the time course of the effect on MEPs. A similar reciprocal effect of TMS on motor and sensory cortex was reported in a previous study of Mochizuki et al. (2004). They showed that weak single-pulse TMS (110%AMT) over right M1 suppressed the MEP evoked from left M1 but facilitated cortical components (N20/P25 and P25/N33) of the right median nerve SEP at interstimulus intervals of 100–200 ms. They reasoned that the interaction between motor and sensory cortices within the left hemisphere occurred via a reciprocal motor-sensory connectivity. Their argument was that TMS over the right M1 suppressed the opposite M1 by transcallosal or other connections and then secondarily increased SEPs recorded from the same side of the brain via the reciprocal motor-sensory connectivity.

Finally, we noted that the duration of the after-effect of TBS over the S1 was shorter (13 min) than that of TBS over M1 (53 min). We can only speculate on the reason for this. It is possible, for example, that there is a threshold difference for TMS effects on sensory and motor cortex.

As in previous reports of the effects of TMS on SEPs (Kujirai et al., 1993; Tsuji and Rothwell, 2002), our data also showed a marginal effect on the frontal P22/N30 component. The origin of the N30 is still debated, with some authors suggesting a site in postcentral regions (Allison et al., 1989), and others in the precentral or supplementary motor areas (Mauguiere et al., 1983; Desmedt and Bourguet, 1985). All these sites are near to or connected with the area of TBS, and may have been influenced by the conditioning.

One other component (N33/P40) of the SEP was affected by TBS. The origin of parietal P40 is also unknown but this component may represent serial sensory processing of the N33 input. If so, increase in size of this component may be a natural reaction following synaptic input from the N33 component enhanced by TBS over M1.

4.2. After-effects on MEPs

The present data confirm a previous report (Huang et al., 2005) that continuous TBS for 40 s over M1 reduces the amplitude of MEPs evoked by a single-pulse TMS at the same site for about 60 min after the end of the train. In addition, it is interesting to note that the time of maximum effect on the MEP was similar in the two studies, being about 10–20 min after the end of TBS. The new finding is that TBS over M1 also suppressed MEPs evoked from the opposite M1 and that the time course of suppression was very similar. This result is similar to that reported by Wassermann et al. (1998) who found that 1 Hz rTMS over M1 reduced excitability of the opposite M1 as evaluated with a recruitment curve measure (Table 2). However, two other reports in the literature have described opposite effects (Table 2): that 1 Hz rTMS over M1 can in fact increase MEP amplitudes evoked from the opposite M1 (Gilio et al., 2003; Schambra et al., 2003). The probable reason for this difference is that the stimulus intensity in the latter studies was 115–117% resting motor threshold (RMT), whereas it was around 100% RMT in the experiments of Wassermann et al. (1998), and even less than that (80% AMT) in the present study. The threshold for transcallosal effects is known to be higher than for corticospinal effects, so that rTMS at 115–117% RMT is likely to activate transcallosal connections directly whereas lower intensities will not (Gilio et al., 2003). If so, then facilitation of the opposite M1 might occur if rTMS activates transcallosal fibres directly whereas lower intensities of stimulation may produce inhibition because they only influence interhemispheric inhibition indirectly.

There are several possible explanations for the crossed decrease in MEP amplitudes that we observed. One relates to the existence of low threshold facilitatory connections between the two hemispheres (Ugawa et al., 1993; Hanajima et al., 2001) that coexist with the higher threshold inhibitory (Ferbert et al., 1992) connections demonstrated using a paired-pulse TMS technique. If ongoing neural activities in both M1 are controlled partly by excitatory interhemispheric connections, suppression of these pathways could lead to a decrease in MEP amplitude. A second possible explanation is that this crossed reduction in MEP amplitudes could be via a conditioning effect on a subcortical structure, such as the basal ganglia, whose output is at least partially bilateral (Graybiel, 1995).

4.3. Comparison between the after-effects of 1 Hz rTMS, paired associative stimulation (PAS) and cTBS

Table 2 summarizes the after effects of 1 Hz rTMS, PAS and cTBS (including present study) on MEPs and SEPs. When applied to M1, all of them lead to after effects on corticospinal excitability. The first point of interest in Table 2 is that induced changes in M1 are not always accompanied by the same effects on the ipsilateral SEP and the MEPs evoked from the contralateral cortex. Thus, suppression of M1 by 1 Hz rTMS or cTBS can be associated with either facilitation or suppression of the ipsilateral SEP. Similarly, suppression of M1 by 1 Hz rTMS or cTBS can lead to facilitation or suppression of contralateral M1. We argued in the previous section that the nature of the effect on contralateral M1 probably relates to whether the conditioning protocol activates transcallosal connections directly or indirectly. A similar argument may explain the differences in effect on ipsilateral SEP: relatively high conditioning intensities (110% AMT, Enomoto et al., 2001; 105% RMT, Tsuji and Rothwell, 2002) might activate directly the connections between M1 and S1. In these cases, the effect on the SEP is similar to the effect on the MEP, so that if MEPs are suppressed, SEPs are also suppressed. Conversely, the low stimulus intensity used with TBS (80% AMT) may be below threshold for activating these projections with the result that the effect on the SEP is opposite to that on the MEP.

In contrast, it appears as if a protocol that facilitates (or inhibits) MEPs when applied over M1 will also facilitate (or inhibit) SEPs when applied over S1. This occurs for

Table 2
Review of the after-effects of 1 Hz rTMS, PAS and cTBS on MEPs and SEPs

Study	Cortical area targeted by rTMS	rTMS intensity	No. of rTMS pulses	Duration of interventions	After-effects	Duration of after-effects
Ipsilateral M1 excitability						
1 Hz rTMS						
Touge et al. (2001)	Left M1	90% RMT	1500	25 min	↓ MEP amplitude	30 min
Lang et al. (2006)	Left M1	115% RMT	900 (Medtronic coil)	15 min	↓ MEP amplitude	≧20 min
Lang et al. (2006)	Left M1	115% RMT	900 (Magstim coil)	15 min	↓ MEP amplitude	10 min
Lang et al. (2006)	Left M1	90% RMT	900 (Medtronic coil)	15 min	↓ MEP amplitude	10 min
Lang et al. (2006)	Left M1	90% RMT	900 (Magstim coil)	15 min	↑ MEP amplitude	≧20 min
PAS						
Stefan et al. (2000)	Left M1	150% RMT	90 pairs (ISI = 25ms)	30 min	↑ MEP amplitude	≧30 min
Wolters et al. (2003)	Left M1	130% RMT	90 pairs (ISI = 25 ms)	30 min	↑ MEP amplitude	Not reported
Wolters et al. (2003)	Left M1	130% RMT	90 pairs (ISI = 10 ms)	30 min	↓ MEP amplitude	75 min
cTBS						
Huang et al. (2005)	Left M1	80% AMT	300	20 s	↓ MEP amplitude	20 min
Huang et al. (2005)	Left M1	80% AMT	600	40 s	↓ MEP amplitude	60 min
Present report	Left M1	80% AMT	600	40 s	↓ MEP amplitude	42 min
Present report	Left S1	80% AMT	600	40 s	no change in MEP amplitude	
Ipsilateral S1 excitability						
1 Hz rTMS						
Enomoto et al. (2001)	Left M1	110% AMT	200	200 s	↓ SEP amplitude (N20/P25, P25/N33)	60 min
Enomoto et al. (2001)	Left S1	110% AMT	200	200 s	↑ SEP amplitude (N20/P25, P25/N33)	15 min
PAS						
Tsuji and Rothwell (2002)	Left M1	105% RMT	180 pairs (ISI = 25ms)	30 min	↑ SEP amplitude (N20/P25, P25/N33)	10 min
Wolters et al. (2005)	Left S1	150% RMT	180 pairs (ISI = N20)	30 min	↑ SEP amplitude (N20/P25)	30 min
Wolters et al. (2005)	Left S1	150% RMT	180 pairs (ISI = N20–20 ms)	30 min	↓ SEP amplitude (N20/P25)	Not reported
cTBS						
Present report	Left M1	80% AMT	600	40 s	↑ SEP amplitude (P25/N33, N33/P40)	53 min
Present report	Left S1	80% AMT	600	40 s	↓ SEP amplitude (P25/N33)	13 min
Contralateral M1 excitability						
1 Hz rTMS						
Wassermann et al. (1998)	Right M1	100% RMT	900	15 min	↓MEP amplitude in contralateral M1	Not reported
Gilio et al. (2003)	Left M1	117% RMT	900	15 min	↑MEP amplitude in contralateral M1	≧20 min

(*continued on next page*)

Table 2 (*continued*)

Study	Cortical area targeted by rTMS	rTMS intensity	No. of rTMS pulses	Duration of interventions	After-effects	Duration of after-effects
Schambra et al. (2003)	Left or right M1	115% RMT	1800	30 min	↑MEP amplitude in contralateral M1	≧15 min
Plewnia et al. (2003)	Left M1	115% RMT	800	13 min 20 s	No MEP change and ↓SICI in contralateral M1	10–15 min
cTBS						
Present report	Left M1	80% AMT	600	40 s	↓MEP amplitude in contralateral M1	≧60 min
Present report	Left S1	80% AMT	600	40 s	No change in MEP amplitude	
Contralateral S1 excitability cTBS						
Present report	Left M1	80% AMT	600	40 s	No change in SEP amplitude	
Present report	Left S1	80% AMT	600	40 s	No change in SEP amplitude	

rTMS, repetitive transcranial magnetic stimulation; PAS, paired associative stimulation; cTBS, continuous theta burst stimulation; RMT, resting motor threshold; AMT, active motor threshold; ISI, interstimulus interval; N20, N20 latency; SICI, short latency intracortical inhibition; Medtronic coil, stimulated with Medtronic coil; Magstim coil, stimulated with Magstim coil.

the PAS protocol (Wolters et al., 2005) as well as with TBS in the present experiments. One exception may be 1 Hz rTMS. Enomoto et al. (2001) found that this increased SEPs when applied over S1, but they did not report what effect if any the protocol had on MEPs when applied over M1. Further work is needed to resolve this point.

In conclusion, TBS for only 40 s can have short-lasting (more than 50 min) after-effects on the somatosensory cortex as well as motor cortex in humans and can influence neural processing not only at the site of stimulation but also at distant sites to which it projects. Therefore, a single session of TBS is an interventional tool that can induce rapid reorganization within cortical somatosensory as well as motor networks in humans.

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電気刺激によるてんかん治療

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脳を刺激することによって，てんかんを治療する方法が注目されている．てんかん発作は大脳皮質神経細胞の異常な電気的過剰活動によって生じるので，脳を刺激するとてんかんを悪化させるのではと危惧されるかもしれない．しかし，脳には興奮を抑制するシステムがあるので，抑制系をうまく刺激すればてんかん原性を抑制することができるはず，というのがてんかんに対する刺激治療法の理論的根拠である．

この刺激治療の着想はすでに30年以上前からあり，Cooperは1973年に小脳に刺激電極を手術で埋め込み電気刺激することにより，てんかん発作が改善したと報告している．しかし，その後の追試では小脳刺激の有効性は認められなかった．しばらく刺激療法研究は停滞していたが，1990年代後半から再び刺激によるてんかん治療が試みられるようになっている．

1．深部電極刺激法

深部電極刺激法は，脳深部に刺入した電極で電気刺激するものである．視床下核，視床，海馬などの刺激治療が試みられている．大脳皮質に広く投射する部位を刺激することにより，間接的にてんかん原性を抑制しようとするものと，海馬のようにてんかん焦点を直接刺激するものがある．視床前核刺激でてんかん抑制効果があったとする複数の報告があり，有望な刺激部位として注目されている．現在，北米で多施設共同研究が進行中である．

2．反復経頭蓋磁気刺激（rTMS）

近年注目されている脳刺激法に，反復経頭蓋磁気刺激（repetitive transcranial magnetic stimulation：rTMS）がある．rTMSは頭部に置いた磁気刺激コイルの電流により磁界を発生させ，それよって脳内に誘発される電流で脳を反復刺激するものである．深部電極刺激と違い，頭蓋外から非侵襲的に痛みを伴わずに脳を刺激できるのが大きな利点である．

当初，rTMSは検査法として臨床導入されたが，神経調節作用があることが分かり，パーキンソン病，うつ病をはじめとして多くの疾患の治療にも用いられるようになった．難治性てんかんの治療にも試みられ，1999年に最初の有効性の報告がある．その後も多数例での報告がなされており，どのタイプのてんかん患者にどのような刺激方法（パラメータ）で刺激すればよいかが現在研究されている．

3．ブレインペースメーカー

心臓の除細動器（defibrillator）と同じように，発作が生じた場合にすぐに対応して発作を頓挫させる方法がブレインペースメーカーである．解析プログラムでてんかん発作を自動的に検知し，即座にその電極を電気刺激して発作を止めるわけである．治療手技は，頭蓋内に記録および刺激電極を埋め込み，皮下に記録および刺激発生装置（一体となっている）を設置する．2006年に北米13施設共同研究の結果が報告された．てんかん発作が50%以上減少したのは，複雑部分発作で36%，二次性全般化発作は64%の患者で認められたという結果である．今後の臨床試験の進展が期待されるとともに，安全性，適応についてさらなる検討が必要である．

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脳波・筋電図の臨床

脊髄性ミオクローヌス様不随意運動の電気生理学的診断

Electrophysiological diagnosis of spinal myoclonus and psychogenic movement disorders

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1）四肢・体幹の一部に限局した不随意運動をみたら，脊髄性ミオクローヌスが疑われるが，確定診断に苦慮することは少なくない．
2）脊髄性ミオクローヌスが疑われて紹介された4例に対して電気生理学的検査を行い2例はpsychogenic movement disorders，1例はpropriospinal myoclonus，1例は心臓ペースメーカーのトラブルと確定診断できた．
3）臨床的観察と電気生理学的検査を繰り返し行うことが診断に重要である．

KEY WORDS 脊髄性ミオクローヌス，心因性運動障害，propriospinal myoclonus

はじめに

ミオクローヌスは病態生理による分類がよく用いられるが，そのなかで脊髄由来のものを脊髄性ミオクローヌスと呼んでいる[1]．さらに脊髄髄節の一部に限局し，律動性の筋収縮を示すものは脊髄髄節性ミオクローヌス[2]，髄節から髄節へlong propriospinal pathwayを通して広がるものは自己固有感覚性脊髄性ミオクローヌスpropriospinal myoclonus[3]と分類される．臨床現場で四肢・体幹の一部に限局した不随意運動をみたら，脊髄性ミオクローヌスを疑うが，確定診断に苦慮することは少なくない．本稿では脊髄性ミオクローヌスが疑われて紹介された4例を呈示し，どのように診断を進めたかを解説する．

症例 1

52歳男性．10年前から両下肢が勝手に動くことを自覚し，某大学神経内科を受診した．脊髄性ミオクローヌスと診断され，クロナゼパム3 mg/day内服で少し改善したが，まだ強く残存し仕事がかなり困難となったために，それ以降は傷病手当を受け続けている．5年前から症状悪化し，仕事がまったくできなくなり，郷里に帰省し，別の大学神経内科を受診した．クロナゼパム増量，バルプロ酸，バクロフェン，ピラセタム，ダントロレンナトリウム（一時著効），スルピリド，クロミプラン，塩酸パロキセチン，塩酸ケタミン点滴，左閉鎖神経ブロック（7時間のみ有効），フマル酸クエチアピン，エクセグラン，クロバザム，

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パロペリドール，ブロモクリプチン（3日有効）が試みられたが明らかな効果はなかった．セカンドオピニオン希望され，当科を受診した．

神経学的診察では意識清明，高次機能低下なし，脳神経系，筋力，腱反射，感覚系すべて正常であった．不随意運動は覚醒時常に持続しており体位で性状が異なっていた．座位では，不随意運動は左大腿内転筋主体に約1.5～2 secに1回の頻度で生じる比較的律動性の持続が少し長い筋収縮で，ときどき右大腿内転筋にも生じるものであった．立位では体幹を前屈させる不随意運動となった．歩行時にはほぼ消失していた．だれも観察していないときにも不随意運動は持続していた．

診断のポイント

①体位によって筋収縮の分布・持続時間・同期性が変化する（図1）．
②動作を切り替えるときに瞬間的に筋収縮が消失する．
③他のことに集中しているときは消失する．
④薬剤が一過性に効果を示す（placebo効果）．
⑤運動に関連した脳電位が記録される．

経　　過

placebo効果を期待して磁気刺激（最大出力の40%刺激強度，1 Hz，100回/日，円形コイルを腰部に置く）1週間施行したら異常筋収縮は完全に消失した．

症例　2

26歳女性．2年前，腰痛が出現したために，近医整形外科で硬膜外ブロックを施行された．痛みが改善しないために硬膜外チューブを再挿入されたときに左大腿部に電撃痛が生じ，その後より左大腿部のぴくつきが生じた．その5ヵ月後，某大学神経内科に紹介された．L4の神経ブロックで消失することから脊髄ミオクローヌスと診断され，バクロフェン，クロナゼパム，フェニトイン，バルプロ酸，カルバマゼピンなどを試されたが無効であった．1年前，脳外科で腰部硬膜下刺激電極(T12のL1-4レベル）による電気刺激治療が開始された．一時的に不随意運動は消失し，歩行が可能となり復職したが，職場に適応は難しいと感じていた．2ヵ月前からreceiver部の疼痛を訴え，左大腿部不随意運動も再び悪化した．また，過換気症候群を繰り返すようになった．実家に戻ることになり，当科を紹介された．

神経学的診察では意識清明，脳神経系，筋力，腱反射，感覚系はすべて正常であった．歩行は両側杖で短距離であれば可能であった．不随意運動は左大腿四頭筋中心に約3 Hzの頻度で律動性収縮を認め，激しいときは筋痛を訴えた．運動・荷重で増強し，睡眠中は消失した．また，入院後も過換気症候群を頻回に起こした．

診断のポイント

①体位により，筋収縮が消失したり，同期性が変化する．
②他のことに集中しているときは消失する（図2）．
③過換気症候群が生じているときは消失する．
④ぴくつきの程度とは無関係に歩行困難となる．過換気症候群が頻発すると歩行困難も悪化する．
⑤悪化する前には心理社会的要因（対人関係や仕事でのトラブル）が存在する．
⑥運動に関連した脳電位の記録．

経　　過

心療内科的治療で一時まったく消失したが，その後ストレスにより増悪を繰り返した．数年後にはまったく消失し，無症状のまま経過している．

心因性不随意運動

心因性運動障害psychogenic movement disorders（PMD）の多くは不随意運動である．専門医を受診した患者の約3%はPMDという報告[4]もあり，日常臨床で遭遇する機会は多い．また，不随意運動の中の約10%は心因性といわれている[5]．PMDで見られるものとしては振戦，ジス

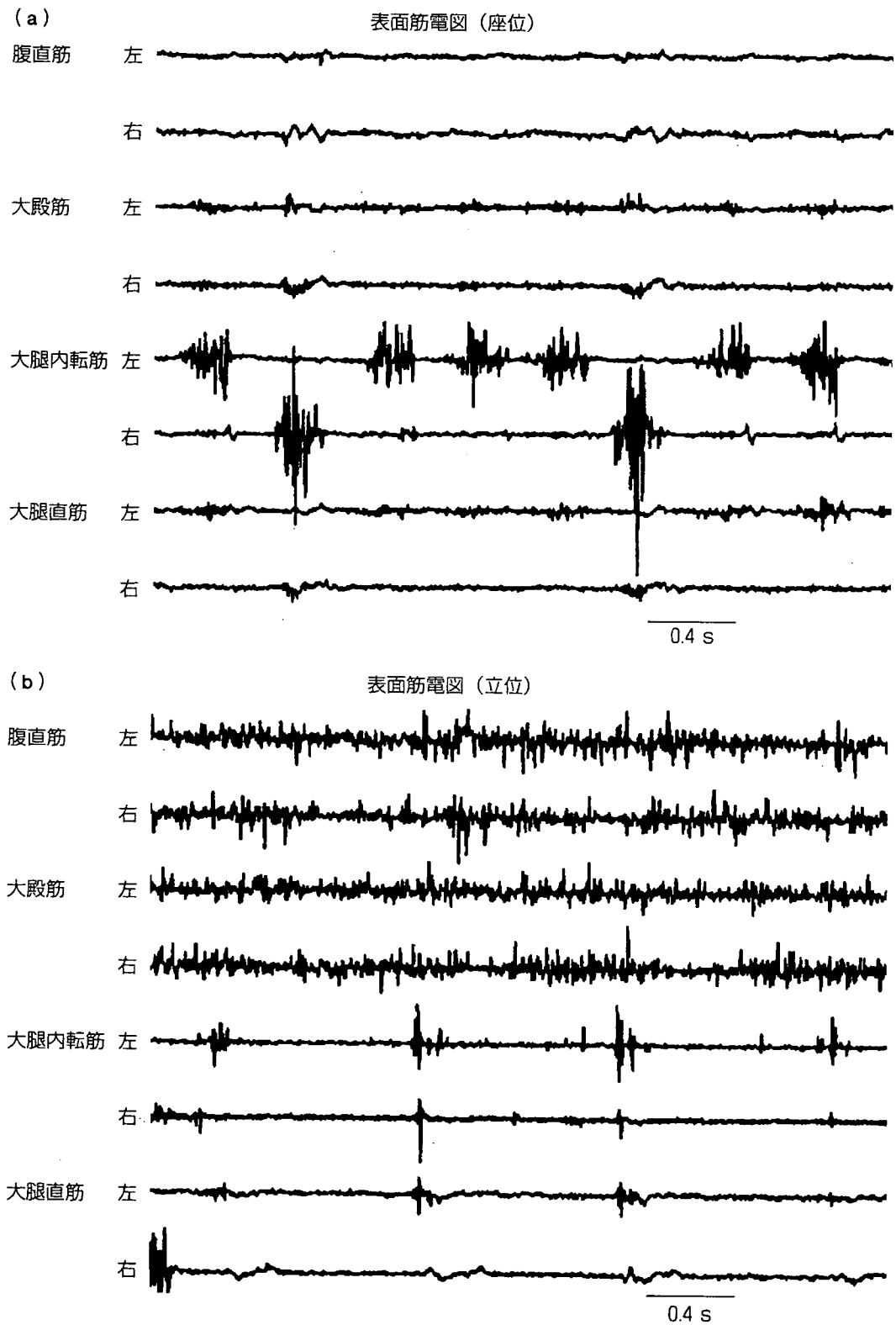

図1　症例1における座位（a）と立位（b）の表面筋電図
体位によって筋収縮の分布とパターンが大きく異なる．

トニア，ミオクローヌスなどと紛らわしい動きが多い．したがって，専門医が診察してもなかなか区別がつかない場合がある．そのような患者に対して過誤の医療行為が行われていることもある．器質的神経疾患を持つ患者に認められることも少なくなく，なおさら複雑にしている．なかには数

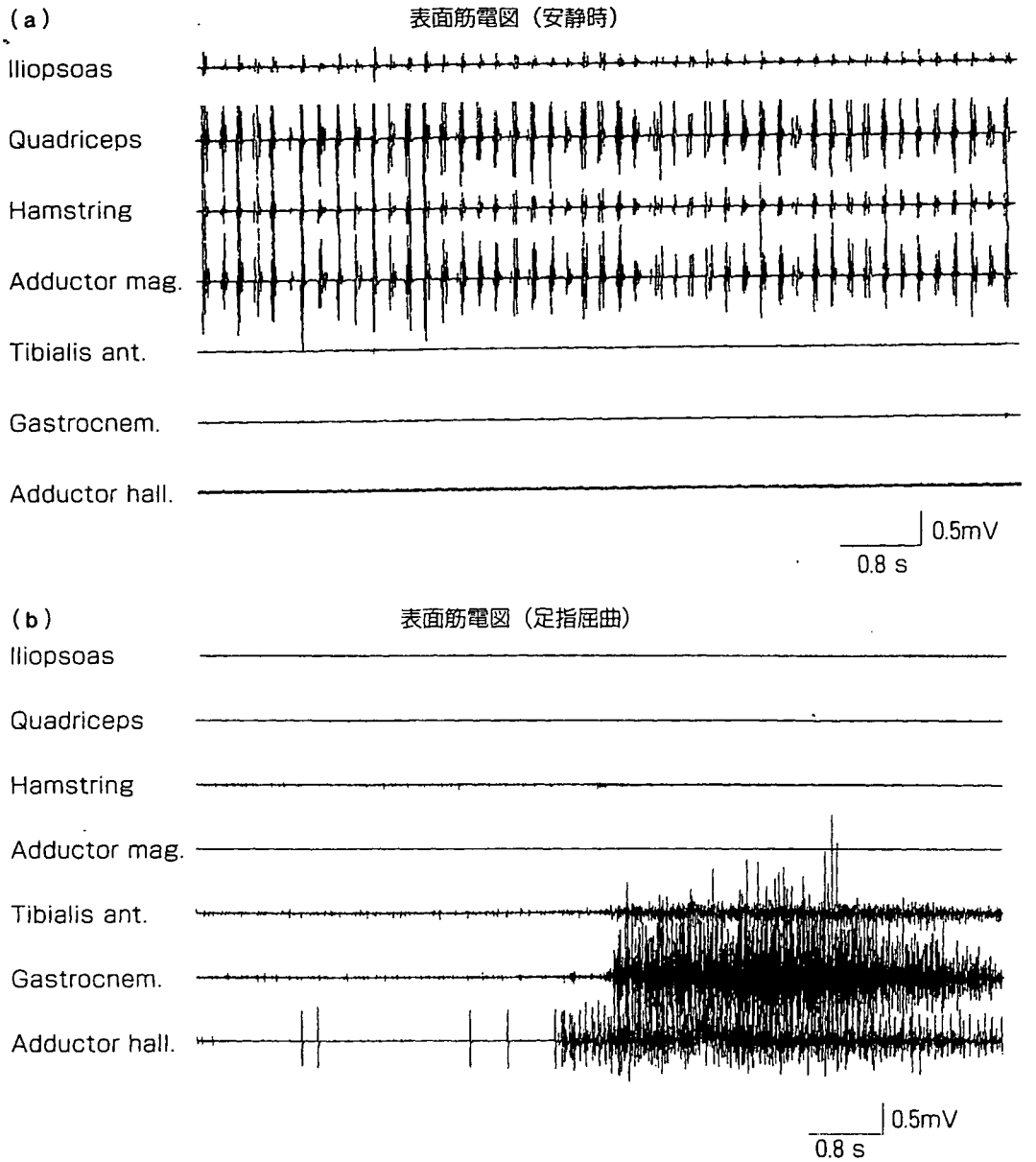

図2　症例2における表面筋電図

a：安静時できわめて規則正しい律動性筋収縮が認められた．心因性とは考えにくい所見であった．

b：足指を屈曲させる．難しく集中しないとできない．指示をするとそれまで認められた律動性筋収縮が消失した．

年間持続している例や他者がまねをできないような難しい動きを示す例もあり診断をさらに困難にしている．精神医学的背景としては転換性障害，うつ病が多いとされている．精神疾患であれば比較的予後はよいが，保障がからんでいる場合や訴訟中の患者は予後が悪い[6]．また，症状が1年以上持続している場合も予後が悪いといわれている．

心因性不随意運動の診断をすすめるために注意すべき臨床的特徴を説明する．①突然出現し，突然消失することが多い．②振幅，周波数，分布が変動しやすい．③診察時や観察中は増悪し，誰もいなくなると緩解する．④placeboやsuggestionで増悪したり緩解する．⑤注意をそらすと著減する．その際はかなり集中しないとできないような複雑な課題を与えるのが効果的である．⑥心理的背景（抑うつ，疾病利得など）が存在する．

次に心因性不随意運動の電気生理学的検査の特徴を示す．①振戦においては拮抗筋の筋収縮が相

反することが基本であり，同期したり相反したり変動する場合は心因性である．②ミオクローヌスにおいては表面筋電図で筋放電の持続時間が70ms以下と短く拮抗筋が同期していれば器質的の可能性が高く，そうでなければ心因性が疑わしい．③それでも鑑別できなければ，運動関連電位（随意運動に伴う脳電位）を記録し，随意運動であることを証明する．これが記録されれば脊髄性起源は完全に否定されるが，大脳起源の一部の不随意運動は運動誘発電位類似の反応が先行することがあり心因性との鑑別に苦労することがある．その場合は患者に通常の随意運動をさせて得られた反応と比較する必要がある．

前述したように心因性不随意運動は診断が遅れると改善が難しいことが多く，積極的に診断するためには観察，電気生理学的検査を繰り返すことが最も重要である．

症例　3

28歳男性．10ヵ月前から首が突然前に曲がるような発作が生じるようになった．車の運転や仕事中など精神的緊張，疲労で誘発された．毎日数回から多いと数分に1回生じるようになったので某大学病院を受診し，バルプロ酸，クロナゼパムなど試みられたが有効でなく，当科を紹介された．

頸部を突然前屈させるような素早い不随意運動が認められた．緊張や前額部の叩打により誘発さ

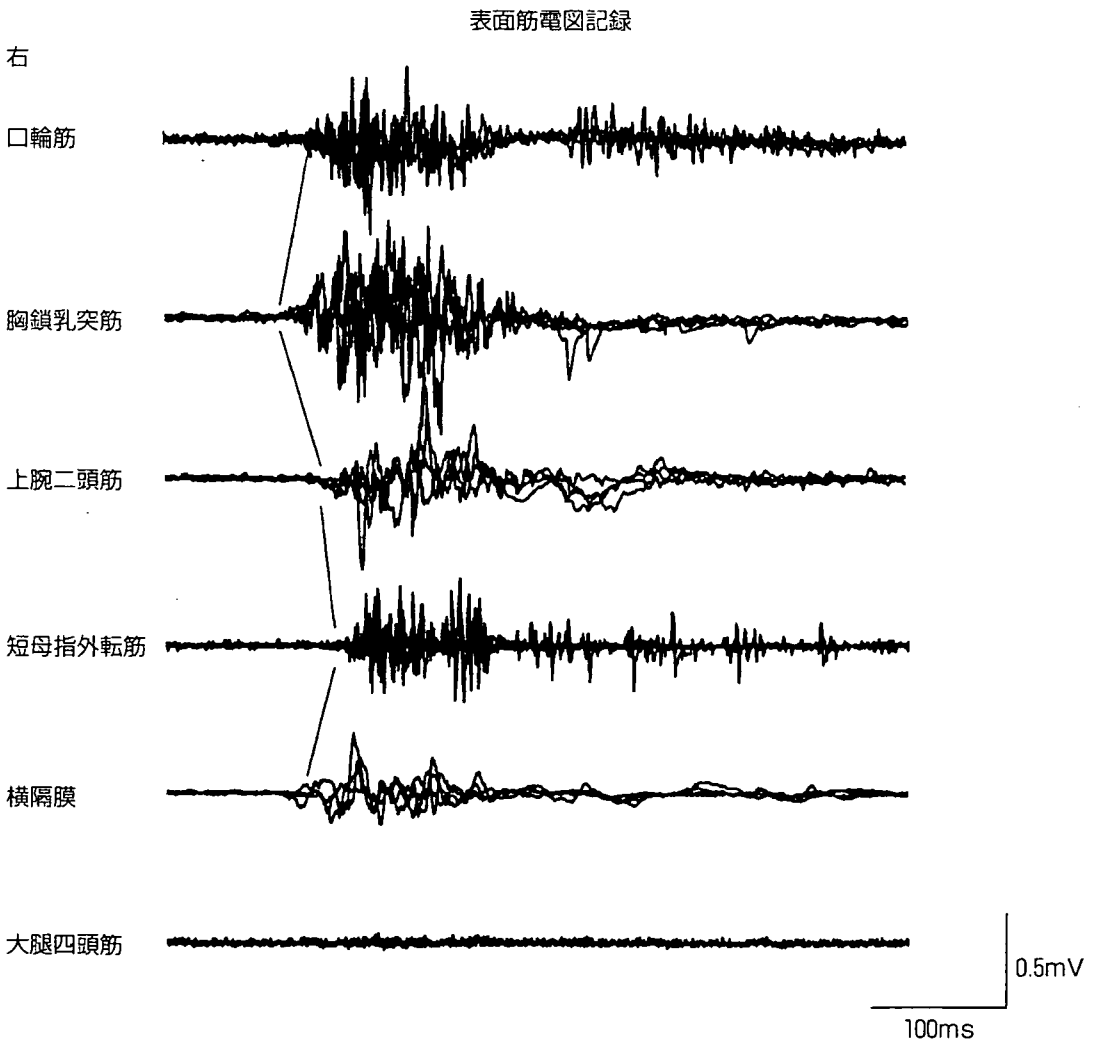

図3　症例3における不随意運動出現時の表面筋電図
胸鎖乳突筋から始まりゆっくり上下の髄節に広がる筋放電が記録された．

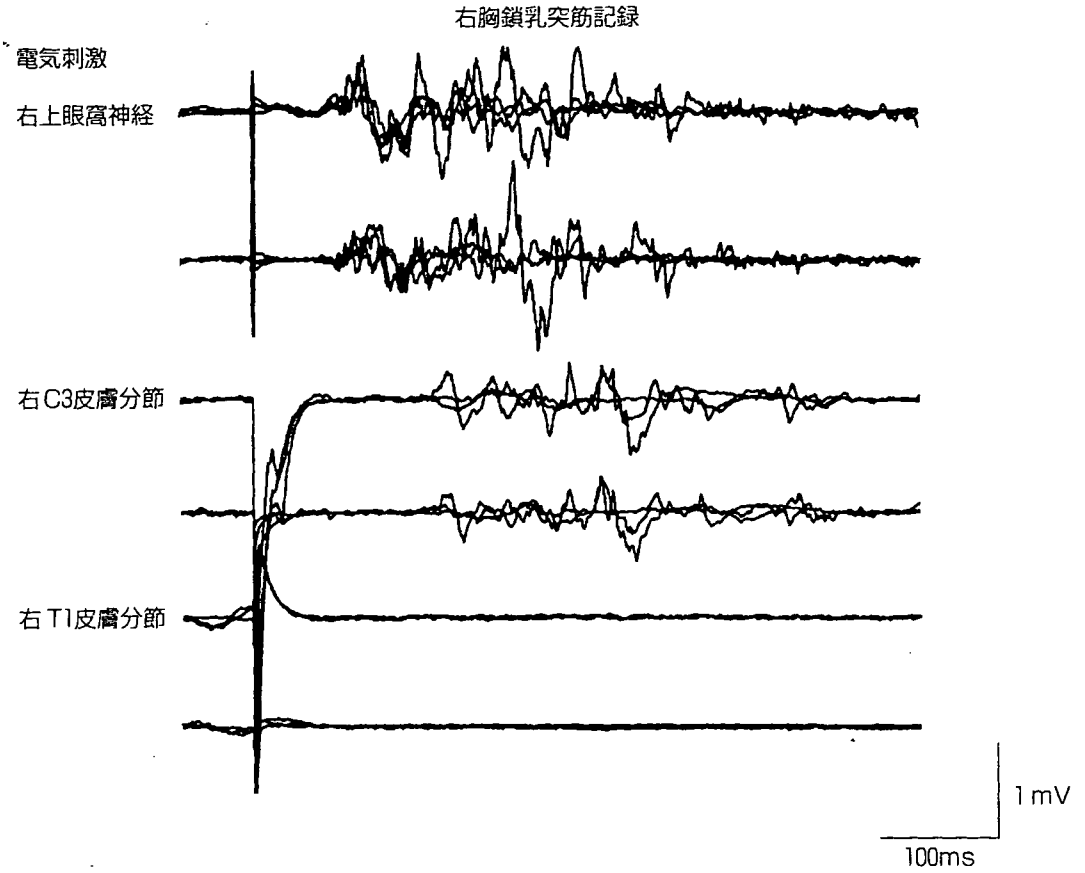

図4　症例3における刺激時の表面筋電図
右上眼窩神経および右C3皮膚髄節の電気刺激では筋収縮が容易に誘発されたが，右T1皮膚髄節の電気刺激ではまったく誘発されなかった．また，刺激から筋収縮までの潜時も刺激によって異なり，再現性も良好であった．

れた．一度生じると不随意運動が連続する傾向があった．動きは一見奇妙であり，心因性を疑わせるものであった．神経学的診察ではそれ以外に異常を認めなかった．頭部・頸部MRI：異常なし．脳波も正常で，体性感覚誘発電位も正常であった．C反射も誘発されなかった．

診断のポイント

①筋収縮のパターンと広がりかたが一定している．

②表面筋電図である髄節から始まり上下の髄節にゆっくり伝播するパターンが一定している（図3）．

③刺激により誘発されるが刺激部位で誘発の有無あるいは誘発までに時間が異なり，再現性もある（図4）．

④ミオクローヌスに関連した運動関連電位が認められない．

経　　過

塩酸トリヘキシフェニジル内服が著効を示し，不随意運動は刺激を加えてもほとんど出現しなくなり，半年後には完全に消失した．その後内服を中止しても再発を認めていない．

propriospinal myoclonus

脊髄には髄節間を連絡するpropriospinal tractが存在すると考えられており，そのなかで経路の長いlong propriospinal tractは両側性に体幹筋や四肢近位筋を支配する．この経路を通して体幹筋をある脊髄の1分節から頭側または尾側にゆっくり異常な興奮が伝わって生じるのがpropriospi-

nal myoclonus である．臨床的には頸部，体幹などに生じる屈曲性筋収縮が観察されることが多い．筋収縮は自発性に生じるが刺激によって誘発される場合がある．脊髄内を伝播する速度は非常にゆっくりであり約3～11m/secのものが多い．刺激で誘発される場合は刺激から90～130msec遅れて筋収縮が始まることが多い．診断するうえで最も重要な検査は表面筋電図であるが，最近正常者でもこのような動きを模倣でき，しかも表面筋電図でもあたかも上下の髄節にゆっくり進展するパターンで記録されることが報告された[7]．したがって，本例のように刺激ごとに決まった潜時で誘発されることを証明することも必要である．またpropriospinal neuronはAch作動性であることが動物実験で示されている[8]．本例で塩酸トリヘキシフェニジルが著効を示したことはこれを支持するものと考えられた．

症例　4

62歳男性．不整脈のために心臓ペースメーカー植え込み術を2年前に受けた．約2ヵ月前から右胸部下部がぴくぴくすることに気づく．ぴくつきは持続性であり，夜間もぴくついて眠れない．脊髄性ミオクローヌスが疑われクロナゼパムを投与されたが無効のため当科を紹介された．右のT6－8髄節レベルの側胸部を中心に律動性の筋収縮が観察された．その周期は規則正しく1分間に約60回の収縮を認めた．

診断のポイント

心拍動と同期した筋収縮である（図5）．体位や睡眠などの影響もみとめられなかった．

経　　過

心臓ペースメーカーの不良（リード線の迷入）により刺激されていると考えられ，ペースメー

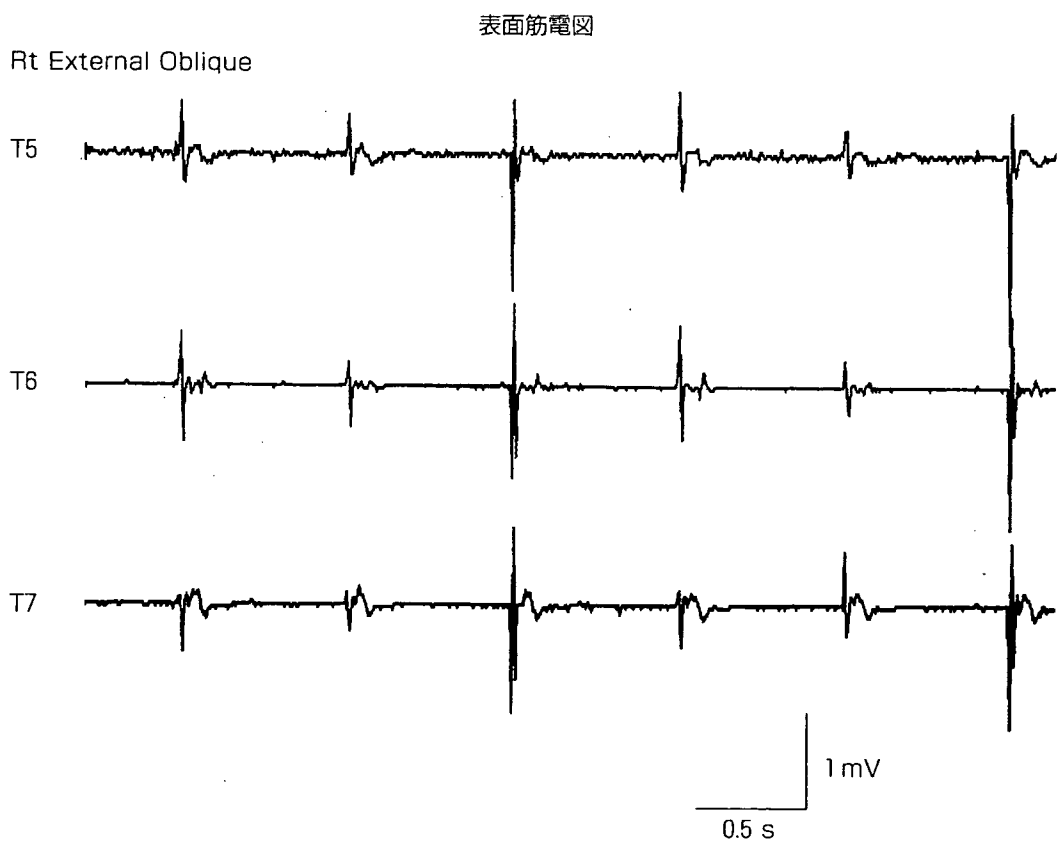

図5　症例4における表面筋電図
持続が短い筋収縮が規則正しく認められた．体位，睡眠などの影響もなかった．

カー入れ替えにより筋収縮は消失した．

おわりに

脊髄性ミオクローヌスの診断は容易でなく，とくに心因性不随意運動の鑑別が重要である．臨床的観察と電気生理学的検査法を納得できるまでくりかえすことが必要である．

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Letter to the Editor

Comparison of different methods for estimating motor threshold with transcranial magnetic stimulation

Motor threshold (MT) is one of the most important parameters measured routinely in studies with transcranial magnetic stimulation (TMS). It is used, for example, to standardize stimulus intensities between individuals; to determine the intensity of the conditioning stimulus in paired pulse studies; and to define the safety range for applications involving rTMS. The IFCN definition of resting MT (RMT) (Rossini et al., 1994; Rothwell et al., 1999) is the intensity at which there is a 50% probability of producing a response in relaxed subjects. A number of ways of estimating this using EMG measures have been published, such as the halfway point between the largest intensity that never produces an MEP and the lowest intensity that always gives an MEP (Mills and Nithi, 1997), but in practice they tend to yield very similar values (Tranulis et al., 2006).

However, RMT is sometimes defined as the intensity at which a visible finger movement is elicited in 50% trials. Some authors have found that this leads to values less than those estimated with EMG measures (Pridmore et al., 1998), whereas others have found the opposite (Conforto et al., 2004). Since RMT is the intensity around which safety parameters for rTMS are defined, such variations are not trivial.

Active motor threshold (AMT) is more difficult to define than RMT since the response has to be distinguished from background muscle activity. However, many authors use it because they want to define the threshold at which a TMS pulse first elicits excitatory synaptic inputs to spinal motoneurones. During activation, there will be some motoneurons that are close to threshold and ready to discharge upon arrival of a minimal excitatory input. Thus AMT is often assumed to be equivalent to the threshold for evoking a descending corticospinal volley. Practically, AMT is usually defined as the intensity at which MEPs with an amplitude of around 200–300 μV can be distinguished from the background activity in 50% of trials (Rothwell et al., 1999). Clearly, intensities below this level may still elicit some excitatory input to spinal cord even though it is too small to lead to a 200 μV MEP. Thus this method of estimation does not give a reliable definition of the threshold for eliciting a corticospinal volley.

These considerations lead us to study how much the MTs differed when measured by different methods. Surface EMGs were recorded from the right first dorsal interosseous muscle (FDI) in ten right handed healthy volunteers (seven men and three women, 30–53 years old). Responses were amplified through filters set at 20 Hz to 3 kHz, rectified when necessary and digitized at a sampling rate of 20 kHz. When measuring AMTs, subjects maintained 8–12% of the maximum voluntary contraction with the aid of an oscilloscope monitor. We placed a figure-8 shaped coil (external diameter at each wing 9 cm) connected to a Magstim 200 magnetic stimulator (The Magstim Company, UK) over the primary hand motor area (M1) of the left hemisphere so that the induced currents in the brain flowed in an anterior-medial direction perpendicular to the central sulcus. The intensity was decreased from suprathreshold level to subthreshold level in steps of 1% maximum stimulator output (MSO).

We compared MTs determined in five different ways (MT_{mov}, MT_{movl}, MT_{raw}, MT_{rawl}, MT_{rec}, see abbreviations below) in relaxed and active muscle (RMT, AMT). The first method for MT determination was visual detection of minimal finger movements. MT_{mov} was defined as the minimal intensities to induce 8 slight twitches of the index finger out of 16 trials in relaxed or active conditions (RMT_{mov}, AMT_{mov}). We also defined the intensity that was needed to induce one visible movement out of 16 trials as MT_{movl}. The second method was that recommended by the IFCN (Rossini et al., 1994; Rothwell et al., 1999): thus RMT_{raw} was defined as the minimal intensity at which half of the stimuli produced MEPs 50 μV or larger in relaxed condition. AMT_{raw} was defined as the lowest stimulus intensity at which 8 of 16 stimuli elicited reliable MEPs larger than 200 μV when the subjects made a voluntary contraction. We also defined AMT_{rawl} as the intensity to elicit MEPs larger than 100 μV during tonic contraction of the target muscle in half of the trials. In the third method, we averaged the rectified EMG evoked by each pulse of TMS. We then defined MT_{rec} as the lowest intensity which evoked a peak that was at least 1.3 times larger than the mean background activity before stimulation.

The following mean threshold values were obtained in the relaxed condition. RMT_{mov} was 55.8 ± 9.0 (mean $\pm$ SD)%, RMT_{movl} was 51.6 ± 8.8%, RMT_{raw} was 49.8 ± 10.3%, and RMT_{rec} was 47.0 ± 10.1%. Repeated measures ANOVA revealed there was a significant

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difference among these values [F (1.33; 10.7) = 18.5 $P < 0.001$]. Post hoc analyses showed RMT_{mov} was different from the other RMTs ($P < 0.001$). RMT_{raw} did not differ from RMT_{movl}($P > 0.05$), and RMT_{rec} was significantly smaller than any other RMTs ($P < 0.001$).

For our estimates of the mean AMT: AMT_{mov} was 43.3 ± 6.5%, AMT_{movl} was 36.5 ± 5.9%, AMT_{raw} was 35.1 ± 6.9%, AMT_{rawl} was 33.4 ± 5.6%, and AMT_{rec} was 29.4 ± 4.9%. An ANOVA revealed that there were significant differences between these values [F(1.80; 16.2) = 24.5, $P < 0.001$]. Post hoc analyses showed AMT_{mov} was different from the other AMTs ($P < 0.001$). AMT_{rec} was significantly lower than AMT_{raw}, AMT_{movl}, or AMT_{mov} ($P < 0.001$), and was about 87% AMT_{raw}, and 68% AMT_{mov}.

We constructed input–output curves of the relationship between mean MEP amplitude and stimulus intensity normalized to RMT_{raw} and AMT_{raw} which were given a value of 1.0 (Fig. 1a and b). Arrows on the right and left of the x-axis indicate the mean values of MT_{mov} and MT_{rec}, respectively, when normalized to MT_{raw}. In relaxed muscle, the size of MEPs approaches zero at RMT_{rec} (the left arrow in Fig. 1a). In active muscle, the size of the averaged MEP was almost the same as the level of ongoing background activity (about 200 μV) at AMT_{rec} (the left arrow in Fig. 1b). Clearly, MT_{mov}, MT_{rec}, and MT_{raw} correspond to quite different points on the input–output curve, in both relaxed and active muscle.

It is no surprise that estimates of MT depend on the method of measurement (see also Conforto et al., 2004). What is unexpected is the extent of the observed differences. Thus AMT_{mov} was equivalent to almost 150% AMT_{rec}, while RMT_{mov} was equivalent to 190% AMT_{rec}. Neurophysiologically, what is happening at these three measures of MT will be very different indeed. rTMS safety parameters have been defined in terms of RMT_{raw} (Wassermann, 1998), and have proved to be remarkably successful since their introduction nearly 10 years ago. However, in some centers, RMT_{mov} is often used instead of RMT_{raw}. Like Conforto et al. (2004) we found that RMT_{raw} was lower than RMT_{mov}: thus RMT_{mov} was equivalent to 113% RMT_{raw}. Such differences mean that parameters of rTMS regarded as within safety guidelines using movement estimates of MT would be regarded as well outside safety limits by those using EMG measures.

Interestingly, Pridmore et al. (1998) found the opposite, that RMT_{mov} was lower than RMT_{raw} in five of six subjects. This may relate to the fact that we only counted movement of the target muscle (FDI), and that we ensured that it was relaxed before stimulation using EMG recordings. Pridmore et al. (1998) allowed movement of any hand and forearm muscles, but did not use EMG recordings to confirm that their subjects had completely relaxed all these muscles. A low level of background contraction could have lowered their threshold and account for the apparent discrepancy in the results.

In physiological studies, AMT_{raw} is sometimes considered as the lowest intensity for activating the pyramidal tracts with the assumption that TMS at and below 90% AMT_{raw} is below the intensity needed to induce any effects on spinal motoneurones. However, the present data show that, as expected from its definition, stimulation at AMT_{raw} elicited an average MEP of 100–200 μV. This indicates that AMT_{raw} is greater than the physiological threshold for activating corticospinal input to motoneurones. In the present study, we even found that stimulation at 90%

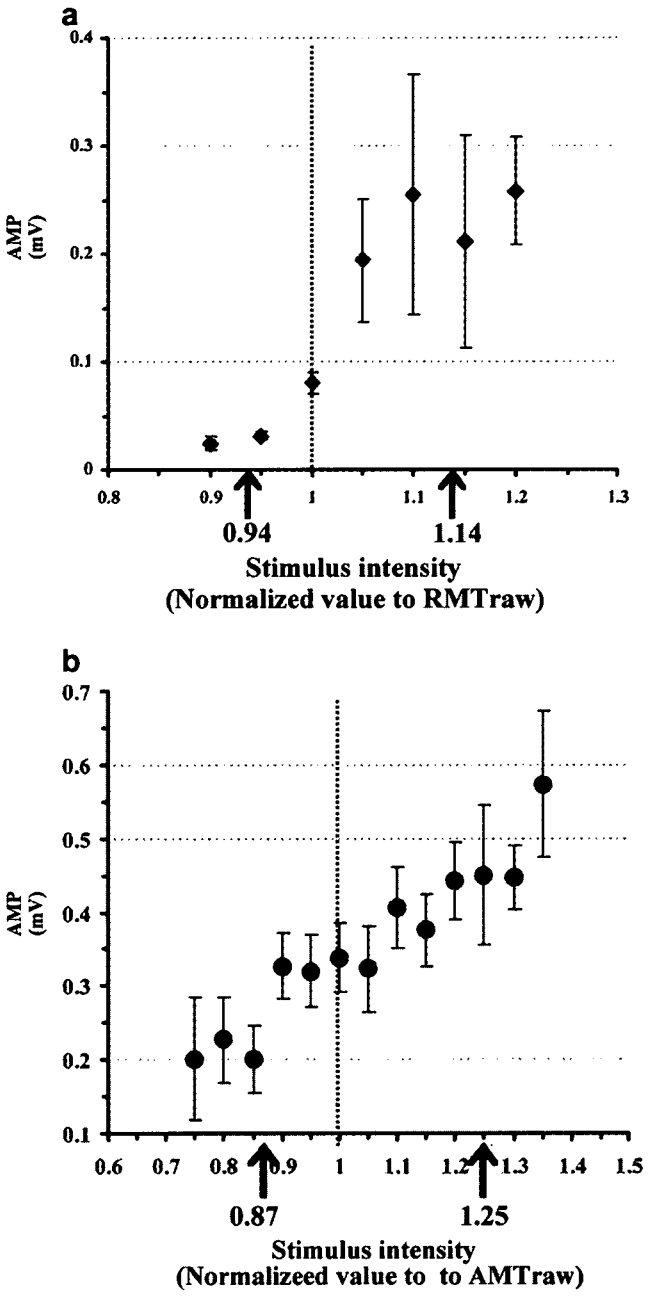

Fig. 1. Input–output curves in relaxed (a) and actively contracting FDI muscle (b). The ordinate plots the amplitude of MEPs (mean ± SE) across all subjects at each intensity of stimulation. The abscissa plots the intensity of TMS expressed relative to MT_{raw} which is given a value of 1.0. In each graph, the arrow to the right of the abscissa represents the mean value of MT_{mov} across all subjects whereas the left arrow shows the mean value of MT_{rec}.

AMT_{raw} evoked small MEPs in averaged records, indicating that corticospinal activity was still occurring. The implication is that AMT_{raw} can be suprathreshold for pyramidal tract activation, and therefore cannot be assumed to have effects limited to supraspinal structures. If estimation of corticospinal threshold is important then we recommend using AMT_{rec} since this is a more sensitive measure of motoneuronal activation and presumably nearer to a real physiological threshold for corticospinal activation. On average, this is equal to about 84% AMT_{raw}, which would be a useful alternative measure if AMT_{rec} is not available.

Where possible we recommend recording EMGs when determining the intensity for safe rTMS, otherwise MT_{movl} should be used instead of MT_{mov}. In that case, however, the examiner should be well trained to detect visible movement of the target muscle. We also propose that AMT_{raw} does not represent the threshold for evoking corticospinal input to spinal motoneurones.

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Median nerve somatosensory evoked potentials and their high-frequency oscillations in amyotrophic lateral sclerosis ☆

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Abstract

Objective: To investigate sensory cortical changes in amyotrophic lateral sclerosis (ALS), we studied somatosensory evoked potentials (SEPs) and their high-frequency oscillation potentials.
Methods: Subjects were 15 healthy volunteers and 26 ALS patients. Median nerve SEPs were recorded and several peaks of oscillations were obtained by digitally filtering raw SEPs. The patients were sorted into three groups according to the level of weakness of abductor pollicis brevis muscle (APB): mild, moderate and severe. The latencies and amplitudes of main and oscillation components of SEP were compared among normal subjects and the three patient groups.
Results: The early cortical response was enlarged in the moderate weakness group, while it was attenuated in the severe weakness group. No differences were noted in the size ratios of oscillations to the main SEP component between the patients and normal subjects. The central sensory conduction time (CCT) and N20 duration were prolonged in spite of normal other latencies.
Conclusions: The median nerve SEP amplitude changes are associated with motor disturbances in ALS. The cortical potential enhancement of SEPs with moderate weakness in ALS may reflect some compensatory function of the sensory cortex for motor disturbances.
Significance: The sensory cortical compensation for motor disturbances is shown in ALS, which must be important information for rehabilitation.

Keywords: Somatosensory evoked potential; High-frequency oscillation; Amyotrophic lateral sclerosis

1. Introduction

Somatosensory evoked potentials (SEPs) have been studied in amyotrophic lateral sclerosis (ALS): some reports revealed no SEP abnormalities (Cascino et al., 1988; Chiappa, 1983; Oh et al., 1985), while others showed abnormalities in upper limb SEPs (Bosch et al., 1985; Cosi et al., 1984; Dasheiff et al., 1985; Radtke et al., 1986; Subramaniam and Yiannikas, 1990; Theys et al., 1999; Zanette et al., 1990) and lower limb SEPs (Georgesco et al., 1997; Matheson et al., 1986; Radtke et al., 1986; Subramaniam and Yiannikas, 1990; Zanette et al., 1996). They are still controversial.

The high-frequency oscillation (HFO), one newly developed SEP analysis, is considered to reflect some sensory cortical information processing. The N20 potential is considered to reflect an initial excitation of neurons in area 3b (Allison et al., 1991; Tiihonen et al., 1989). In contrast, the generators of HFOs remain to be determined, even though several candidates have been proposed; such as brainstem, thalamus, thalamocortical presynaptic action potentials and somatosensory cortex (Curio et al., 1997; Eisen et al., 1984; Gobbelé et al., 1998, 2004; Hashimoto et al., 1996, 1999; Klostermann et al., 2002; Shimazu et al., 2000). We

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previously reported changes in HFOs in movement disorders (Mochizuki et al., 1999). However, the high-frequency oscillations (HFOs) of median nerve SEP have not been studied in ALS.

In addition, several studies using transcranial magnetic stimulation (TMS) showed that pure sensory input facilitated the primary motor cortex (M1) (Hamdy et al., 1998; Kaelin-Lang et al., 2002; Ridding et al., 2000; Rosenkranz and Rothwell, 2003; Rosenkranz and Rothwell, 2004; Terao et al., 1995, 1999) and a number of gating studies confirmed an attenuation of the early cortical responses to median nerve stimulation by motor interferences (Gobbelé et al., 2003; Kakigi et al., 1995; Mochizuki et al., 2004; Rossini et al., 1999; Tanosaki et al., 2002; Valeriani et al., 1999). These reports indicate there are several kinds of interactions between the motor and sensory systems in humans. Those integrations of the sensorimotor information must be necessary for precise and purposeful movements.

One functional magnetic resonance imaging study revealed cortical reorganization in ALS (Konrad et al., 2002). They concluded that a partial compensation between motor areas was a strategy to optimize motor performances in ALS. We hypothesize that similar compensation for motor dysfunction might occur in the somatosensory system in ALS.

To solve the above-mentioned three issues; (1) the inconsistency of SEP results, (2) the lack of HFO studies, (3) sensory compensation for weakness, in the present communication, we studied median nerve SEPs in patients with ALS.

2. Subjects and methods

2.1. Subjects

We studied 26 patients with ALS. The diagnosis was based on the revised El Escorial criteria (Brooks et al., 2000): 15 had definite, five probable, and six probable-laboratory-supported ALS at the time of the examination. Their clinical features are summarized in Table 1. The age ranged from 33 to 78 years (mean ± SD; 62.1 ± 10.2 years). The duration of the illness at the time of our experiment ranged from 3 to 48 months (16.7 ± 15.9 months).

Table 1
Clinical characteristics of the patients F, female: M, male

Case No.	Age (year)	Sex	Disease duration (months)	El Escorial criteria	Clinical onset	Recorded side	Severity
1	33	M	7	Probable-laboratory-supported	Limb	Right	Mild
2	43	M	6	Probable-laboratory-supported	Limb	Right	Mild
3	45	M	14	Probable-laboratory-supported	Limb	Left	Mild
4	52	M	26	Probable	Limb	Right	Severe
5	57	M	14	Definite	Bulbar	Right	Mild
						Left	Mild
6	57	M	13	Definite	Limb	Left	Severe
7	58	M	12	Probable	Limb	Left	Mild
8	59	F	6	Probable	Limb	Right	Moderate
9	59	F	3	Definite	Limb	Right	Mild
						Left	Mild
10	60	F	9	Probable	Bulbar	Right	Mild
						Left	Mild
11	62	M	11	Probable	Limb	Left	Mild
						Right	Mild
12	63	F	20	Definite	Limb	Left	Mild
13	64	M	35	Definite	Bulbar	Right	Mild
14	64	M	36	Definite	Limb	Right	Severe
15	64	F	6	Definite	Bulbar	Right	Mild
						Left	Moderate
16	64	F	3	Definite	Limb	Right	Mild
17	66	M	48	Probable-laboratory-supported	Limb	Left	Mild
18	68	M	24	Definite	Limb	Right	Mild
						Left	Moderate
19	68	F	72	Definite	Limb	Right	Mild
						Left	Mild
20	69	M	10	Definite	Limb	Right	Severe
						Left	Severe
21	70	F	10	Definite	Bulbar	Right	Moderate
22	71	F	10	Probable-laboratory-supported	Limb	Right	Mild
						Left	Severe
23	72	F	11	Definite	Bulbar	Right	Mild
						Left	Mild
24	73	M	8	Definite	Limb	Right	Moderate
25	74	M	4	Definite	Limb	Left	Moderate
26	79	M	24	Probable-laboratory-supported	Limb	Left	Mild

Fifteen healthy, age matched, volunteers were also studied. They all were free from neurological or other diseases and their ages ranged from 41 to 83 years (60.9 ± 12.4 years).

The purpose of the study was explained to every subject, and the informed consent to participation in the study was obtained from all the subjects. The study was approved by the Ethics Committee of the University of Tokyo.

In the patients, the right median nerve was stimulated in nine subjects, left in seven, and both in 10 (Table 1). In total, 36 SEPs were obtained from 26 patients. In the 15 healthy volunteers, the right median nerve was stimulated in 10 and both in five, and 20 SEPs were recorded in total. Because the amplitudes and latencies of every SEP component did not differ significantly between two sides ($P > 0.1$, unpaired Student's t-test), normal values were made from all the results obtained from both sides.

To see the clinico-physiological correlations, the strength of a median nerve innervated abductor pollicis brevis (APB) muscle at the stimulated side was assessed at the time of examination in ALS patients by manual muscle testing using the Medical Research Council (MRC) scale (scores from 0 to 5). The studied limbs were divided into three groups according to the muscle strength of APB: muscle strength of MRC 5-4 (defined as mild weakness group), MRC 3 (moderate), and MRC 2-0 (severe). In the 36 limbs, 24 APB muscles had mild weakness (MRC 5-4), 6 moderate (MRC 3), and 6 severe (MRC 2-0) (Table 2). In these patients, the level of weakness correlated with the degree of recruitment reduction in needle electromyographic studies of APB. There were no significant differences in age and body height among the four groups (mild, moderate, severe weakness and control) (age: [$F(3, 52) = 0.636$, $P = 0.595$]; body height: [$F(3, 52) = 0.516$, $P = 0.674$]) and in duration of the illness among the three groups ([$F(2,33)=0.681$, $P = 0.513$]) (Table 2).

2.2. Data recordings

Somatosensory evoked potentials (SEPs) were elicited after electrical stimulation of the median nerve at the wrist using a constant current square wave pulse (0.2 ms duration). The anode was placed over the median nerve at the wrist, and the cathode 2.5 cm proximal to the anode. The stimulus intensity was about 4 times sensory threshold which was almost equivalent to 1.5 times motor threshold. The stimuli were delivered at a repetition rate of 2–3 Hz. Since the alertness has a profound influence on the HFOs (Emerson et al., 1988; Gobbelé et al., 2000; Yamada et al., 1988), we kept the subjects awake during the experiments. The alertness was monitored by EEG recordings from a midfrontal electrode (Fz) of the international 10-20 system with ear (A1) reference. For SEPs, recording electrodes were placed at two locations: the spinous process of C6 (CV 6), and C3′ or C4′ (2 cm posterior to the C3 (C4) of the international 10-20 system), with Fz reference. To confirm that stimuli activated peripheral nerves adequately in the experiments, the electrode was placed on the ipsilateral Erb's point for recording the N9 potential. The electrode impedances were kept less than 5 kΩ. Responses were amplified with filters set at 20 and 3000 Hz. 1000–2000 responses were averaged and then digitized with an analogue to digital converter at a sampling rate of 20 kHz. An epoch of 50 ms duration was obtained. At least two averaged responses were obtained under the same conditions to ascertain the reproducibility of SEPs.

We used C3′ (C4′)-Fz montage for recording HFOs because it is the best montage for recording oscillation potentials clearly (Curio et al., 1994; Hashimoto et al., 1996; Mochizuki et al., 1999). The oscillation potentials were obtained by digitally filtering raw SEPs from 500 to

Table 2
Main clinical characters and mean (±SD) latencies of SEP and number of HFOs for different groups of subjects

Group of subjects (Number of limbs)	Control ($N = 20$)	ALS total ($N = 36$)	Mild ($N = 24$)	Moderate ($N = 6$)	Severe ($N = 6$)
Age (years)	63.1 ± 12.8	62.9 ± 9.2	61.4 ± 10.0	68.0 ± 5.7	63.7 ± 7.6
Body height (cm)	156.8 ± 7.9	159.1 ± 6.7	158.9 ± 7.0	156.6 ± 2.9	160.8 ± 7.7
Disease duration (months)	–	17.0 ± 16.9	18.7 ± 19.4	9.7 ± 7.3	17.5 ± 11.0
Latency					
N13 onset (ms)	11.7 ± 0.5	11.5 ± 0.7	11.4 ± 0.8	11.9 ± 0.5	11.8 ± 0.6
N13 peak (ms)	12.7 ± 0.4	12.5 ± 0.7	12.4 ± 0.8	13.2 ± 0.4	12.7 ± 0.5
N20 onset (ms)	15.7 ± 0.7	15.5 ± 0.8	15.5 ± 0.8	15.8 ± 0.6	15.4 ± 1.1
N20 peak (ms)	18.8 ± 0.7	19.2 ± 0.9	19.1 ± 0.9	19.6 ± 1.5	19.2 ± 0.4
P25 peak (ms)	23.2 ± 2.0	24.9 ± 1.7*	25.1 ± 1.4*	24.9 ± 1.9	24.2 ± 2.5
N20 onset–N20 peak (ms)	3.0 ± 0.7	3.6 ± 0.7*	3.6 ± 0.6	3.7 ± 0.8	3.9 ± 1.0
N13 peak–N20 peak (CCT) (ms)	6.1 ± 0.7	6.6 ± 0.7*	6.5 ± 0.7	7.1 ± 0.7	6.7 ± 0.3
N13 onset–N20 onset (ms)	4.1 ± 0.5	4.0 ± 0.5	4.0 ± 0.5	4.2 ± 0.5	4.4 ± 0.3
HFO: Number of peaks					
Onset–N20 peak	2.4 ± 0.5	2.4 ± 0.4	2.2 ± 0.4	2.5 ± 0.5	2.2 ± 0.4
Later than N20 peak	3.2 ± 0.7	2.9 ± 0.7	2.9 ± 0.7	3.5 ± 0.5	2.7 ± 0.5
CMAP (APB) (mV)	13.9 ± 2.6	6.9 ± 5.0*	9.5 ± 4.1**	6.5 ± 3.4**	0.7 ± 0.7**

Age, body height and SEP latencies of 15 control subjects and 24 ALS patients. "N" indicates number of studied limbs. 20 limbs from normal subjects and 36 limbs from the patients.
Asterisk indicates significant difference from the control data (*$P < 0.05$, **$P < 0.01$).

1000 Hz (Butterworth type, 12 dB/octave), using a Neuropack Micro computer system (Nihon Kohden, Japan).

In wide-band SEPs, onset latencies of N13 (N13o) and N20 (N20o), peak latencies of N13 (N13p), N20 (N20p) and P25 (P25p) components were measured. Sonoo et al. (1996) reported that the N13 (they named N13′ to distinguish from the components recorded with a non-cephalic reference) onset in the CV6-Fz lead nearly coincided with the P13/14 onset. The origin of P13/14 is thought to be localized at a small region around foramen magnum and cuneate nucleus, whereas the N13 onset and P13/14 onset are not always coincident completely (Sonoo et al., 1996). On the basis of these facts, special attention must be needed to evaluate latencies. Therefore, we measured the interval between the onsets of N13 and N20 (N13o–N20o), which may represent conduction from a site around the foramen magnum to the sensory cortex, to evaluate the intracranial sensory conduction. We also measured an interval between N13 peak and N20 peak (N13p–N20p) which was conventionally called the central sensory conduction time (CCT). We measured amplitudes of N20 onset-peak (N20o–N20p) and N20 peak-P25 peak (N20p–P25p) in wideband recordings.

For identification of HFOs, we used the same method as that described by Hashimoto and colleagues (Nakano and Hashimoto, 1999, 2000; Inoue et al., 2004). The oscillations after the onset of primary cortical response (N20) with an amplitude of twice or larger than that of background noises were considered as components of HFOs. The noise level was measured between 8 and 14 ms after the stimulus. Because early and late HFOs are considered to be generated by different mechanisms (Haueisen et al., 2000; Klostermann et al., 1999, 2000; Mochizuki et al., 1999; Nakano and Hashimoto, 1999), we analyzed two parts of HFOs separately: the early HFOs (HFOs from the onset to peak of N20) and the late HFOs (HFOs later than the N20 peak). The HFO whose peak was identical to the N20 peak was treated as a component of early HFOs (Inoue et al., 2004). We calculated the average amplitude of the early and late HFOs and compared these values between the patients and normal subjects. The amplitude ratios of early or late HFOs to the N20o–N20p were used to evaluate relations between SEP main components and HFOs. We also counted the number of negative peaks of HFOs within early and late parts.

We also recorded compound muscle action potentials (CMAPs) from APB and measured their sizes. Their relation to the muscle strength assessed by the MRC scale (de Carvalho and Swash, 2000) was also evaluated. CMAP was recorded with surface Ag/AgCl electrodes: an active electrode placed over the muscle belly and a reference electrode over the tendon. A ground electrode was placed between the wrist and the recording electrode. A conventional bipolar electrical stimulation (0.2 ms duration, cathode distal) was applied to the median nerve at 3 cm proximal to the distal crease of the wrist. Supramaximal stimulation was ensured by increasing the stimulus intensity until no further enlargement was obtained in CMAPs (Kimura, 2001). Usually, we recorded CMAPs elicited at intensity 1.3 times the minimal intensity to elicit maximal CMAPs. Responses were amplified with filters set at 2 Hz and 3 kHz. Sampling rate was 20 kHz. The peak to peak amplitude was measured.

2.3. Data analysis

We compared latencies (N13o, N13p, N20o, N20p, P25p, N13o–N20o, N20o–N20p, and N13p–N20p) and the numbers of HFOs peaks at each part between the patients and healthy volunteers using unpaired Student's *t*-test. We also compared those latencies, amplitudes (CMAP, N20o–N20p and N20p–P25p) and the numbers of HFOs peaks among four groups (control, mild, moderate, and severe weakness) using one way analysis of variance (ANOVA), and post hoc comparisons were made with Bonferroni method to compensate for multiple comparisons. P values less than 0.05 after compensation for multiple comparisons were considered to be significant.

3. Results

In all examined subjects, SEPs and HFOs were recorded clearly.

3.1. SEP amplitudes, HFO amplitudes and number of HFOs peaks

Typical SEPs and HFOs of patients with different levels of weakness are shown in Fig. 1. Two SEPs are superimposed in every trace. In the patient with moderate weakness (case 18), the N20 was larger than that of the patient with mild weakness (case 12). In the patient with severe weakness (case 6), the N20 was abnormally small though the amplitudes of N9 and N13 were normal (Fig. 1c). The amplitudes of early and late HFOs were in parallel with those of main components of SEP (Fig. 1b).

The N20o–N20p and N20p–P25p amplitudes of all subjects were sorted by the levels of weakness and plotted (Fig. 2). One way ANOVA revealed that the group of subjects had a significant effect on both N20o–N20p [$F(3,52) = 10.904$. $P < 0.001$] and N20p–P25p amplitudes [$F(3,52) = 11.368$. $P < 0.001$]. Post hoc analysis revealed following differences. The N20o–N20p amplitude of moderate weakness group (mean ± SD; 5.40 ± 1.81 μV) was significantly larger than those of healthy control (2.38 ± 1.11; $P < 0.001$), mild (3.45 ± 1.50; $P = 0.018$) and severe weakness groups (1.43 ± 1.17; $P < 0.001$). The N20p–P25p amplitude of moderate weakness group (9.92 ± 2.44) was significantly larger than that of control (4.60 ± 1.64; $P = 0.001$). Its amplitude of severe weakness group (1.76 ± 1.74) was significantly smaller than that of mild (6.80 ± 3.54; $P = 0.001$) or moderate weakness group ($P < 0.001$), whereas it was not significantly smaller than the size of healthy subjects ($P > 0.1$).