Wernicke's encephalopathy [16,17]. Thiamine-responsive megaloblastic anemia associated with diabetes mellitus and deafness results from a mutation of the gene encoding the high-affinity thiamine transporter protein [18–20]. This genetic defect preferentially involves hematopoietic cells, pancreatic islet cells, and auditory apparatus cells. Seasonal ataxic syndrome in western Nigeria, which is caused by eating the pupae of an African silkworm that possesses a heat-resistant thiaminase, is known to manifest ataxia as the main clinical feature of thiamine deficiency [21,22]. Ethnic variation of genetic background may explain the clustering of clinical symptoms in thiamine deficiency on ataxia in this region.

Since the introduction of high-performance liquid chromatography in the 1980s [23,24], direct thiamine evaluation has become widely used in routine practice. Before this method became available, thiamine status mostly had been evaluated indirectly through a functional determination of

activity of erythrocyte transketolase, a thiamine-dependent enzyme [25]. In addition, pyruvate and lactate may accumulate in thiamine deficiency because pyruvate, the final glycolytic product, cannot be utilized in the citric acid cycle for adenosine triphosphate generation; instead, it is converted to lactate [26]. Therefore, elevation of serum pyruvate or lactate concentration may support the diagnosis of thiamine deficiency. Because genetic factors have been suggested to determine individual susceptibility to thiamine deficiency [3,12,15,16], laboratory and clinical data should be assessed in a comprehensive manner. In our patients total thiamine concentrations in whole blood evaluated by high-performance liquid chromatography were abnormally low and neuropathic symptoms improved by thiamine supplementation. However, one may argue that deficiencies of other vitamins, including nicotinic acid [27], vitamin B2 [28], vitamin B6 [29], vitamin B12 [30,31], or folate [32], might have contributed the pathogenesis of neuropathy in our patients. However, characteristic symptoms associated with these individual vitamin deficiencies were not present. These clinical pictures include anorexia, diarrhea, erythematous and hyperkeratotic dermatides, and mental changes in pellagra (nicotinic acid deficiency); cheilosis, glossitis, keratoconjunctivitis, and dermatitis involving nasolabial folds, scrotum, and labia in vitamin B2 deficiency; and myelopathy in vitamin B12 and folate deficiency. Thus, we believe that these vitamins were not major causal factors of neuropathy in our patients.

As for the prognosis of beriberi neuropathy, some residual deficits persist in many patients, although the functional status improved after thiamine administration [12]. According to a previous study, substantial functional recovery, particularly in motor involvement, was achieved by thiamine supplementation within 6 mo, but sensory symptoms and Korsakoff's psychosis were likely to show residual deficits [12]. Indeed, patient 1, whose muscle weakness progressed even after admission to the hospital and various symptoms associated with thiamine deficiency other than neuropathy had appeared, took longer to recover ambulation than patient 2, whose clinical manifestations are those related to neuropathy alone. Thus, treatment should be initiated as early as possible.

In conclusion, thiamine deficiency should be actively considered as a possible cause of polyneuropathy, and variability of its clinical features also should be taken into consideration.

References

[1] Takahashi K. Thiamine deficiency neuropathy, a reappraisal. Int J Neurol 1981;15:245–53.

[2] Ohnishi A, Tsuji S, Igisu H, Murai Y, Goto I, Kuroiwa Y, et al. Beriberi neuropathy. Morphometric study of sural nerve. J Neurol Sci 1980;45:177–90.

[3] Koike H, Iijima M, Mori K, Hattori N, Ito H, Hirayama M, et al. Postgastrectomy polyneuropathy with thiamine deficiency is identical to beriberi neuropathy. Nutrition 2004;20:961–6.

[4] Victor M, Adams RD. On the etiology of the alcoholic neurologic diseases with special reference to the role of nutrition. Am J Clin Nutr 1961;9:379–97.

[5] Koike H, Iijima M, Sugiura M, Mori K, Hattori N, Ito H, et al. Alcoholic neuropathy is clinicopathologically distinct from thiamine-deficiency neuropathy. Ann Neurol 2003;54:19–29.

[6] Handler CE, Perkin GD. Anorexia nervosa and Wernicke's encephalopathy: an underdiagnosed association. Lancet 1982;2:771–2.

[7] Lavin PJ, Smith D, Kori SH, Ellenberger C Jr. Wernicke's encephalopathy: a predictable complication of hyperemesis gravidarum. Obstet Gynecol 1983;62(suppl):13s–5.

[8] McGready R, Simpson JA, Cho T, Dubowitz L, Changbumrung S, Bohm V, et al. Postpartum thiamine deficiency in a Karen displaced population. Am J Clin Nutr 2001;74:808–13.

[9] Koike H, Mori K, Misu K, Hattori N, Ito H, Hirayama M, et al. Painful alcoholic polyneuropathy with predominant small-fiber loss and normal thiamine status. Neurology 2001;56:1727–32.

[10] Koike H, Sobue G. Alcoholic neuropathy. Curr Opin Neurol 2006; 19:481–6.

[11] Zak J III, Burns D, Lingenfelser T, Steyn E, Marks IN. Dry beriberi: unusual complication of prolonged parenteral nutrition. JPEN 1991; 15:200–1.

[12] Koike H, Misu K, Hattori N, Ito S, Ichimura M, Ito H, et al. Postgastrectomy polyneuropathy with thiamine deficiency. J Neurol Neurosurg Psychiatry 2001;71:357–62.

[13] Juhasz-Pocsine K, Rudnicki SA, Archer RL, Harik SI. Neurologic complications of gastric bypass surgery for morbid obesity. Neurology 2007;68:1843–50.

[14] Koike H, Watanabe H, Inukai A, Iijima M, Mori K, Hattori N, et al. Myopathy in thiamine deficiency: analysis of a case. J Neurol Sci 2006;249:175–9.

[15] Singleton CK, Martin PR. Molecular mechanisms of thiamine utilization. Curr Mol Med 2001;1:197–207.

[16] Blass JP, Gibson GE. Abnormality of a thiamine-requiring enzyme in patients with Wernicke-Korsakoff syndrome. N Engl J Med 1977; 297:1367–70.

[17] Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. Lancet Neurol 2007;6:442–55.

[18] Labay V, Raz T, Baron D, Mandel H, Williams H, Barrett T, et al. Mutations in SLC19A2 cause thiamine-responsive megaloblastic anaemia associated with diabetes mellitus and deafness. Nat Genet 1999;22:300–4.

[19] Fleming JC, Tartaglini E, Steinkamp MP, Schorderet DF, Cohen N, Neufeld EJ. The gene mutated in thiamine-responsive anaemia with diabetes and deafness (TRMA) encodes a functional thiamine transporter. Nat Genet 1999;22:305–8.

[20] Diaz GA, Banikazemi M, Oishi K, Desnick RJ, Gelb BD. Mutations in a new gene encoding a thiamine transporter cause thiamine-responsive megaloblastic anaemia syndrome. Nat Genet 1999;22:309–12.

[21] Adamolekun B, Adamolekun WE, Sonibare AD, Sofowora G. A double-blind, placebo-controlled study of the efficacy of thiamine hydrochloride in a seasonal ataxia in Nigerians. Neurology 1994;44: 549–51.

[22] Nishimune T, Watanabe Y, Okazaki H, Akai H. Thiamin is decomposed due to *Anaphe spp.* entomophagy in seasonal ataxia patients in Nigeria. J Nutr 2000;130:1625–8.

[23] Kimura M, Fujita T, Itokawa Y. Liquid-chromatographic determination of the total thiamin content of blood. Clin Chem 1982;28:29–31.

[24] Warnock LG. The measurement of erythrocyte thiamin pyrophosphate by high-performance liquid chromatography. Anal Biochem 1982;126:394–7.

[25] Dreifus PM. Clinical application of blood transketolase determinations. N Engl J Med 1962;267:596–8.
[26] Blass JP. Disorders of pyruvate metabolism. Neurology 1979;29:280–6.
[27] Spies TD, Chinn AB, McLester JB. Severe endemic pellagra: a clinical study of fifty cases with special emphasis on therapy. JAMA 1937;108:853–7.
[28] Cotran RS, Kumar V, Robbins SL. Nutritional disease. In: Robbins pathologic basis of disease. 4th ed. Philadelphia: WB Saunders; 1989, p. 435–67.
[29] Raskin NH, Fishman RA. Pyridoxine-deficiency neuropathy due to hydralazine. N Engl J Med 1965;273:1182–5.
[30] Kosik KS, Mullins TF, Bradley WG, Tempelis LD, Cretella AJ. Coma and axonal degeneration in vitamin B12 deficiency. Arch Neurol 1980;37:590–2.
[31] McCombe PA, McLeod JG. The peripheral neuropathy of vitamin B12 deficiency. J Neurol Sci 1984;66:117–26.
[32] Botez MI, Peyronnard JM, Bachevalier J, Charron L. Polyneuropathy and folate deficiency. Arch Neurol 1978;35:581–4.

Neuropathic pain correlates with myelinated fibre loss and cytokine profile in POEMS syndrome

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ABSTRACT

Objective: To reveal characteristic clinicopathological correlates of polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy and skin changes (POEMS) syndrome.

Methods: The clinical features of 22 patients with POEMS syndrome were investigated and correlated with the histopathological features of sural nerves and serum cytokine profiles.

Results: More than half of the patients complained of pain in the lower extremities, which is closely related to hyperalgesia. Assessment of the total nerve fibre population using complete transverse sural nerve cross-sections, excluding the marked enlargement of endoneurial areas due to intrafascicular oedema, showed that myelinated fibres, especially small myelinated fibres, were reduced, whereas unmyelinated fibres were preserved. Uncompacted myelin lamellae and segmental demyelination were seen more frequently in the small, rather than the large, myelinated fibres. The presence of hyperalgesia was electrophysiologically associated with a reduction of sensory nerve action potentials in the sural nerve ($p<0.05$) and histopathologically associated with myelinated fibre loss ($p<0.01$). Serum levels of proinflammatory cytokines (interleukin-1β, interleukin-6 and tumour necrosis factor-α), but not their soluble receptors, were significantly elevated in patients with hyperalgesia ($p<0.05$–0.01).

Conclusions: Hyperalgesia seen in patients with POEMS syndrome is closely related with a reduction in the myelinated, but not unmyelinated, fibre population. Elevation of proinflammatory cytokines is also correlated with hyperalgesia. The painful symptoms in POEMS syndrome may be generated by well-preserved unmyelinated C-fibres due to the lack of inhibitory myelinated A-fibres, along with cytokine sensitisation.

POEMS syndrome—an acronym for polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes—is a unique multisystem disorder that is also known as Crow–Fukase syndrome.[1] Because it is strongly associated with plasma-cell dyscrasia, especially osteosclerotic myeloma, monoclonal proliferation of plasma cells has been thought to play an important role in the development of various POEMS symptoms.[1 2] In addition, serum concentrations of cytokines, such as interleukin-1β (IL-1β), interleukin-6 (IL-6), and tumour necrosis factor-α (TNF-α), are elevated.[3] Recent studies implicate vascular endothelial growth factor (VEGF) as another pathogenetic factor.[4 5] As this syndrome manifests a variety of symptoms, it has been typically examined from the viewpoint of wide-ranging organ involvement;[1 2 6 7] reports exclusively examining its neuropathic features are relatively rare. Furthermore, because electrophysiological and histopathological features are those of demyelinating neuropathy,[7 8] neuropathy in POEMS syndrome has often been diagnosed as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) when the associated symptoms other than neuropathy are not conspicuous.[9 10] New therapeutic approaches to POEMS syndrome have been described that differ from CIDP approaches.[6 10–13] Therefore, clarification of the clinical and pathological features and their correlations unique to POEMS syndrome is needed to improve the diagnostic accuracy and subsequent therapeutic consequences.

The present study describes the clinical, pathological and cytokine profile features that are unique to POEMS syndrome.

PATIENTS AND METHODS

Patients

Twenty-two consecutive patients with POEMS syndrome who were referred to the Department of Neurology of Nagoya University Hospital from 1987 to 2007 were investigated. Patients included 13 men and 9 women aged 54.8 ± 13.6 (mean ± SD) years. Clinical features and laboratory data assessed before the initiation of treatment are summarised in table 1. As for the assessment of neuropathic pain, patients were asked whether they have spontaneous pain. Mechanical stimuli, both normally painful and normally non-painful, were applied on the distal portion of the lower limbs (dorsum of foot and lateral surface of the lower leg) by examiners to evaluate hyperalgesia. The patient's subjective responses to these stimuli were qualified and the amount of pain was described in categorical scale (none, mild, moderate and severe). Because patients with POEMS syndrome lack a contralateral homologous normal side due to their symmetrical polyneuropathy pattern, responses to normally painful stimuli such as pinprick and pinwheel were compared with those on a more proximal portion of the limbs (anterior thigh). Abnormal sensations without pain were not considered to be hyperalgesia. Patients' functional status was assessed at the peak phase according to the modified Rankin Scale.[14] Motor and sensory conduction was measured in the median, tibial and sural nerves in all patients during their initial clinical assessment by neurologists, using a standard method with surface electrodes for stimulation and recording.