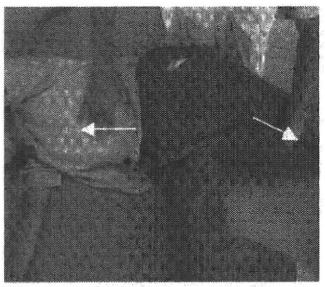
図9 腹直筋と大腿直筋

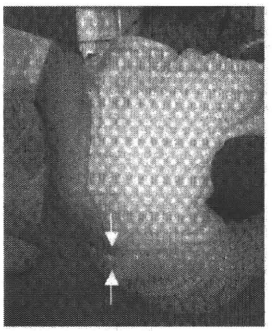
図10

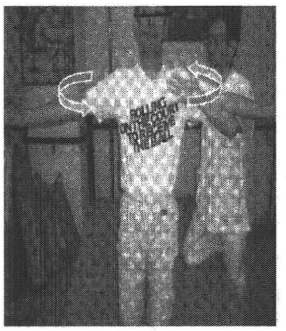
図11 膝立ち位

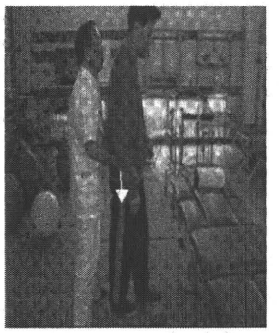
図12 タンデム立位

多系統萎縮症でパーキンソン症状のある場合は、頭部を前方に変移した姿勢の要因となる、筋緊張の亢進した筋群[19]を支配する神経群（副神経・肋間神経・長胸神経・胸背神経）の緊張を抑制することが大切です。

施行時間は40分/1回、施行回数は入院期間中の10回としました。

リハアプローチ前後の検討

リハアプローチの効果については、International-co-operative ataxia rating scale(ICARS)[20]の姿勢および歩行項目、10m自立歩行可能者数、最大歩行速度、ケーデンス、歩行時のBalance efficacy scale (BES)、Berg balance scale(BBS)[21]、閉眼・閉脚(30秒間）可能者数について、リハアプローチ施行前後で比較検討しました。

結　果

ICARSの姿勢および歩行項目、10m自立歩行可能者数、10m最大歩行速度、ケーデンス、歩行時のBES、BBSにおいて、リハアプローチ施行後で有意に改善しました。閉眼・閉脚可能者数については、差は認められませんでした(表2)。

考　察

今回のリハアプローチにより、ICARSの姿勢および歩行項目の改善、全症例の10m自立歩行の獲得、歩行速度のスピードアップ、ケーデンスの正常値化傾向、歩行時の恐怖心の指標であるBESの減少、バランス指標であるBBSのスコア向上による転倒リスク減少の効果がありました。磁気治療との相乗効果もありますが、本院でのリハアプローチは、SCDの立位·歩行障害の改善に有益であったと言えます。

立位·歩行障害の改善した理由として、脳神経、末梢神経の神経モビライゼーションと求心性神経である皮神経の伸張で、正確な情報の提供と反応が引き出され、体幹動揺や両足を開いた姿勢が改善し、立位·歩行能力の向上が得られたと言えます。また立位と歩行能力の向上を考慮したアプローチにより、立位・歩行バランス能力の向上と歩行に必要なCPGの賦活が得られたと言えます。

閉眼・閉脚の可能者数の有意な改善が得られなかったのは、閉眼での体幹の揺れの増大により下オリーブ核から登上線維への複雑スパイクの発生頻度が多くなります[22]。閉眼による平行線維からのスパイクの頻度も多くなり、それらの入力が同期して起こる機会が増え、平行線維とプルキンエ細胞間の伝達効率は減弱(長期抑圧[23]）します。そのために、適度なプルキンエ細胞の発火が得られず、閉眼・閉脚の改善度が難しかったのではと考えます。リハアプローチとしては、刺激の量と入力のタイミングを考慮する必要があったと思われます。

今後は症例を増やし、神経モビライゼーションに基づいたリハアプローチの方法の確立を目指したいと思います。

表2　結果

評価項目	リハ施行前	リハ施行後
Ⅰ．ICARS：姿勢および歩行項目（点）	17.6±6.8	10.1±3.8**
Ⅱ．10m自立歩行者数(n)	5	10*
Ⅲ．最大歩行速度(秒)	14.1±4.4	11.5±4.9*
Ⅳ．ケイデンス（歩数/分）	108.9±17.6	118.1±9.7*
Ⅴ．歩行時のBES（mm）	67.8±23.3	25.6±20.4**
Ⅵ．BBS（点）	28.5±11.5	40.5±8.6**
Ⅶ．閉眼・閉脚立位可能者数(n)	2	5

mean±SD　*:p<0.05 **:p<0.01

最後に

SCDの立位·歩行障害に対しては、非常に多くの事柄を考慮する必要があり、リハアプローチに確立されたものが無いことが頷けます。そのために、SCDのリハを求めて

来られた患者さんやご家族が病院を訪れられた時に、「私共の病院ではSCDのリハは行っていません。」と、いうような事態がある事も事実です。そのような状況の改善に、少しでもお役に立てれば嬉しく思います。

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パーキンソン病の長期治療：内科の立場から

中村 雄作

Pharmacological management of Parkinson disease

Yusaku Nakamura

Abstract: The most effective treatment for Parkinson's disease (PD) is dopamine replacement with levodopa. After several years starting from levodopa, PD symptoms do not respond to levodopa. After then, patients usually experience "wearing off" and dyskinesias. The several strategies have been designed to try to ameliorate the motor complications of levodopa therapy. Levodopa, peripherally, is catabolized by aromatic amino acid decarboxylase and COMT. The concept of COMT inhibition is enhancing the bioavailability and efficacy of levodopa. This study showed the patients with "wearing of off" after treatment of COMT inhibitor (Entacapone) showed daily "off" time decrease. The patients with non-motor fluctuation have also improvement of Parkinson symptom with adding Entacapone. The role of COMT inhibitors in the management of PD is that administering levodopa in combination with a COMT inhibitor could not only reduce motor fluctuation but also make modification of the disease, avoidance of dyskinesia and good motor improvement.

Keywords: Levodopa; COMT inhibitor; Wearing of off

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機能的脳神経外科 49(2010)28-29

はじめに

パーキンソン病（PD）に関する薬物治療の目標は，短期的には，パーキンソン症状の改善であり，長期的にはPDの進行を抑制し，wearing off現象やジスキネジアなどの中後期合併症を予防することにある。PDへの薬物療法で，L-DOPA療法は最も有効な治療法であり必要不可欠な重要な薬剤である。しかしながら，症状の進行とともにL-DOPAの治療域は狭くなり，L-DOPA効果時間の短縮（wearing off現象）やL-DOPA治療によるジスキネジア（Dopa-induced dyskinesias; DID）などが見られるようになる。そのため，L-DOPA療法による中後期合併症を防ぐ対策が重要である。Entacaponeは，末梢性COMT阻害薬で，L-DOPAから3-OMD合成を抑制[1]するため，DA血中濃度が安定し中枢内のL-DOPA濃度は上昇しDAに代謝されwearing off現象などの運動合併症が改善することが報告されている[2]。本研究では，第一に，Entacaponeのwearing offやDIDなどのmotor fluctuationへの治療効果，第二にnon-motor fluctuationの患者で，固縮や無動などのパーキンソン症状の悪化へのCOMT阻害薬の治療効果を検討した。

対象と方法

対象は，当院通院中の特発性PD患者31名（男性16名，女性15名）で，平均年齢67±7.4歳，発症年齢59.9±8.8歳，罹病期間9±5.8歳，ヤール重症度3±0.8，L-DOPA服用量282.3±77.5 mg/日，併用薬は，Selegilineが16名（52%）で5±1.3 mg/日，Ropinirolが6名（20%）で10±2.0 mg/日，Pramipexoleが19名（62%）で2.4±0.9 mg/日であった。motor fluctuation合併症は，wearing off 22名（73.3%），DID 7名（22.6%）に認めた。評価方法は，神経学的診察により，パーキンソン病症状や重症度，不随意運動などを検討した。検討項目は，Entacapone投与目的，治療前後での症状の変化，副作用を検討した。投与方法は，L-DOPA 100 mgに対してEntacapone 100 mgあるいは200 mgの割合で同時に服用させた。

結　果

患者群をnon-motor fluctuation（no wearing off）群9名とwearing off群22名に分け，またwearing off群の中でDIDのない14名とDIDを合併した8名に分け検討した。発症年齢はnon-motor fluctuation群が，64.2±6.9歳であるのに対して，DIDを伴うwearing off群では53.3±8.5歳で有意に発症年齢が若かった。Non-motor fluctuation群の罹病期間は，4.1±1.7年で，wearing off群では7.9±3.1年で有意に長かった。また，DIDを伴うwearing off群では，11±2年でnon-motor fluctuation群に対して有意に罹病期間が長かった。non-motor fluctuation群のヤール重症度は，2.9±0.8で，wearing off群では3.1±0.8で有意差はなかった。しかし，DIDを伴うwearing off群では，3.9±1.1でnon-motor fluctuation群に対して有意に重症度は高かった。non-motor fluctuation群のL-DOPA服用量は，238.9±56.8 mg/日で，wearing off群では304.8±83 mg/日で有意に多かった。また，DIDを伴うwearing off群では，336±126.5 mg/日でnon-motor fluctuation群に対して有意に多かった。

Entacaponeの主な投与目的は，wearing off症状で，14例

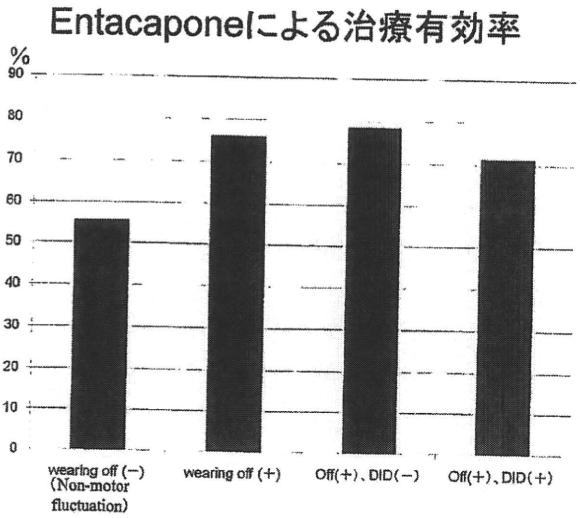

Fig.1 Effect of Entacarpone on PD symptom. There was more effectiveness in patients with "wearing off" than patients with non-motor fluctuation after administrating Entacapone.

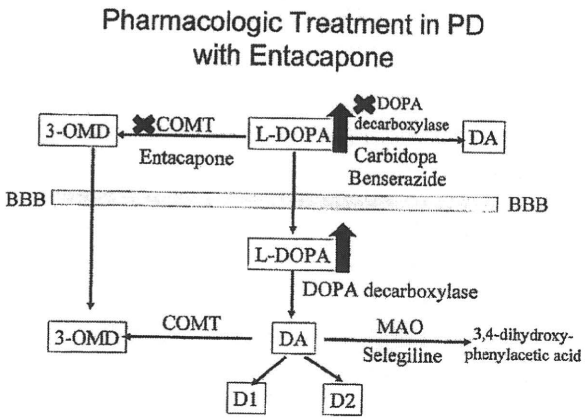

Fig.2 Pharmacologic treatment in PD with Entacapone. Entacapone can peripherally inhibit the methylation of levodopa and generally increase of the levodopa content in the brain.

(45%)に見られ，改善効果が12例(85.7%)に認められた。PD症状の悪化は，7例(23%)に見られ，投与により4例(57.1%)に改善が認められた。Entacaponeの治療有効率は，wearing offのない患者群で56%，wearing off患者群で76%，wearing off患者でDIDのない患者では79%で，wearing off患者でDIDも伴った患者では71%と低下した(Fig.1)。Wearing off症状に高い有効性を示したがDIDを合併した場合には有効性は低下した。

【副作用】

31例中副作用は，4例(12.9%)に認められ，不眠，DIDの悪化，硬直感，吐き気などが見られた。3例(9.7%)が服薬を中止した。

考　察

本研究での結果をまとめると，Entacaponeの効果は，14例(87.5%)にoff時間の短縮などの効果を認めた。効果は，DIDを伴わないwearing off症例で有効であったが，DIDを有する症例ではEntacaponeの有効率は低下した。Entacaponeは，DIDを合併する以前に投与を開始することが必要であると考えられた。次に，Entacaponeのnon-motor fluctuationへの効果は，PD症状の悪化，動作緩慢，固縮の悪化，すくみ足など11例で，その内6例(54.5%)に改善効果を認めた。Entacaponeを服用することにより，L-DOPAの増量なしにパーキンソン症状の改善が得られた。Wearing offなどのmotor fluctuationがない罹病期間の短い症例でも，PD症状改善に有用性を示した。

次に，COMT阻害薬の有効性の機序を検討すると，L-DOPAは，血中ではDOPA脱炭酸酵素によりドーパミン(DP)に，もうひとつはCOMTにより3-OMDに代謝される[1]。DOPA脱炭酸酵素阻害薬を含むL-DOPA製剤を服用すると，L-DOPAの末梢での血中濃度は上昇するが，一方COMTにより代謝され，その結果，3-OMDに代謝される。Fig.2に示すように，末梢性COMT阻害薬であるEntacapone投与すると，3-OMD合成は抑制されるため，L-DOPA血中濃度が上昇し，中枢神経内でのL-DOPA濃度も上昇しDA濃度が上昇・安定する。Olanowらの報告ではL-DOPA/Carbidopaのみの治療では，DA血中濃度の変動が著明でありwearing offが見られるがEntacapone追加により，DA血中濃度が安定しwearing off現象が改善している。

COMT阻害薬の位置づけについて，COMT阻害薬は末梢での阻害薬であるEntacaponeと中枢での作用を有するTolcaponeがある。パーキンソン病における運動合併症状，wearing offやジスキネジアを予防する対策として，第一に，ドーパミンの持続的刺激治療(CDS)の重要性が指摘[3]されており，COMT阻害薬はCDS効果を有する薬剤である。第二には，末梢でのCOMT代謝阻害によりDA濃度の上昇が得られるため，L-DOPA服用量を抑えることが可能な薬剤であるため，現在DOPA脱炭酸酵素阻害薬に加えてCOMT阻害薬含むL-DOPA製剤が開発されている。PD治療の開始薬としてCOMT阻害薬の役割も期待されており，運動症状などの合併症がない早期の段階から併用することが必要と考えられる。

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Supramaximal responses can be elicited in hand muscles by magnetic stimulation of the cervical motor roots

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Background
The amplitude of compound muscle action potentials (CMAPs) evoked in response to magnetic cervical motor root stimulation (MRS) has rarely been used as a diagnostic parameter because of the difficulty in obtaining supramaximal CMAPs.

Objective
To clarify whether supramaximal CMAPs could be elicited by MRS, and if so, whether their amplitude and area could be used to evaluate the conduction of proximal motor roots.

Method
With the use of a custom-made high-power magnetic stimulator, the CMAPs evoked in response to MRS of the first dorsal interosseous, abductor digiti minimi, and abductor pollicis brevis (APB) muscles were compared with those evoked by electrical stimulation at the wrist, brachial plexus, and cervical motor roots. The collision technique was also used to exclude volume conduction. The correlation between MRS-induced CMAP latency and body height was evaluated.

Results
In 32 of 36 normal subjects, supramaximal CMAPs were obtained in response to MRS. The size of CMAPs occurring in response to MRS was the same as the size of those occurring in response to high-voltage electrical cervical motor root stimulation. The collision technique revealed that the APB muscle was highly contaminated by volume conduction from adjacent muscles. CMAP latency correlated significantly with body height.

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Conclusions
Supramaximal CMAPs can be obtained in most normal subjects. In subjects exhibiting confirmed supramaximal CMAPs in response to MRS, not only the latency of these CMAPs but also their amplitude and area can be clinically useful, excluding CMAPs in the APB muscle.

Keywords compound muscle action potential; magnetic stimulation; motor-evoked potential; peripheral nerve

Magnetic stimulation has been widely used to evaluate central and peripheral motor conduction in humans ever since its initial clinical application.[1] Response latency has frequently been used as a parameter aiding in the diagnosis of many relevant conditions. Response amplitude, in contrast, has rarely been used for diagnostic purposes, probably because magnetic stimulation cannot always evoke supramaximal responses.[2-4]

In this study, we demonstrate that supramaximal responses can be obtained in response to magnetic cervical motor root stimulation (MRS) by using a magnetic stimulator that is more powerful than most. We compared supramaximal responses obtained in response to MRS with those obtained in response to electrical stimulation at the wrist, Erb's point (EP), and the cervical motor roots (Root). Furthermore, we studied the relationship between response latency and body height.

Subjects and methods

Subjects

The subjects enrolled in this study were 36 right-handed healthy volunteers (23 men and 13 women; age range, 24-57 years [mean ± SD, 34.2 ± 7.4 years]) without any history of cervical spondylosis, diabetes mellitus, central nervous system disorders, peripheral neuropathies, or other neuromuscular diseases. The mean ± SD of their body heights was 167.3 ± 8.0 cm (range: 153-182 cm). One patient was recruited to show the clinical use of our method, which is described in detail in the *Results* section. The results of this patient will be given as a case presentation. Written informed consent was obtained from all subjects. The experiments were performed according to the Declaration of Helsinki; and the procedures were approved by the Ethics Committee of the University of Tokyo.

Recording

During the examination, subjects were seated on a reclining chair with their arms relaxed on the arm rests. Compound muscle action potentials (CMAPs) were recorded from the following three distal muscles: the first dorsal interosseous ([FDI] C8-T1; ulnar nerve), the abductor digiti minimi ([ADM] C8-T1; ulnar nerve), and the abductor pollicis brevis ([APB] C7-T1; median nerve). Disposable silver-silver chloride disk electrodes, 9 mm in diameter, were placed in a belly-tendon montage. Signals were amplified through a Biotop amplifier (GE Marquette Medical Systems, Tokyo, Japan) with filters set at 20 Hz and 3 kHz, and recorded onto a computer (Signal Processor DP-1200; GE Marquette Medical Systems). Subjects' skin temperature was maintained at around 33°C-34°C. At least three CMAPs, either supramaximal or at the stimulus intensity of maximal stimulator output, were recorded from each subject to confirm the reproducibility of the findings. The peak-to-peak amplitude (mV), negative area (mV × milliseconds), and onset latency (milliseconds) of each CMAP were measured. The SPSS 14 statistical software package (SPSS, Chicago, IL) was used for all statistical analyses. *P* values less than .05 were considered significant.

Stimulation

MRS was delivered through a custom-built enhanced power Magstim 200 stimulator (Magstim, Whitland, UK) with a round coil 10 cm in mean diameter; this stimulator is about 1.4 times as powerful as the commercially available Magstim 200 stimulator. Electrical stimulation at the wrist was delivered through a conventional electrical stimulator (Electronic stimulator 3F46, NEC-San Ei, Tokyo, Japan), whereas electrical stimulation at the EP and the Root (electrical cervical motor root stimulation [ERS]) was delivered through a D180A high-voltage electrical stimulator (Digitimer, Welwyn Garden City, UK).

For MRS, the upper edge of a round coil was positioned on the seventh cervical (C7) spinous process so that a part of its edge was over the exit of each spinal nerve from the intervertebral foramina. With the coil firmly held against the spine, an examiner pulled the subject's chest backward so that the coil was as close as possible to the target spinal nerves. The coil currents were directed clockwise as seen from behind in our examination of the right hand muscles so that the induced currents in the body were directed from the muscles to the spinal cord at the upper edge of the coil (Figure 1). A previous study has confirmed that this direction is suitable for producing maximal CMAPs (minimal threshold) in MRS.[4] The stimulus intensity was gradually increased until supramaximal CMAPs were obtained.

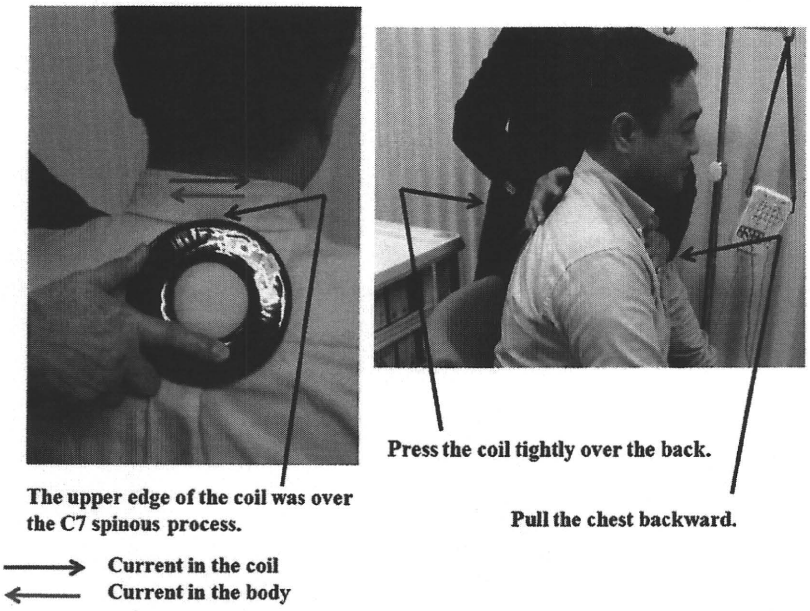

Figure 1 Back and lateral views of magnetic cervical motor root stimulation. The examiner is firmly pressing a round coil to the subject's back and forcefully pulling his chest backward.

We considered a supramaximal CMAP to have been obtained only when the size of superimposed CMAPs was saturated before the stimulus intensity reached a value equal to 1.3 times the lowest intensity that resulted in a maximal CMAP.

Electrical stimuli were applied at the wrist, EP, and Root. At the wrist and EP, each anode was placed a few centimeters proximal to the cathode. At the Root, a cathode was placed over the C7 spinous process, and an anode was placed 5 cm rostral to it.[5,6] All electrodes were then securely attached to the skin. The stimulus intensity was increased gradually until a supramaximal CMAP was obtained (i.e., until the stimulus intensity reached a value 1.3 times that of the lowest intensity capable of eliciting a maximal CMAP).

Experiment 1: Collision experiment

Nine subjects participated in this experiment. Given that MRS activates several nerves simultaneously because each root connects with several peripheral nerves, it seemed likely that volume conduction from nontarget muscles might affect the size of CMAPs occurring in response to MRS. Our collision experiment was designed to determine the degree to which this occurs.[7]

CMAPs from the right hand muscles were elicited by simultaneous MRS and electrical stimulation at the wrist and recorded. We expected that, if CMAPs were produced in response to MRS from the target muscle only, MRS would elicit no potentials because the orthodromic descending impulses generated by MRS would completely collide with the antidromic ascending impulses generated by wrist stimulation. If, on the other hand, some other nontarget muscles were contributing to the CMAPs in response to MRS (volume conduction effect), or if the recorded muscle were partly innervated by nontarget nerves, then MRS would provoke some potential at a longer latency than CMAPs not contaminated by volume conduction. The amplitude of the later potential was expressed as a percentage relative to that of the CMAPs in response to wrist stimulation. This value indicated the amount of volume conduction from other muscles that was contaminating the CMAPs. In our experiments, wrist stimulation was delivered to the ulnar (for FDI and ADM) or median nerve (for APB).

Experiment 2: Analyses of supramaximal CMAPs evoked by MRS

All 36 subjects participated in this experiment. CMAPs were recorded from the right FDI and ADM muscles in all subjects (72 muscles). APB was excluded because of considerable volume conduction (discussed in *Results, experiment 1*).

We determined how often supramaximal CMAPs could be obtained in response to MRS. If supramaximal CMAPs were obtained, the ratios of the amplitude and area of MRS-induced CMAPs and of CMAPs induced by electrical stimulation to the EP to those of wrist stimulation-induced CMAP were calculated, as were the ratios of the amplitude and area of MRS-induced CMAP to those of CMAPs induced by electrical stimulation to the EP.

To analyze the relationship between body height and CMAP latency, we performed a linear regression analysis.

Moreover, to analyze the difference between the responses generated in the two sides of each individual's body, CMAPs were also recorded from the left FDI and ADM muscles in 22 of 36 subjects (44 muscles).

Experiment 3: Comparison between MRS and ERS

Twenty-two subjects exhibiting supramaximal CMAPs participated in this experiment. CMAPs were recorded from bilateral FDI and ADM muscles. To confirm supramaximal CMAPs, we compared the amplitudes of MRS-induced CMAPs with those of ERS-induced CMAPs using the paired *t* test.

Results

Subjects reported that the discomfort caused by MRS delivered by our high-power stimulator was not different from that caused by MRS delivered by a standard stimulator; the form of MRS used in the present study was well tolerated by all subjects. No side effects were noted. Figure 2 illustrates an example of supramaximal CMAPs recorded from the FDI of one subject.

Experiment 1: Collision experiment

Representative waveforms of the collision experiment are shown in Figure 3. The amplitudes of late responses were very small in the FDI (Figure 3, left) and the ADM (data not shown), whereas responses of considerable amplitude were elicited in the APB (Figure 3, right). The amplitudes of the later responses, expressed as percentages relative to the CMAP amplitudes, were 8.2% ± 3.0% in the FDI, 3.2% ± 1.6% in the ADM, and 28.8% ± 15.0% in the APB (mean ± SD).

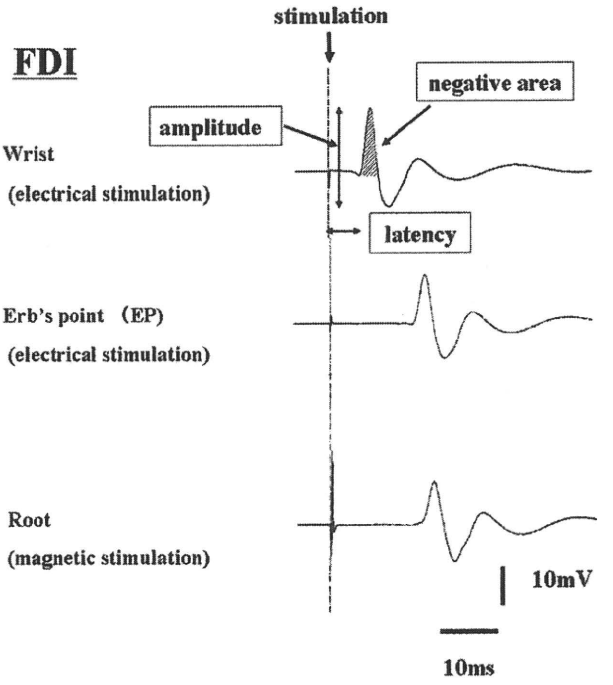

Figure 2 Representative waveforms of compound muscle action potentials (CMAPs) in one subject. CMAPs are elicited by means of electrical stimulation at the wrist and at Erb's point (EP) as well as by means of magnetic stimulation at the cervical motor roots (Root), and recorded at the first dorsal interosseous (FDI) muscle.

Experiment 2: Analyses of supramaximal CMAPs evoked in response to MRS

In 32 of 36 subjects (19 men, 13 women; age range 23-57 years [mean ± SD, 34.7 ± 7.6 years]; body height 153-179 cm [mean ± SD, 165.9 ± 7.3 cm]), MRS induced supramaximal CMAPs, that is, CMAPs did not increase in size even when the stimulus intensity was increased to

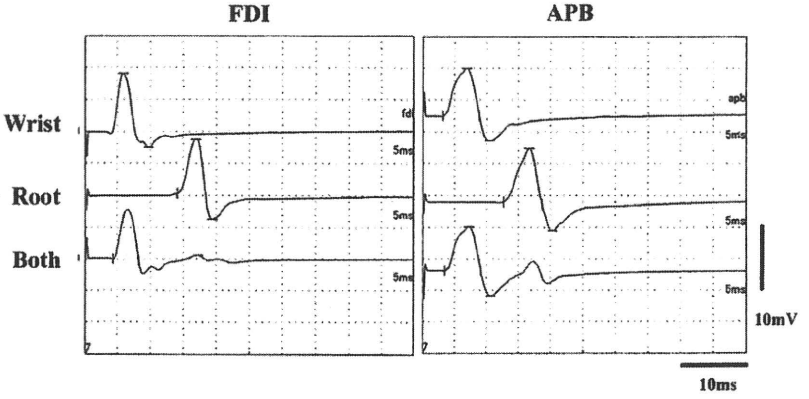

Figure 3 Responses in collision experiment. Compound muscle action potentials (CMAPs) elicited by means of electrical stimulation at the wrist, magnetic stimulation at the cervical motor roots (Root), and simultaneous stimulation at the wrist and Root are shown at the first dorsal interosseus (FDI) (left) and the abductor pollicis brevis (APB) (right). At the wrist, the ulnar nerve is stimulated to elicit responses from the FDI and the median nerve is stimulated to elicit responses from the APB. A very small late response is obtained by simultaneous stimulation in the FDI, whereas a later response of considerable size occurs in the APB.

1.3 times the minimal value that induced a maximal CMAP. This final intensity corresponded to 60-95% of the maximal stimulator output. In the four remaining subjects, supramaximal CMAPs could not be elicited even by using the maximal stimulator output; all four subjects were comparatively large and deep-chested men with heights ranging from 176-182 cm.

The amplitude, area and latency data obtained from the 32 subjects exhibiting supramaximal CMAPs are shown in Table 1. In the FDI, the CMAP amplitude ratio of Root/EP was 91.9% ± 6.7% (mean ± SD); the lowest normal limit was 78% (mean −2 SD). The area ratio of Root/EP was 96.8% ± 9.1%; the lowest normal limit was 78%. In the ADM, the CMAP amplitude ratio of Root/EP was 93.5% ± 8.6%; the lowest limit was 72%. The area ratio of Root/EP was 94.7% ± 8.0%; the lowest limit was 78%.

In the FDI, the correlation between CMAP latency after MRS and body height is shown in Figure 4. A significant and positive linear relation was observed ($P < .001$; latency = 0.11 × body height − 5.04). A similar correlation was observed in the ADM ($P < .001$; latency = 0.12 × body height − 6.74).

Experiment 3: Comparison between MRS and ERS

Among the 22 subjects who participated in this experiment, there was no significant difference in amplitude, area or latency between CMAPs occurring in response to MRS and those occurring in response to ERS in either the FDI or the ADM muscles (FDI amplitude: MRS 13.5 ± 3.1 mV, ERS 13.2 ± 3.4 mV, $P = .218$; area: MRS 19.7 ± 4.5 mV × millisecond, ERS 19.2 ± 4.8 mV × millisecond, $P = .077$; latency: MRS 12.9 ± 1.0 millisecond, ERS 12.9 ± 1.0 millisecond, $P = .609$; ADM amplitude: MRS 11.7 ± 2.2 mV, ERS 11.8 ± 2.5 mV, $P = .830$; area: MRS 19.8 ± 4.1 mV × millisecond, ERS 19.5 ± 4.4 mV × millisecond, $P = .183$; latency: MRS 12.6 ± 1.2 milliseconds, ERS 12.6 ± 1.2 milliseconds, $P = .333$).

Case presentation

Here we report on one patient whose response to MRS provided us with clinically useful information concerning the proximal regions of his peripheral nerves.

A 57-year-old man complained of acute shoulder pain and had muscular weakness of the right arm develop 3 days later. The clinical diagnosis was neuralgic amyotrophy. Conventional nerve conduction studies were all normal. F-wave latency was within the normal range, although the occurrence rate of F-waves was reduced to 50% of normal. Figure 5 shows CMAPs from the right ADM elicited in response to MRS or electrical stimulation at several sites. The CMAPs in response to electrical stimulation at the

Table 1 Data from subjects exhibiting supramaximal CMAPs

	FDI	ADM
Peak-to-peak amplitude (mV)		
Wrist	15.9 ± 4.0	15.6 ± 3.3
EP	14.6 ± 3.5	12.8 ± 2.7
Root	13.4 ± 3.2	11.9 ± 2.5
Root (laterality)	2.1 ± 1.7	2.0 ± 1.7
Ratio (%)		
EP/wrist	92.6 ± 10.6 (77-125)	82.7 ± 7.4 (64-98)
Root/wrist	85.2 ± 12.5 (60-118)	77.3 ± 10.0 (53-98)
Root/EP	91.9 ± 6.7 (78-112)	93.5 ± 8.6 (75-123)
Negative area (mV × milliseconds)		
Wrist	20.4 ± 5.2	23.5 ± 5.4
EP	20.4 ± 5.3	20.6 ± 4.4
Root	19.6 ± 4.7	19.4 ± 4.2
Root (laterality)	3.1 ± 2.2	4.3 ± 3.5
Ratio (%)		
EP/wrist	100.0 ± 7.9 (84-117)	88.4 ± 8.2 (71-113)
Root/wrist	96.9 ± 11.8 (74-125)	83.8 ± 10.5 (57-109)
Root/EP	96.8 ± 9.1 (76-123)	94.7 ± 8.0 (78-112)
Onset latency (milliseconds)		
Wrist	3.7 ± 0.4	2.8 ± 0.4
EP	11.8 ± 1.0	11.8 ± 1.1
Root	12.8 ± 1.0	12.6 ± 1.2
Root (laterality)	0.5 ± 0.4	0.3 ± 0.3
EP-Root	1.0 ± 0.4	0.7 ± 0.3

Data are shown as mean ± SD (range). ADM = abductor digiti minimi; CMAPs = compound muscle action potentials; EP = Erb's point; FDI = first dorsal interosseus; Root = cervical motor roots; SD = standard deviation.

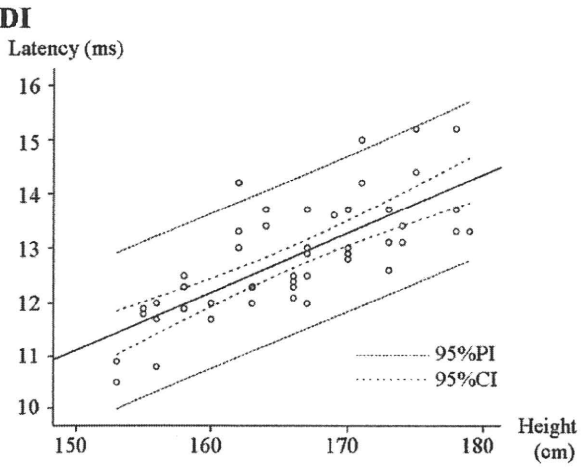

Figure 4 Significantly positive correlation between compound muscle action potential (CMAP) latency and body height. Data from the first dorsal interosseus (FDI) muscle are plotted. The formula for the relationship between latency and body height is as follows: latency = 0.11 × body height – 5.04 ($P < .001$, $R^2 = 0.55$). PI = prediction interval; CI = confidence interval.

wrist, below the elbow, and at the EP were all normal in amplitude, area, and latency. The supramaximal CMAP that occurred in response to MRS, however, had an amplitude that was obviously smaller than those of the other distal CMAPs. The amplitude of the CMAP in response to MRS was 40% of that of the CMAP in response to EP stimulation, which itself was smaller than the mean –2 SD (72%) of our normal values shown previously. Based on these results, we concluded that a conduction block was present between these two sites, that is, between the brachial plexus and the exit of the cervical spinal nerves from the intervertebral foramina. The patient's symptoms improved after treatment with intravenous immunoglobulin. After the symptoms had improved, the amplitude of his CMAPs occurring in response to MRS recovered to 96% of that of his CMAPS occurring in response to EP stimulation.

Discussion

The current data show that magnetic stimulation can be useful for evaluating conduction in the proximal regions of peripheral nerves as well as for central motor conduction studies. If this is confirmed, magnetic stimulation may come to be used in the diagnosis of neuropathies such as inflammatory demyelinating polyneuropathy,[8,9] brachial plexus injury,[10] and radiculopathy.[1,3,9] Magnetic or electrical stimulation over the cervical enlargements is often termed motor "root" stimulation, but neither method actually activates the spinal motor roots; instead, stimulation is delivered to the spinal nerves as they exit from the spinal canal through the intervertebral foramina.[2,4,11,12] Accordingly, "spinal nerve stimulation" would be a more correct nomenclature; however, because MRS has been commonly used, we use this term to describe our method in this article.

Several reports have demonstrated the clinical usefulness of data acquired through MRS, especially data on the latency of responses.[2,3,13,14] Data on the amplitude and area of responses, in contrast, have rarely been used as parameters for evaluation, probably because MRS cannot always elicit supramaximal CMAPs. The reported amplitudes of CMAPs occurring in response to MRS[2,3] have ranged from 10%-45% to 9%-100% and 16%-77% of the amplitudes of CMAPs occurring in response to peripheral nerve stimulation[4] in normal subjects. In our study, the amplitudes of CMAPs occurring in response to MRS ranged from 78%-100%. Moreover, supramaximal CMAPs could be obtained in 32 of 36 subjects, and the occurrence of supramaximal CMAPs in these subjects was verified by using high-voltage electrical stimulation. Our success in obtaining supramaximal CMAPs from most of the subjects might be explained by our use of a high-power magnetic stimulator that is about 1.4 times as powerful as commercially available stimulators. Another important technical point is that we pressed the coil firmly to the back of each subject while forcefully pulling the chest backward to place the coil as close as possible to the target spinal nerves.

Supramaximal stimulation is necessary for measurement of the CMAP amplitude in the detection of conduction blocks in neurophysiologic studies.[15,16] In the current study, the difference in amplitude between CMAPs in the ADM induced by EP stimulation and those induced by Root stimulation was about 6.5%; the highest normal limit (mean –2 SD) was 28%. This result is similar to one previously reported by Arunachalam et al.,[15] who conducted

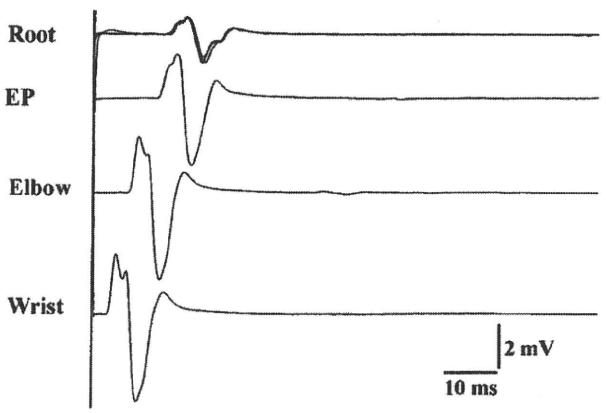

Figure 5 Compound muscle action potentials (CMAPs) in a patient with neuralgic amyotrophy. CMAPs from the right abductor digiti minimi (ADM) were elicited by means of electrical stimulation at the wrist, below the elbow, and at Erb's point (EP). CMAPs were also elicited by means of magnetic stimulation at the cervical motor roots (Root). The amplitude of MRS-induced CMAPs was only 40% of that of EP stimulation-induced CMAPs.

cervical motor root stimulation using a high-voltage electrical stimulator. Therefore, when supramaximal MRS is achieved and the difference in amplitude between CMAPs induced by EP stimulation and those induced by Root stimulation is above the highest normal limit, this indicates a conduction block, as in the case presentation.

The collision experiment revealed that volume conduction accounted for less than 9% of the responses in the FDI and less than 4% of those in the ADM. In the APB, however, volume conduction was substantially greater (by approximately 30%) than in the other two muscle. These amounts of volume conduction are similar to those previously reported in a study that used a high-voltage electrical stimulator.[15] The high-volume conduction commonly observed in CMAPs from the APB in response to both MRS and ERS is explained by the fact that the APB is surrounded by ulnar-nerve-innervated muscles (the flexor pollicis brevis and the adductor pollicis), as well as by the fact that APB itself is sometimes partly innervated by the ulnar nerve. Based on our results, we concluded that MRS-induced CMAPs from the APB are not suitable for amplitude evaluation.

A positive correlation between the latency of CMAPs occurring in response to MRS and body height has been reported.[3,13,17] Cervical motor root stimulation by means of a needle electrode has revealed an identical correlation.[18] Our normal values were consistent with these previously described values, and the formulas obtained through our study are useful for the evaluation of the latency of CMAPs in response to MRS.

ERS is an alternative method for cervical motor root stimulation, but magnetic stimulation offers two advantages over it. First, magnetic stimulation produces less discomfort than electrical stimulation, which can sometimes elicit severe pain. Second, magnetic stimulation can be used for patients on whose skin it is not possible to fix cutaneous electrodes because of skin problems.[19]

Our study has some limitations. First, the number of subjects was fairly small and their age range was fairly restricted; this makes it less likely that our data are normative. Data from additional healthy subjects must be acquired to make our data set comprehensive and normative. Second, supramaximal CMAPs cannot be obtained in all subjects. If CMAPs continue to enlarge as stimulation intensity increases, we cannot exclude the possibility of suboptimal stimulation. If this is the case, then amplitude inconsistencies in CMAPs occurring in response to MRS do not necessarily indicate conduction blocks in patient analyses. Another disadvantage of our stimulation method is the current spread to distal regions far from the expected stimulation point at very high stimulus intensities (such as stimulation with 95% or 100% maximal stimulator output). In this case, the existence of a conduction block may be missed because the stimulation site may jump to a more distal position lying beyond the region of the conduction block. Despite these limitations, however, MRS can provide us with useful information about proximal motor conduction when supramaximal CMAPs are obtained in response to MRS, as in the case study reported here.

This study has yielded two new findings with regard to MRS: (1) though previous studies have reported otherwise, supramaximal CMAPs can be elicited in response to MRS in most normal subjects. The amplitude and area of CMAPs can also be used as diagnostic parameters in patients who exhibit supramaximal CMAPs. (2) CMAP latency correlates significantly with body height; the formulas for this relationship have been provided.

Acknowledgments

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Prominent cauda equina involvement in patients with chronic inflammatory demyelinating polyradiculoneuropathy

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ABSTRACT

In chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), it has not been well known which segment of the peripheral nerves, distal or proximal, is more often involved in electrophysiological examination. This study compares nerve conductions at proximal segments with those at distal segments in 11 patients with CIDP. To obtain cauda euqina conduciton time (CECT), compound muscle action potentials (CMAPs) were elicited by magnetic stimulation using a MATS coil from the abductor hallucis muscle. CECT was prolonged in 9 patients (81.8%), whereas the ankle–knee conduction was delayed in 4 (36.4%). The proximal segments are more frequently involved than the distal segments in this disorder.

1. Introduction

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is a relapsing or chronically progressive disorder most commonly presenting with limb weakness, distal sensory disturbance, and hyporeflexia [1,2]. In the process of demyelination, the immune-mediated pathogenesis such as unknown antibodies or some other circulating factors might be involved [2,3]. Nerve conduction studies in the distal extremities usually show slowing of motor conduction [2,3]. F-wave studies also reveal the high frequency of proximal peripheral nerve lesions [4,5]. However, F-wave method alone cannot allow us to localize the peripheral nerve lesions. Therefore, it has not been well known which segment of peripheral nerves, distal or proximal, is more often involved in electrophysiological examination.

Recently, we have developed a novel magnetic stimulation method to measure cauda equina conduction time (CECT) using a specially devised powerful coil designated as a Magnetic Augmented Translumbosacral Stimulation (MATS) coil [6,7]. This method enables us to activate the spinal nerves at the both proximal and distal sites of cauda equina.

In this investigation, we compared nerve conductions at proximal segments with those at distal segments using the above mentioned new stimulation method as well as the conventional nerve conduction studies.

2. Subjects and methods

2.1. Subjects

We studied 11 CIDP patients (6 men and 5 women) diagnosed according to the established diagnostic criteria [8]. The age and body height of the patients were 54.1 ± 16.8 (mean ± standard deviation (SD); range 26–83 years and 163.5 ± 10.1 (145–175) cm, respectively. Patients in whom reliable compound muscle action potentials (CMAPs) were unobtainable by electrical stimulation or magnetic stimulation were excluded from this study. The clinical profile of the patients is summarized in Table 1. Their disabilities were assessed using the Hughes functional grading scale (grade 4 = bound to bed, grade 3 = able to walk 5 m with aid, grade 2 = ambulates independently, and grade 1 =minimal signs and symptoms and able to run) [9].

Informed consent to participate in this study was obtained from all subjects. The protocol was approved by the Ethics Committee of the University of Tokyo. The experiments were conducted in accordance with the ethical standards of the Declaration of Helsinki.

2.2. Stimulation, recording and analysis

During the examination, patients lay comfortably on a bed in prone position. CMAPs were recorded from the abductor hallucis

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Table 1
Clinical profile and results of 11 CIDP patients.

Case	Age	Sex	Disease duration	Hughes scale	Diagnostic categories	MCV (m/s)	CECT (ms)
1	42	M	6 months	3	Definite CIDP	42	5.1
2	51	M	7 months	1	Possible CIDP	44	3.8
3	33	F	1 year	2	Definite CIDP	50	6.9↑
4	57	F	1 year	2	Definite CIDP	45	10.1↑
5	71	M	1 year	2	Definite CIDP	31↓	9.1↑
6	26	F	5 years	1	Definite CIDP	31↓	10.3↑
7	57	M	7 years	2	Definite CIDP	42	5.9↑
8	66	F	11 years	2	Definite CIDP	38↓	7.1↑
9	44	M	19 years	3	Definite CIDP	27↓	9.8↑
10	63	F	24 years	4	Definite CIDP	41	8.1↑
11	83	M	29 years	4	Definite CIDP	44	6.8↑
Normal values (mean ± SD, $n = 20$ subjects)						49.3 ± 4.4	3.7 ± 0.8
Mean − or + 2.5SD (lower limit or upper limit)						38.3	5.7

MCV: motor conduction velocity, CECT: cauda equina conduction time, SD: standard deviation, ↓: abnormal decrement, ↑: abnormal increment.

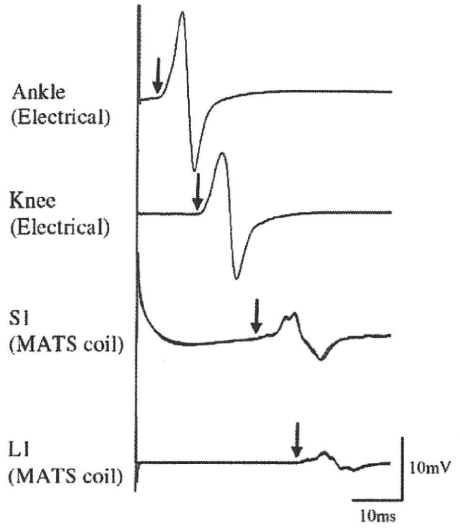

Fig. 1. MATS coil stimulation study in case 3. Motor conduction velocity (MCV) between ankle and knee is normal (50.0 m/s). In contrast, CECT calculated by using S1 and L1 level MATS coil stimulations is prolonged (6.9 ms, upper limit of normal values is 5.7 ms).

muscle (AH) on the more affected side. Disposable silver–silver chloride disc electrodes of 9 mm diameter were placed in a belly-tendon montage over AH. Signals were amplified with filters set at 20 Hz and 3 kHz and recorded by a computer (Neuropack MEB-9100, Nihon Kohden, Japan). The skin temperature was maintained at around 32–33 °C.

For distal segment nerve conduction studies, the posterior tibial nerve was stimulated at the posterior medial malleolus of ankle and the popliteal fossa with a conventional electrical stimulator (Neuropack MEB-9100, Nihon Kohden, Japan). The motor conduction velocity (MCV) was calculated dividing the ankle–knee length by the latency difference. For proximal segment conduction studies (measuring CECT), magnetic stimulation was performed with a monophasic stimulator, Magstim 200 (The Magstim Co, UK) using a MATS coil (diameter 20 cm, 0.98 T; The Magstim Co, UK) [6,7]. For the most distal cauda equina level stimulation, the edge of MATS coil was positioned over the 1st sacral (S1) spinous process for inducing currents to flow 60° downward from horizontal direction [6]. The most proximal cauda equina was activated by the MATS coil whose edge was positioned over the 1st lumbar (L1) spinous process for inducing currents to flow upward [7]. The CECT was obtained by subtracting the CMAP latency to S1 level stimulation from that to L1 level stimulation.

CECT and MCV of the patients were compared to those of age and body height matched control subjects. The frequencies in abnormities of CECT and MCV were statistically compared between two groups using Wilcoxon's signed rank test. P values less than 0.05 were considered to be significant.

3. Results

Fig. 1 displays the representative CMAPs in a patient with CIDP (case 3). Although MCV calculated by using ankle and knee stimulations was normal (50.0 m/s), CECT calculated by using S1 and L1 level MATS coil stimulations was abnormally prolonged (6.9 ms, upper limit of normal values is 5.7 ms). The results of MCV and CECT in all the patients are summarized in Table 1. MCV was abnormally decreased in 4 patients (36.4%). CECT was significantly prolonged in 9 patients (81.8%). All the patients with prolonged CECT had been suffering from CIDP for more than one year. The other 2 patients with normal CECT (cases 1 and 2) had relatively short disease duration (6 and 7 months). CECT prolongation was observed at a significantly higher frequency compared to MCV decrease ($P = 0.0253$).

4. Discussion

CECT prolongation was more frequently observed as compared to MCV reduction in CIDP. It suggests the high frequent spinal nerve involvement in the spinal canal. Prior studies of magnetic resonance images reveal that the spinal nerves in the spinal canal are frequently involved in CIDP [10–12]. Therefore, our results have verified the prominent spinal nerve involvement in the spinal canal electrophysiologically.

Similar comparison in the upper extremities has been reported by Inaba et al. [13]. The cervical root conduction time in the spinal canal was prolonged in 7 out of 11 CIDP patients (63.6%) and MCV between wrist and elbow was decreased in 9 patients (81.8%). These values should not be directly compared with our results because the spinal canal segment of cervical spinal nerves is very short as compared with cauda equina. Considering the short length, this indicates that the cervical spinal nerves in the spinal canal also must be very frequently involved.

Why are the segments within a spinal canal so frequently involved? This might be explained by some anatomical reasons. The blood nerve barrier needs to be broken for the demyelinating process of distal peripheral nerves [14]. In contrast, the proximal spinal nerves in the spinal canal are lacking blood nerve barriers and these are directly exposed to cerebrospinal fluid [15]. These anatomical structures might allow unknown antibodies or some other circulating factors to gain direct access to the spinal nerves including the cauda equina. Based on these discussions, we conclude that the cauda equina is very vulnerable to the immunological attack in CIDP.

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Guidelines

Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research ☆

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ABSTRACT

This article is based on a consensus conference, which took place in Certosa di Pontignano, Siena (Italy) on March 7–9, 2008, intended to update the previous safety guidelines for the application of transcranial magnetic stimulation (TMS) in research and clinical settings.

Over the past decade the scientific and medical community has had the opportunity to evaluate the safety record of research studies and clinical applications of TMS and repetitive TMS (rTMS). In these years the number of applications of conventional TMS has grown impressively, new paradigms of stimulation have been developed (e.g., patterned repetitive TMS) and technical advances have led to new device designs and to the real-time integration of TMS with electroencephalography (EEG), positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). Thousands of healthy subjects and patients with various neurological and psychiatric diseases have undergone TMS allowing a better assessment of relative risks. The occurrence of seizures (i.e., the most serious TMS-related acute adverse effect) has been extremely rare, with most of the few new cases receiving rTMS exceeding previous guidelines, often in patients under treatment with drugs which potentially lower the seizure threshold.

The present updated guidelines review issues of risk and safety of conventional TMS protocols, address the undesired effects and risks of emerging TMS interventions, the applications of TMS in patients with

☆ A Consensus Statement from the International Workshop on "Present and Future of TMS: Safety and Ethical Guidelines", Siena, March 7–9, 2008.

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implanted electrodes in the central nervous system, and safety aspects of TMS in neuroimaging environments. We cover recommended limits of stimulation parameters and other important precautions, monitoring of subjects, expertise of the rTMS team, and ethical issues. While all the recommendations here are expert based, they utilize published data to the extent possible.

Contents

1. Introduction

Transcranial magnetic stimulation (TMS) is a neurostimulation and neuromodulation technique, based on the principle of electromagnetic induction of an electric field in the brain. This field can be of sufficient magnitude and density to depolarize neurons, and when TMS pulses are applied repetitively they can modulate cortical excitability, decreasing or increasing it, depending on the parameters of stimulation, even beyond the duration of the train of stimulation. This has behavioral consequences and therapeutic potential.

The last decade has seen a rapid increase in the applications of TMS to study cognition, brain-behavior relations and the pathophysiology of various neurologic and psychiatric disorders (Wassermannn and Lisanby, 2001; Kobayashi and Pascual-Leone, 2003; Gershon et al., 2003; Tassinari et al., 2003; Rossi and Rossini, 2004; Leafaucheur, 2004; Hoffman et al., 2005; Couturier, 2005; Fregni et al., 2005a,b; Hallett, 2007; George et al., 2007; Málly and Stone, 2007; Rossini and Rossi, 2007; Devlin and Watkins, 2007; Ridding and Rothwell, 2007). In addition, evidence has accumulated that demonstrates that TMS provides a valuable tool for *interventional neurophysiology applications*, modulating brain activity in a specific, distributed, cortico-subcortical network so as to induce controlled and controllable manipulations in behavior.

Repetitive transcranial magnetic stimulation (rTMS) has been found to be a promising noninvasive treatment for a variety of neuropsychiatric conditions (Devlin and Watkins, 2007; George et al., 2007; Aleman et al., 2007; Fregni and Pascual-Leone, 2007), and the number of applications continues to increase with a large number of ongoing clinical trials in a variety of diseases. Therapeutic utility of TMS has been claimed in the literature for psychiatric disorders, such as depression, acute mania, bipolar disorders, panic, hallucinations, obsessions/compulsions, schizophrenia, catatonia, post-traumatic stress disorder, or drug craving; neurologic diseases such as Parkinson's disease, dystonia, tics, stuttering, tinnitus, spasticity, or epilepsy; rehabilitation of aphasia or of hand function after stroke; and pain syndromes, such as neuropathic pain, visceral pain or migraine. A large industry-sponsored trial (O'Reardon et al., 2007) and a multi-center trial in Germany (Herwig et al., 2007) of rTMS in medication of refractory depression have been completed, and other appropriately controlled and sufficiently powered clinical trials of TMS are ongoing.

Most claims of therapeutic utility of TMS across conditions need further support and evidence-based clinical trial data, but the potential clinical significance is huge, affecting a large number of patients with debilitating conditions. A number of clinics have been set up worldwide offering TMS for treatment of various diseases, and rTMS is already approved by some countries for treatment of medication-refractory depression (i.e., Canada and Israel). In October 2008, a specific rTMS device was approved by the Food and Drug Administration in the United States for the treatment of patients with medication-refractory unipolar depression who have failed one good (but not more than one) pharmacological trial. It is reasonable to expect that the use of rTMS and its penetrance in the medical community will continue to increase across different medical specialties.

The number of laboratories using TMS for therapeutic or neuroscientific purposes, and consequently the number of healthy individuals and patients with various neurological or psychiatric diseases studied worldwide, has been increasing yearly for the past 20 years (Fig. 1). A further increase in the wide-spread use of TMS in medical therapeutic applications and research is expected. This makes the need for clear and updated safety guidelines and recommendations of proper practice of application critical.

Current safety precautions and practice recommendations remain guided by the consensus conference held at the National Institutes of Health in June 1996 and summarized in Clinical Neurophysiology (Wassermannn, 1998). These recommendations were adopted with minor modifications by the International Federation for Clinical Neurophysiology (Hallett et al., 1999). Ethical considerations on the application of TMS to health and disease were initially dealt with by Green et al. (1997) during the early stages of rTMS testing, and more recently have been addressed by several publications (Wolpe, 2002; Mashour et al., 2005; Illes et al., 2006; Steven and Pascual-Leone, 2006). However, as previously mentioned, the use of TMS has grown dramatically in the past decade, new protocols of TMS have been developed, changes in the devices have been implemented, TMS is being increasingly combined with other brain imaging and neurophysiologic techniques including fMRI and EEG, and a growing number of subjects and patients are being studied with expanding numbers of longer stimulation sessions.

The safety of TMS continues to be supported by recent meta-analyses of the published literature (see Machii et al., 2006; Loo et al., 2008; Janicak et al., 2008), yet there is a clear need to revisit the safety guidelines, update the recommendations of practice, and

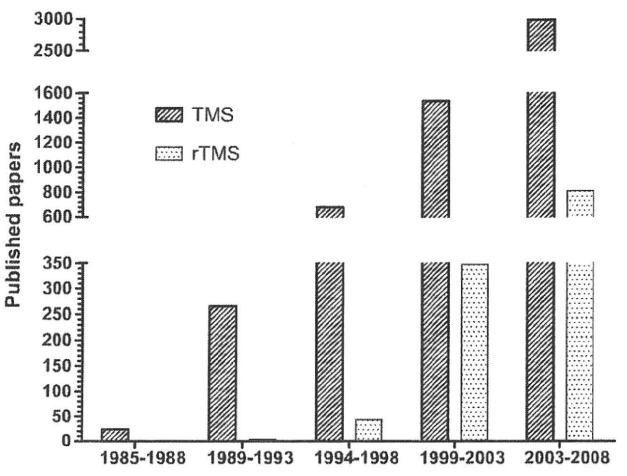

Fig. 1. Number of published papers per/year on Transcranial Magnetic Stimulation. Medline search updated to December 2008. Key words used are "Transcranial magnetic stimulation" (left bars) and "repetitive TMS" (right bars).

improve the discussion of ethical aspect to be reflective of the expanding uses of these powerful and promising techniques. Towards this end, a consensus conference took place in Certosa di Pontignano, Siena (Italy) on March 7–9, 2008. As in the 1996 NIH Consensus Conference, the 2008 meeting brought together some of the leading researchers in the fields of neurophysiology, neurology, cognitive neuroscience and psychiatry who are currently using TMS for research and clinical applications. In addition, representatives of all TMS equipment manufacturers were invited and those of Magstim, Nexstim, and Neuronetics were present, along with representatives from various regulatory agencies and several basic and applied scientists, including physicists, and clinicians whose work has bearing on decisions regarding the safe and ethical use of rTMS. The present article represents a summary of the issues discussed and the consensus reached. It follows the outline of the 1998 consensus statement, addressing all issues raised previously to provide corrections or updates where necessary, and including various new topics needed given technological advances.

2. Principles of TMS

2.1. Nomenclature

TMS can be applied one stimulus at a time, *single-pulse TMS*, in pairs of stimuli separated by a variable interval, *paired-pulse TMS*, or in trains, *repetitive TMS*. Single-pulse TMS can be used, for example, for mapping motor cortical outputs, studying central motor conduction time, and studying causal chronometry in brain-behavior relations. In paired pulse techniques TMS stimulation can be delivered to a single cortical target using the same coil or to two different brain regions using two different coils. Paired pulse techniques can provide measures of intracortical facilitation and inhibition, as well as study cortico–cortical interactions. Pairing can also be with a peripheral stimulus and a single TMS stimulus, paired associative stimulation (PAS).

When multiple stimuli of TMS are delivered in trains, one can differentiate "conventional" and "patterned" protocols of repetitive stimulation. For conventional protocols (Fig. 2), there is universal agreement that the term 'repetitive TMS' (rTMS) has replaced earlier uses of the terms 'rapid TMS' and 'rapid-rate TMS' and should be used to refer to the application of regularly repeated single TMS pulses. The term 'fast' or 'high-frequency' rTMS should be used to refer to stimulus rates of more than 1 Hz, and the term 'slow' or 'low-frequency' rTMS should be used to refer to stimulus rates of 1 Hz or less. Such a classification is based on the different physiological effects and degrees of risk associated with low- and high-frequency stimulation.

Patterned rTMS refers to repetitive application of short rTMS bursts at a high inner frequency interleaved by short pauses of no stimulation. Most used to date are the different theta burst (TBS) protocols in which short bursts of 50 Hz rTMS are repeated at a rate in the theta range (5 Hz) as a continuous (cTBS), or intermittent (iTBS) train (Huang et al., 2005; Di Lazzaro et al., 2008) (Fig. 2).

Lasting inhibitory aftereffects of 1 Hz rTMS and cTBS and facilitatory after-effects following high-frequency rTMS and iTBS were found on motor corticospinal output in healthy subjects, with a neurophysiologic substrate that remains unclear. Various mechanisms are worth considering, including synaptic changes resembling experimental long term depression (LTD) and long term potentiation (LTP) mechanisms, as well as shifts in network excitability, activation of feedback loops, activity-dependent

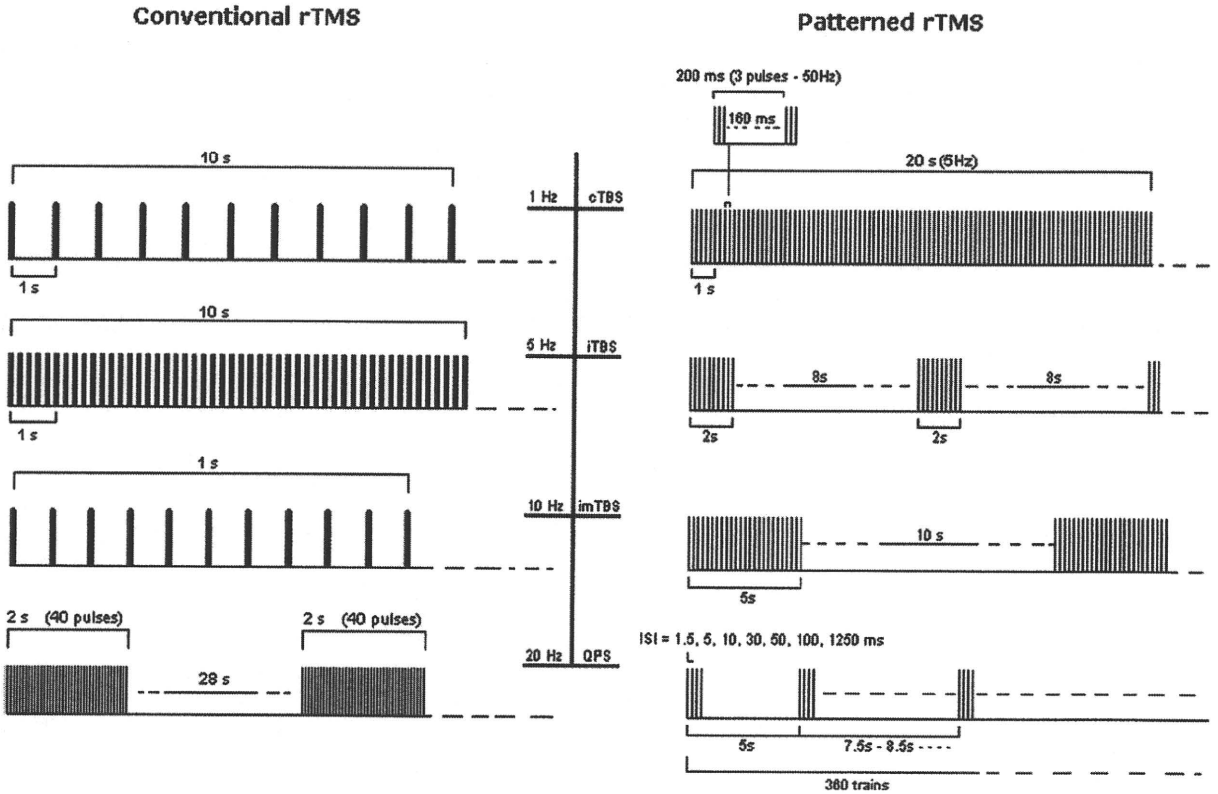

Fig. 2. Left panel (Conventional rTMS). From the top: examples of 10 s of rTMS at 1 Hz (first trace) and at 5 Hz (second trace); 1 s of rTMS at 10 Hz and a typical example of 20 Hz application for therapeutic purposes (trains of 2 s interleaved by a pause of 28 s). Right panel (Patterned rTMS). From the top: 20 s of continuous theta burst (first trace); intermittent theta burst (second trace) and intermediate theta burst (third trace). The fourth trace represents protocols of quadripulse stimulations (QPS).

metaplasticity (Gentner et al., 2008; Iezzi et al., 2008) etc. In the context of the present manuscript, a few issues are worth pointing out as they are relevant for the safety of TMS.

Regarding rhythmic, conventional repetitive, rTMS it is noteworthy, that in order to comply with present safety guidelines, protocols of slow rTMS ($\leqslant$1 Hz stimulation frequency) generally apply all pulses in a continuous train, whereas protocols of fast rTMS (e.g., $\geqslant$5 Hz stimulation frequency) apply shorter periods of rTMS separated by periods of no stimulation (e.g., 1200 pulses at 20 Hz and subthreshold stimulation intensity might be delivered as 30 trains of 40 pulses (2 s duration) separated by 28 s intertrain intervals (Fig. 2). There is only limited safety information on the effect of inserting pauses (intertrain intervals) into rTMS protocols (Chen et al., 1997). However, considering metaplasticity arguments (Abraham and Bear, 1996; Bear, 2003), it is likely that such pauses also have a significant impact on the effect of rTMS, both in terms of efficacy and safety. Therefore, further investigations are needed.

Regarding patterned rTMS, most TBS protocols employed to date replicate the original ones explored by Huang et al. (2005): for cTBS 3 pulses at 50 Hz are applied at 5 Hz for 20 s (300 total stimuli) or 40 s (600 stimuli). For iTBS twenty 2 s periods of cTBS each separated from the following by 8 s are applied (Fig. 2). Obviously, there are an infinite variety of combinations of such protocols, and it is important to emphasize that the effects and safety of the different protocols may differ, and that small changes, may have profound impact.

Recently, quadripulse stimulation (QPS) (Hamada et al., 2008) has been added to patterned rTMS procedures able to induce long-term changes of cortical excitability (see Fig. 2). Repeated trains of four monophasic pulses separated by interstimulus intervals of 1.5–1250 ms produced facilitation (at short intervals) or inhibition (at longer intervals), probably through a modulatory action on intracortical excitatory circuitry (Hamada et al., 2008).

The combination of repeated sub-motor threshold 5 Hz repetitive electrical stimulation of the right median nerve synchronized with sub-motor threshold 5 Hz rTMS of the left M1 at a constant interval for 2 min, or paired associated stimulation (PAS), is another protocol to temporally enhance rTMS effects at cortical level on the basis of a previously demonstrated interaction of the conditioning and test stimuli at the cortical level (Mariorenzi et al., 1991), perhaps through (meta)-plasticity mechanisms (Quartarone et al., 2006).

Repetitive paired-pulse stimulation (not included in Fig. 2) has be performed at ICF periodicity (Sommer et al., 2001) or i-wave periodicity (Di Lazzaro et al., 2007) [(also termed iTMS (Thickbroom et al., 2006) or rTMS (Hamada et al., 2007)]. Although higher excitability increases could be observed in comparison to single-pulse rTMS no seizures have been reported so far with this technique.

In all studies introducing new TMS protocols, safety should be addressed by including careful monitoring of motor, sensory and cognitive functions before, during, and after the intervention.

2.2. Interaction of magnetic field with tissue

In TMS, electric charge stored in a capacitor is discharged through a stimulation coil, producing a current pulse in the circuit that generates a magnetic field pulse in the vicinity of the coil. According to Faraday's law of electromagnetic induction, this time-varying magnetic field induces an electric field whose magnitude is proportional to the time rate of change of the magnetic field, which in the case of TMS is determined by the rate of change of the current in the coil. If the coil is held over a subject's head, the magnetic field penetrates scalp and skull, and induces an electric field in the brain. The induced electric field causes ions to flow in the brain, without the need for current to flow across the skull and without charged particles being injected into the scalp. In contrast, in transcranial electric stimulation (TES) charge is injected into the scalp at the electrodes and current must flow through the skull. Due to the low conductivity of the skull, in TES a large potential difference must be applied between the electrodes in order to achieve a current density in the brain high enough to stimulate neurons, and this leads to a much higher current density in the scalp. Thus, the ratio of the maximum current density in the brain is much lower in TMS than for TES, allowing TMS to stimulate cortical neurons without the pain associated with TES.

The flow of ions brought about by the electric field induced in the brain alters the electric charge stored on both sides of cell membranes, depolarizing or hyperpolarizing neurons. The existence of passive ion channels renders the membrane permeable to these ions: an increased membrane conductance decreases the amplitude of the change in membrane potential due to the induced electric field and decreases the time constant that characterizes the leakage of the induced charge. Experimental evidence (Amassian et al., 1992; Maccabee et al., 1993) and theoretical calculations (Nagarajan et al., 1993) indicate that stimulation occurs at a lower threshold where axons terminate, or bend sharply, in the relatively uniform electric field induced by the TMS stimulation coil. Accordingly, stimulation should occur where the electric field is strongest and points along the direction of an axon that terminates, for example at a synapse, or bends sharply. Axons with larger length constants, and hence larger diameters, are expected to be stimulated at lower stimulus intensity.

The stimulators and coils currently in production develop about 1.5–2.0 Tesla (T) at the face of the coil, produce currents changing at rates up to 170 A/μs (Thielscher and Kammer, 2002) and induce electric fields in the cortex of up to about 150 V/m. They are thought, depending by the stimulation intensity, to be able to activate cortical neurons at a depth of 1.5–3.0 cm beneath the scalp using standard Figure 8, circular or double-cone coils. The Figure 8 coil produces a more focal and shallower stimulation, whereas the double-cone coil was especially designed for stimulation of deeper cortical targets. When using intensities below 120% of motor threshold, the stimulation can not induce direct activation at depth of more than 2 cm beneath the scalp (Roth et al., 2002, 2007; Zangen et al., 2005; Roth et al.,).

Stimulus waveform and current direction have a significant impact on stimulation threshold. Shorter stimulus duration requires larger pulse amplitude but lower pulse energy to achieve stimulation (Barker, 1991; Hsu et al., 2003; Peterchev et al., 2008). For monophasic pulses over the motor cortex, a lower threshold is observed when the induced current flows in the brain in posterior-anterior direction. For biphasic pulses, the threshold is lowest when the induced current flows in the posterior-anterior direction in the second phase, and hence in the opposite direction from the first phase (Kammer et al., 2001). This effect can be explained in terms of the delayed (capacitive) response of the membrane (Davey and Epstein, 2000; Corthout et al., 2001). Stimulation threshold is lower for biphasic stimuli than for monophasic stimuli only if compared in terms of the energy stored in the stimulator's capacitors. In practice, the relative value of these two thresholds may be different for different stimulators (Kammer et al., 2001), which might have relevance in terms of safety.

Several simulation models have been developed to provide a view of the electromagnetic field distributions generated in biological tissue during TMS (Wagner et al., 2007). The simplified geometries of early models argued for the absence of currents normal to the superficial cortex and limited effects of surrounding tissues or altered anatomies, but more realistic head models indicate that such conclusions are inaccurate. For example, the conjecture that radial currents are absent during TMS, has influenced the