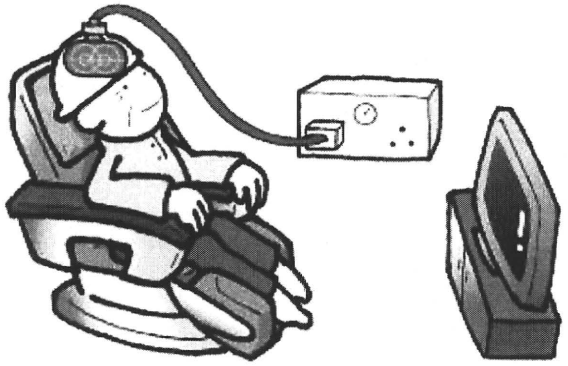

図8
在宅において，症状改善を目的とした経頭蓋磁気刺激が可能となれば，図のように自宅でマッサージチェアに腰掛けて，テレビを見ながら，経頭蓋磁気刺激療法を繰り返すことになろう。

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脳卒中後疼痛に対する脊髄硬膜外電気刺激療法

一話週

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慢性疼痛が最近クローズアップされているが、最も治療に難渋して、増加傾向にあるのが脳卒中後疼痛であると考えられる。日本の食事が欧米型になるにつれて、脳卒中も変化し、大型の出血、主幹動脈の閉塞が減少し、小型の出血、穿通枝梗塞が増加している。結果として麻痺は比較的軽症であるが、痛みで困る症例が増加している。

痛みの種類としては、複合性局所疼痛症候群（complex regional pain syndrome；CRPS）とされる肩手症候群と中枢性脳卒中後疼痛（central post-stroke pain；CPSP）の2種類である。前者は脳卒中後に肩関節の亜脱臼を来し、同側の手に浮腫を伴い、肩の拘縮と上肢の運動障害、自律神経の障害によると思われる皮膚温や発汗の異常を呈する。後者の疼痛の性状としては、「ぴりぴり、ひりひり」などの火傷の後のような痛みと、「しびれ痛い」というのが代表的で、「切られる」「針で刺されるようだ」などと表現するケースもある。冷気が当たる、触覚刺激が疼痛を誘発することがあり、異痛症（allodynia）と呼ばれる。疼痛は一般に出血、梗塞を起こしてすぐに痛くなるというよりは、痛みは遅れて出現し、増していくことが多い。疼痛はいったん熟睡してしまうと痛くない。しかし朝目覚めると痛みを感じ、程度は変動するが1日中痛みを感じる。

肩手症候群とは

肩手症候群は、経験的に脳卒中片麻痺の5％未満に生じ、麻痺の重症度、痙縮、感覚障害、肩関節亜脱臼との相関が示唆されている。肩手症候群は脳卒中発症2週から3カ月に見られ、5カ月を過ぎるとほとんどないとされる。CPSP、痙縮、感覚障害との鑑別が必要である。肩手症候群の明確な診断基準はないが、指の腫脹、安静時または運動時の肩・指の痛み、手の発赤などを特徴とする。

治療としてはステロイドの経口投与が最も有効とされ、三環系抗うつ薬、抗てんかん薬のガバペンチンも選択される。消炎鎮痛薬でもケトプロフェンが抗プロスタグランジン作用とともに、抗ブラディキニン作用、抗プロスタサイクリン作用があるのでよく使用される。研究段階として、ボツリヌス毒素注射も有効と言われる。同時にリハビリ訓練も機能維持、改善を目的として重要である。侵襲的治療として、脊髄硬膜外電気刺激（spinal cord stimulation；SCS）、交感神経節ブロックも有効性が報告されているが、肩手症候群

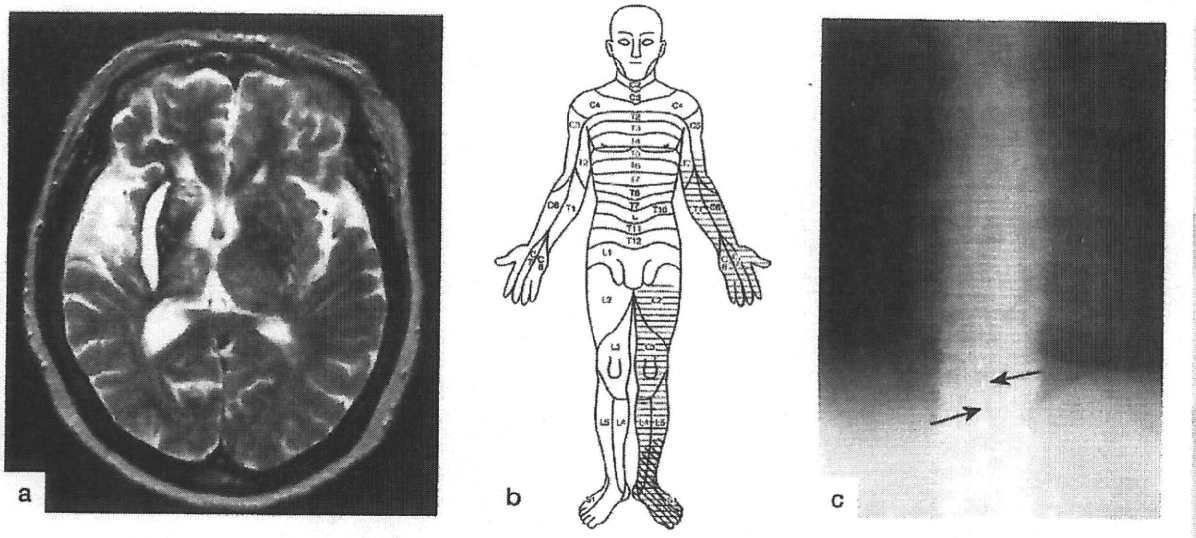

図　脊髄硬膜外電気刺激療法（SCS）の概要

a：右被殻出血　左半身が痛いが，特に手足が痛く，その中でも足が痛いのが典型的症例である．
b：斜線部分が痛みの部位である．
c：胸椎に２本電極（矢印）を留置し，頸椎にも同様に２本電極を留置することにより，１個の刺激装置で多彩に刺激を行うことが可能である．

の場合、自然軽快もあるので慎重な対応が必要である。

中枢性脳卒中後疼痛（CPSP）に対するSCS

一方、慢性化しやすいのはCPSPである。投薬治療が中心であり、肩手症候群と同様の抗うつ薬、抗てんかん薬が使用されることが多いが、有効性は高いとは言えない。結局、様々な治療をしながら、我慢の日々を患者は送っている。欧米では、CPSPに対するSCSは有効性が高くないので、施行すること自体、推奨されていない。しかし、日本では幸にして保険償還されるので、筆者らはSCSトライアルを積極的にCPSPの患者に対して施行している。

SCSの概略は、現在の刺激装置として日本で認められているのはメドトロニクス社とセントジュード社の２社の製品である。刺激装置も進化して、16極刺激が可能となり、充電式小型装置も選択できるようになってきた。CPSPの場合、痛みが四肢の末梢に強いことが多いので、頸椎、（胸）腰椎の両方に電極を留置することで、対応が可能である（図）。本療法の欠点としては、留置した後MRI撮影すると刺激装置が壊れることがあり、MRI撮影が自由にできないことである。刺激装置のMRI対応化が望まれる。

さて、筆者らがこれまで施行した経験では、まずトライアルを施行して、除痛効果があるか、患者が埋め込みを希望するかどうかを十分に見極めた上で、刺激装置を埋め込んできた。それらの割合はトライアル施行した患者の４割ほどである。これらの患者は痛みが30％以上低下し、長期に使用を継続している[1]。この数字は満足できるものではないが、いずれも難治性の慢性痛であり、他の有効な治療法がない以上、選択肢として加えるべきと考えている。

CPSP治療の今後

CPSPの治療として、大脳一次運動野刺激療法も選択肢としてあるが、開頭術を要し侵襲性が高い。将来的には、非侵襲法である反復経頭蓋磁気刺激療法も選択肢に加えられよう。SCSは侵襲性が高いとは言えず、今後のデバイスの工夫によっては、もっと重要度を増す可能性があると考えられる。

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診断・治療

パーキンソン病に対する反復経頭蓋磁気刺激(rTMS)治療

Therapy of Parkinson's disease with repetitive transcranial magnetic stimulation (rTMS)

特集

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パーキンソン病

Key words パーキンソン病 反復経頭蓋磁気刺激 高頻度刺激

1985年にBarkerらは経頭蓋磁気刺激装置を開発した．本方法は非侵襲で，安全であるため，中枢神経系の研究に広く普及していき，反復刺激することで神経難病の治療が可能になるのでないかと考えられ，パーキンソン病を反復経頭蓋磁気刺激(rTMS)で治療しようとする臨床研究が世界的に行われており，有効性を報告するものと無効を報告するものとが存在する．すでに報告総数は164件を超えている[3]．意見が分かれる原因としては，rTMSの刺激強度，刺激頻度，1日の刺激回数，刺激部位，刺激期間等が報告者で異なるためと考えられる．

今回，世界の代表的報告例をレビューし，パーキンソン病治療としての可能性についてまとめた．

rTMSの方法

まず刺激方法として高頻度刺激(5，10，25Hz)と低頻度刺激(0.2，0.5Hz)に分けることができる．刺激の強度としては，80～120％のmotor thresholdが採用されている．刺激コイルとしては円形コイルか8の字コイルが使用されているが，ほとんどが後者である．刺激部位としては一次運動野(M1)，背側前頭前野(DLPFC)が代表的である．rTMSの機器としては，Magstim社とMagVenture社(かつてのDantec社)がほとんどで，なかでも前者の占める割合が大きい．

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メタアナリシス

Elahiがsystematic review[3]をまとめているので，まずその結果を報告し，その補完を行うことにする．

Elahiは，164件のなかから10件の臨床研究報告を選び，275例を抽出した．そのうちシャム刺激が行われていたのは125例であり，これを対照群とした．一方，135例をrTMS群とした．これら10件の臨床研究はすべてrandomized controlled clinical studyである．ほとんどの研究では，UPDRSの点数は治療割付に対してblindになっている．DelOlmo[2]とIkeguchi[6]の論文ではblindかどうかが不明である．Elahiらも10の臨床研究

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を2群に分けて解析しているが，1群は刺激頻度が1Hzを超えるもの(高頻度刺激)，もう1群は刺激頻度が1Hz以下のもの(低頻度刺激)に分けている．理由としては一次運動野を刺激したときに，高頻度刺激では皮質興奮性変化に働き，低頻度刺激では皮質抑制性変化に働くことが報告されているからである．152例が高頻度刺激，123例が低頻度刺激である．Lefaucheaur et al[9]の研究は高頻度，低頻度の両者をシャム刺激と比較しているので，両者ともデータを採用している(**表1**)．

7つの高頻度刺激によるパーキンソン病治療の報告は，刺激部位がM1またはDLPFC，刺激回数も200～2,250回とさまざまで，コイルはすべて8の字コイルで施行されているが，すべての報告で，有意に運動機能の改善を認めた(**図1**)．それに対して4つの低頻度刺激による治療では，有意な治療効果が見出せていない．

シャム刺激も一定ではなく5つの報告ではシャムコイルを使用し，3つの報告ではコイルの角度を変化させ，1つの報告では後頭部を刺激し，1つの報告ではコイルの端を頭部にあてただけである．しかし，高頻度刺激の効果判定はどのシャム刺激でも同様であり，シャム刺激がさまざまであることは大きな問題ではないと考えられた．UPDRSのmotor sectionの評価は広く使用され，信頼でき，価値が高い．このメタアナリシスによって，高頻度刺激を行うことで，パーキンソン病患者の機能低下した脳領域を制御して，臨床的に有意な運動機能回復を起こしたと考えられる．一方，低頻度刺激はより安全だが，そのような効果がない．しかし，低頻度刺激は，このメタアナリシスでは評価していないドーパミン誘発のジスキネジアには効果があるかもしれない．

高頻度刺激はけいれん誘発を含めた有害事象の可能性があるが，安全性ガイドラインにそって施行されれば，一般的には安全である[12]．このメタアナリシスでは，高頻度刺激がパーキンソン病の運動機能改善に非常に有望な治療法となる可能性が示唆された．

補足運動野(SMA)高頻度刺激

Okabeらは99例を無作為に本刺激とシャム刺激に割り当てて，double blind placebo-controlled studyを行った．週1回，両側のSMAを5Hz，10秒間rTMSして50秒のインターバルで，20トレイン施行した．強度は110% active motor thresholdである．結果は治療開始4週間後よりシャム刺激に対して，有意にUPDRSスコアの改善が得られた(**図2**)．この報告はElahiらのメタアナリシスの後の報告であるが，やはり高頻度刺激は症状を改善した[11]．

連日rTMS治療の報告

エジプトからの報告で興味深いものがある[8]．

55例のパーキンソン病患者で，全例，定期の投薬治療を受けていない．投薬を少なくとも臨床研究の1週間前から受けていない．ヤールのstage Ⅰ-Ⅱの10例には25Hzで両側M1の手と足の領域を刺激した(グループ1)．他の45例ではヤールのstage Ⅲ-Ⅳで，病歴が長かった．うち25例は，25Hzで両側M1の手と足の領域を刺激した(グループ2)．次の20例はランダムに10例ずつ2群に分けた．10例は10Hzで両側M1の手と足の領域を刺激した(グループ3)．他の10例は後頭部(inionの2cm上方)を25Hzで刺激した(グループ4)．8の字コイルのDantec社製を使用した．M1の両足の領域をグループ1，2，3で1,000回ずつ刺激し，右左の順にM1の手の領域を1,000回ずつ刺激した．強度は100% resting motor thresholdである．25Hzは4秒間で，50秒のインターバルで10トレイン施行して，計1,000回刺激した．グループ3は10Hz(20トレイン；それぞれ5秒間で，50秒のインターバル)．1日1回，6日継続を行った．グループ1，2は1，2，3ヵ月後に3日ずつの追加刺激を施行し，グループ3は1ヵ月後だけ3日間の追加刺激を施行した．

表1 Summary of included studies

Study	Blinding	Mean age (yr)	PD duration (yr)	Men/ women	H&Y stage	Evaluation time after rTMS	PD drug status	rTMS parameters						Part of UPDRS used	UPDRS after sham rTMS	UPDRS after real TMS
								Intensity	Pulses per day	Days	Frequency (Hz)	Coil	Site			
Siebner et al.,2006[15]	Nonblinded	57		7/3	1-2.5	1hr	Off	90% MT	2,250	1	5	F8	M1	Part Ⅲ	24.7±7.4	18.0±6.3
Okabe et al.,2003[11]	Blinded rater	67.2	8.8±5.1	48/37		16wk	Off	110% MT	100	1	0.2	C	M1	Part Ⅲ	20.7±12.1	24.8±14.1
Shimamoto et al.,2001[14]	Blinded rater	65.1	7.0±4.2	7/2	1.5-4	2mo	On	0.31 T	60	1	0.2	C	Frontal	Total	45.0±21.1	22.6±12.2
del Olmo et al.,2007[7]	?	61.7		6/7	1-3	10days	On	90% MT	450	10	10	F8	DLPFC	Part Ⅲ	26.5±12.2	25.9±16.4
Khedr et al.,2003[7]	Blinded rater	57.7	3.26±2.8	23/13	2-3	1mo	Off	120% MT	2,000	10	5	F8	M1	Part Ⅲ	23.7±7.6	15.6±6.5
Fregni et al.,2004[1]	Blinded rater	65.6	7.5	26/16	1-4	8wk	Off	110% MT	200	10	15	F8	Left DLPC	Part Ⅲ	40.1±17.6	34.5±15.6
Lomarev et al.,2006[10]	Blinded rater	64.5	13.8±6.8	15/3	2-4	1mo	On	100% MT	1,200	1	25	F8	Bilateral DLPFC	Part Ⅲ	25.4±11.1	22.0±8.7
Boggio et al.,2005[3]	Blinded rater	65.2		15/10		8wk	On	110% MT	200	10	15	F8	Left DLPFC	Part Ⅲ	37.3±16.9	27.7±11.7
Ikeguchi et al.,2003[6]	?	68.8	7.8±4.5	12subjects	1-4	Immediate	Off	70% output	30	6	0.2	C	Prefrontal	Part Ⅲ	−25±12[a]	−24±10[a]
Lefaucheur et al.,2004[9,11]	Blinded rater	64		7/5	2.5-4	Immediate	Off	80% MT	600	1	0.5	F8	Left M1	Part Ⅲ	−32±10[a]	−28±10[a]
Lefaucheur et al.,2004[9,12]	Blinded rater	64		7/5	2.5-4	Immediate	Off	80% MT	2,000	1	10	F8	Left M1	Part Ⅲ	−32±10[a]	−28±10[a]

PD duration and UPDRS scores are expressed as mean＋SD.

PD：Parkinson's disease H&Y：Hoehn and Yahr scale rTMS：repetitive transcranial magnetic stimulation MT：motor threshold T：tesla F8：figure of eight C：circular M1：motor cortex DLPFC：dorsolateral prefrontal cortex UPDRS：Unified Parkinson's Disease Rating Scale

(Elahi B, et al：Mov Disord 24：357-363, 2009より)

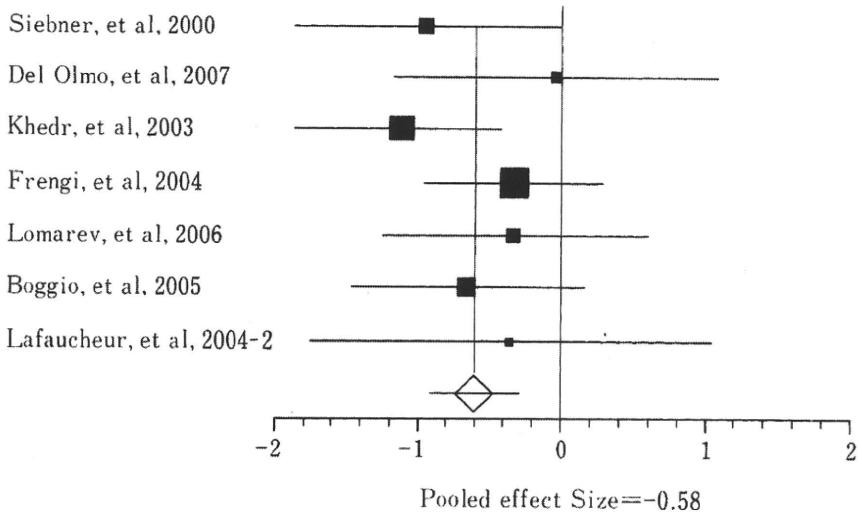

図 1
高頻度刺激での有効性を UPDRS motor section で評価した個々の報告と，全体をまとめたものである．四角の大きさがサンプルのサイズを表している．(文献 3 より)

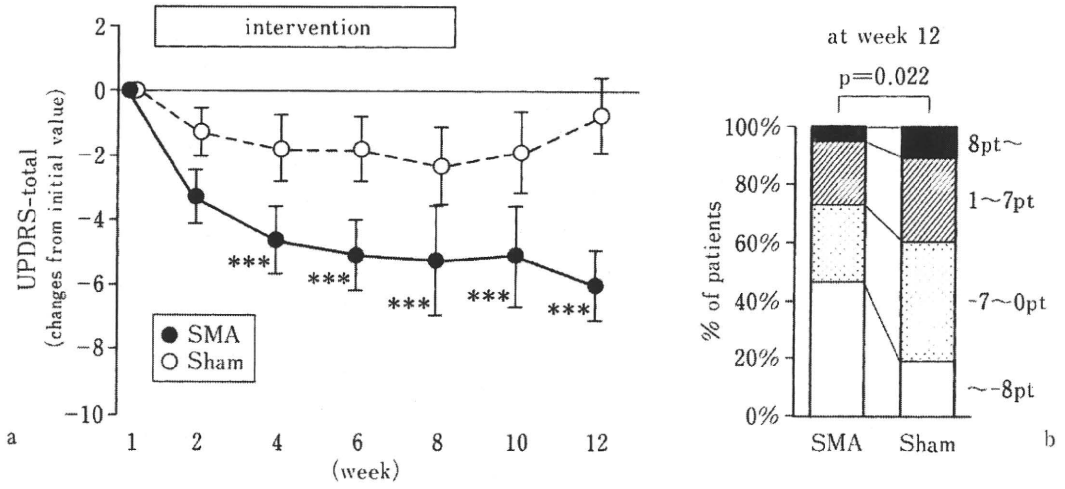

図2 UPDRS score の変化を示した(mean+SE)
4 週から12週まで SMA 高頻度刺激によって有意な症状改善が得られたのに対して，シャム刺激では変化が見られない．(文献 5 より)

25m の歩行試験，self assessment scale，キーボードタッピング試験で運動機能を評価した．

1. 結果(図3)

全例，試験は履行できた．時折，一時的な頭痛以外，明らかな副作用はなかった．軽症例であるグループ 1 のみ他のグループと比べて，rTMS 前の UPDRS が低く，キーボードタッピングと歩行が速かった．グループ 4 では UPDRS スコアは改善がなかった．他の 3 グループは 6 日間の継続治療のあと休止して30日目には UPDRS スコアは 6 日間の治療直後に比べて悪化していた．しかし 3 日間の追加治療で UPDRS スコアは改善をした．2，3 ヵ月後も同様であった．

キーボードタッピング試験の結果も UPDRS スコアとほぼ同様であった．グループ 3，4 では継続治療による改善効果がなかった．追加治療はグループ 1，2 で効果が見られた．

歩行スピードはグループ 4 では変化がなかった．グループ 3 の変化は小さかった．グループ 1，2 では UPDRS スコア，キーボードタッピングと同様に継続治療による経時的な改善が得られてい

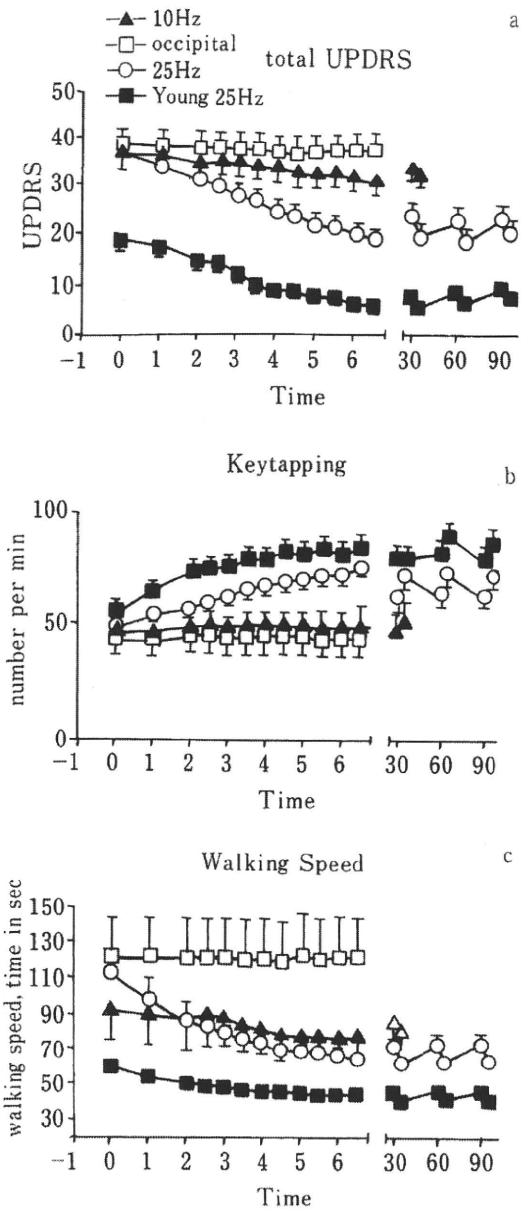

図3 a：UPDRS score, b：Key-tapping rate (per minute), c：walking speed

■：グループ1（軽症，ヤールⅠ-Ⅱ），●：グループ2（重症，ヤールⅢ-Ⅳ，25Hz刺激），△：グループ3（重症，ヤールⅢ-Ⅳ，10Hz刺激），□：グループ4（後頭部刺激，25Hz）

Time 0：治療前，Time 1：第1回治療直後，Time 2-6：治療の前後のスコア，Time 30，60，90：6日治療後の日数で，3日ずつ追加治療を行った前後のスコア，データはmean+SE，グループ4は6日間の治療で終了．グループ3は30日後のみ追加治療施行（文献8より）

る．追加刺激によってグループ2では改善が得られた．

Self assessment scoreではグループ4は改善なし（平均：19.5±3.3～19.5±3.3），グループ3で有意だが小さな改善（平均：18.6±2.8～17.7±2.8），グループ1，2では劇的な改善が得られた（グループ2：19.8±3.2～14.7±2.5，グループ1：15.7±1.6～12.6±2）．

2. 考　　察

この研究では，25HzのrTMS治療を6日間継続することで，30日後まで効果が持ちこされることが示された．Khedrらは過去に5Hz，120% RMTの10日連続治療が有効と報告しているが，その効果は今回の25Hzのものとあまり変わらないようである．

本研究では，抗パーキンソン病薬を内服していない患者でrTMS治療の有効性が確認された．これまでの報告は，すべて抗パーキンソン病薬を使用中の患者での有効性を報告していたので，今後，抗パーキンソン病薬とrTMS治療とのかかわりについての検討が必要となろう．パーキンソン病初期（グループ1）とパーキンソン病後期（グループ2）のともにrTMS治療が見られたことより，脳内のドーパミン含量にはrTMS効果は左右されない可能性が示唆された．しかし，過去の報告では抗パーキンソン病薬のON，OFFでrTMSの効果が異なるとの報告もある．歩行速度が改善することから，手，足のM1領域をrTMSすることで体幹症状も改善することが示された．

純粋無動症に対するrTMS治療の報告

われわれはドーパミン抵抗性の純粋無動症に対し，両側M1の下肢の領域を5Hz（10トレイン，10秒間刺激，50秒のインターバル，90% RMT）で500回ずつrTMSすることで，約6時間にわたってすくみ足など，運動機能改善が得られることを報告している[15]．また，その患者では両側の補足運動野（SMA）刺激では改善が得られなかった．その患者は，M1上に電極を留置して，継続的に電気刺激することで，症状改善が得られており，電気刺激の代わりに，連日rTMSを繰り返しても症状改善は得られたと私は推測している

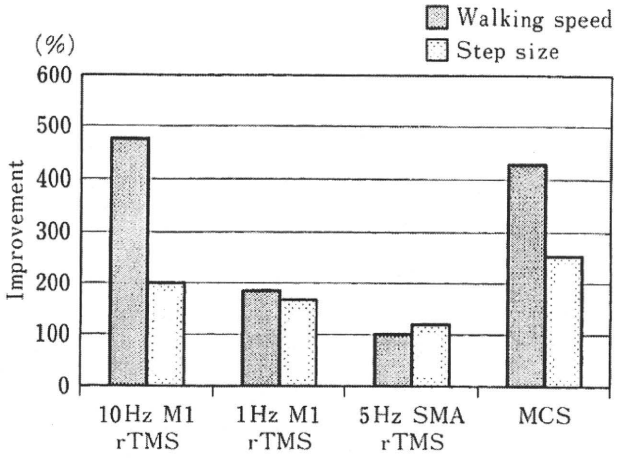

図 4

10Hz での M1刺激，および MCS(motor cortex stimulation，電極埋め込みでの刺激)が顕著に歩行速度と，歩幅が改善した．5 Hz の SMA 刺激は改善が見られなかった．(文献15より)

(図4)．

このように，パーキンソン病以外の神経変性疾患でも rTMS による治療の可能性はあると考えられる．

メカニズム

大脳皮質の後頭部(inion の 2 cm 上方)を高頻度刺激しても，症状改善は得られないようであるが[7)8)]，刺激部位として最も有効性の高い部位を見出す必要性がある．現在，報告されているのは M1，DLPFC，SMA であり，純粋無動症では SMA 刺激では有効性は得られなかった[15)]．連日 M1の高頻度刺激で血清中のドーパミン濃度が上昇するという報告もあるが，ドーパミン不応の純粋無動症で顕著な改善が得られるということは，脳内のドーパミン系とは関係のないメカニズムかもしれない．今後，刺激部位，パラメータによる脳内での変化の詳細な検討が必要となろう．

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BRAIN STIMULATION

RETROSPECTIVE STUDY

Impact of Subthalamic Nucleus Stimulation on Young-Onset Parkinson's Disease

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ABSTRACT

Objective. To clarify the efficacy of subthalamic nucleus (STN) stimulation in young-onset Parkinson's disease (PD), we compared the effects of STN stimulation on the motor symptoms between young-onset PD (YOPD) and late-onset PD (LOPD). **Methods.** We analyzed the effects of STN stimulation on motor function and motor fluctuations in 15 patients with YOPD, and 113 patients with LOPD who underwent STN stimulation during the same period. The Unified Parkinson's Disease Rating Scale (UPDRS) was evaluated during the on-period and off-period, which are defined as the times at which the motor symptoms are the best and worst during the daily active time with sustaining anti-parkinsonian drugs. The dyskinesia severity rating scale (DSRS) also was employed to assess the severity of peak-dose dyskinesia. We analyzed the changes in levodopa equivalent daily dose (LED), motor fluctuations, DSRS, and UPDRS part 3 score after STN stimulation, and compared the changes in each score between the two groups (YOPD vs. LOPD). **Results.** The LED was reduced, and the on-off motor fluctuation index, dyskinesia rating scale score (on-period), and UPDRS part 3 score (on- and off-periods) were improved in both the YOPD and LOPD groups. The improvement rates of the UPDRS part 3 scores in both the on- and off-periods in the YOPD group were superior to those in the LOPD group. The results of multivariate logistic regression analysis demonstrated that YOPD itself is the best responder to STN stimulation. **Conclusions.** STN stimulation can reduce the LED and improve motor fluctuations in patients with YOPD. The effects of STN stimulation on the motor symptoms of YOPD patients are superior to those in LOPD. The present findings suggest that YOPD patients suffering from several problems related to pharmacological therapy are probably good candidates for STN stimulation.

KEY WORDS: *Brain stimulation, neuromodulation, Parkinson's disease, subthalamic nucleus, young onset.*

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Introduction

The motor symptoms of Parkinson's disease (PD) commonly develop above the age of 50 years, with a mean age of onset of around 60 years (1). However, there is a group of patients in whom the motor symptoms of PD begin at a younger age. Such patients are designated as young-onset PD (YOPD), and their age of developing PD is between 21 and 40 years (2). YOPD patients display several clinical features which are different from those of patients who develop PD at above 40 years old (late-onset PD; LOPD). In comparison with LOPD patients, levodopa is more effective for YOPD patients, while patients with YOPD often experience treatment-induced motor complications, such as on-off motor fluctuations and dyskinesia which develop from the introduction of levodopa treatment in a short year (3–6). Many patients with YOPD therefore suffer from such motor complications of levodopa in the prime time of their life.

Stimulation of the subthalamic nucleus (STN) can ameliorate the on-off motor fluctuations and levodopa-induced dyskinesia (7–9). The effects of STN stimulation on the cardinal motor symptoms of PD are similar to those of a maximal dose of levodopa in each patient (8,10–12), and a presurgical good levodopa-reactivity in terms of motor disabilities is known to be a predictive factor for postsurgical improvement of motor function (9,13,14). Based on such clinical profiles of STN stimulation, YOPD patients can be regarded as the better candidates for STN stimulation therapy. However, although STN stimulation can improve the motor disability in patients with YOPD (15), it is not known whether the improvement effect of STN stimulation for YOPD patients is actually greater than that for LOPD patients. To clarify this issue, we examined the effects of STN stimulation on the motor symptoms of YOPD in comparison with LOPD.

Patients and Methods

Fifteen patients with YOPD underwent STN stimulation at our hospital (Itabashi Hospital, Nihon University School of Medicine) between October 2002 and August 2005. The characteristics of these YOPD patients are summarized in Table 1. We analyzed the effects of STN stimulation on motor function and motor fluctuations (i.e. on-off motor fluctuations and dyskinesia) in the YOPD patients preoperatively and at six months postoperatively. Furthermore, 113 non-YOPD patients who underwent STN stimulation during the same period also were analyzed for comparison with YOPD. Although the total 128 patients were clearly responsive to levodopa, their parkinsonian symptoms could not be controlled sufficiently with practically optimal pharmacological therapy. They also suffered from levodopa-induced side-effects, such as on-off motor fluctuations and dyskinesia. All patients underwent implantation of electrodes (model 3387; Medtronic, Inc., Minneapolis, MN, USA) and pulse generators for deep brain stimulation of the STN bilaterally. Preoperative and postoperative assessments of motor disability were performed using methods described in a previous publication (9). Briefly, the Unified Parkinson's Disease Rating Scale (UPDRS) (16) was evaluated during the on-period, which is defined as the time at which the motor symptoms are the best during the daily active time, and the off-period, which is defined the time at which the motor symptoms are the worst during the daily active time, with sustaining antiparkinsonian drugs. The preoperative characteristics of the two groups are summarized in Table 2. The preoperative mean levodopa equivalent daily dose (LED) (17) and UPDRS scores were not significantly different between the two groups (Table 2). The dyskinesia severity rating scale (DSRS) (18) was employed to assess the severity of peak-

TABLE 1. Characteristics of YOPD Patients

Patient	Sex	Age at onset (years)	Age at surgery (years)	Duration of PD (years)	Family history of PD
1	F	32	47	15	+*
2	M	30	44	14	–
3	F	34	42	8	–
4	M	34	42	8	–
5	M	39	52	13	–
6	F	31	49	18	–
7	F	23	53	30	–
8	F	39	62	23	–
9	M	35	55	20	–
10	M	38	66	28	+†
11	F	31	44	13	–
12	F	39	61	22	–
13	M	33	52	19	–
14	M	36	57	21	–
15	M	36	51	15	–

*Autosomal recessive juvenile PD; †sister is PD, mode of inheritance is unknown.
LOPD, late-onset PD; PD, Parkinson's disease; YOPD, young-onset PD.

TABLE 2. Patient Characteristics in the YOPD and LOPD Groups

Characteristic	YOPD	LOPD	*p* value
Sex (male, female)	8 M, 7 F	55 M, 58 F	
Age at onset (years)	34.0 ± 4.3	54.6 ± 6.9	<0.01
Age at surgery (years)	51.8 ± 7.4	64.4 ± 6.1	<0.01
Duration of PD (years)	17.8 ± 6.5	9.8 ± 4.9	<0.01
LED (mg/day)	641.0 ± 346.2	620.0 ± 316.9	NS
UPDRS part 2			
On-period	7.7 ± 5.9	9.9 ± 7.7	NS
Off-period	24.5 ± 9.2	22.1 ± 8.1	NS
UPDRS part 3			
On-period	22.8 ± 12.8	21.5 ± 13.3	NS
Off-period	43.6 ± 16.1	37.3 ± 13.8	NS
DSRS	12.9 ± 7.8	9.0 ± 6.7	NS
On-Off MF index	20.8 ± 15.1	15.8 ± 11.6	NS

DSRS, Dyskinesia Severity Rating Scale; LED, levodopa equivalent daily dose; LOPD, late-onset PD; MF, motor fluctuation; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; YOPD, young-onset PD.

dose dyskinesia, scoring the dyskinesia in six body parts (neck, trunk, and each of the four extremities) on a 5-point scale (ranging from 0 to 4, e.g., 0 = absent, 4 = severe). The incidence of peak-dose dyskinesia in the YOPD group (80.0%; 12 of 15 patients) was higher than that in the LOPD group (55.8%; 63 of 113 patients), whereas the DSRS score was not statistically significantly different between the two groups (Table 2). To estimate the severity of on-off motor fluctuations, we defined the score obtained by subtracting the UPDRS part 3 score at the off-period from the UPDRS part 3 score at the on-period as the "On-Off Motor Fluctuation Index." The presurgical On-Off Motor Fluctuation Index was not significantly different between the two groups. In order to exclude factors which could affect the motor activity, mini-mental status examination and Hamilton depression test were undertaken. The postsurgical stimulation parameters also were compared between the two groups.

Statistical Analysis

We compared each score for the YOPD group and LOPD group between before and after surgery, utilizing the Wilcoxon signed-rank test. We also compared the percentage reduction rate of LED (100 × [preoperative LED − postoperative LED]/preoperative LED) and the percentage improvement rates of the On-Off Motor Fluctuation Index, DSRS score, UPDRS part 2 and UPDRS part 3 scores (100 × [each preoperative score − each postoperative score]/each preoperative score) between the two groups employing the Mann–Whitney test. Multivariate logistic regression analysis was used to capture the common odds ratio between the postoperative improvement of the UPDRS part 3 score and various presurgical factors. Simple regression analysis was performed to assess the correlation of independent variables such as duration of disease and percentage improvement of motor score.

Results

We adjusted the stimulation parameters (intensity, frequency, pulse width, and contact) and levodopa so as to inhibit motor fluctuations and not to cause stimulation-induced side-effects (viz. spasticity, paresthesia, diplopia, dyskinesia, psychological symptoms, etc.) in each patient. No statistically significant difference in stimulation parameters between the two groups was evident at six months after chronic STN stimulation. Presurgical and six-month postsurgical examinations of both mood and cognitive function also revealed no significant differences between the two groups.

Changes in Motor Function, On-Off Motor Fluctuations, and ADL

The pre- and postoperative scores related to motor function in the on- and off-periods are shown in Table 3. In the YOPD group, the mean total motor score (UPDRS part 3) in both the on-period and off-period at six months after surgery were improved by bilateral STN stimulation (on-period, $p < 0.01$; off-period, $p < 0.01$; Table 3). The mean total motor score (UPDRS part 3) at six months after surgery in the LOPD group also was significantly reduced (on-period, $p < 0.01$; off-period, $p < 0.01$; Table 3). The percentage improvement rate of the motor score (UPDRS part 3) in each on- and off-period was significantly higher in the YOPD group ($p < 0.05$; Table 3).

The On-Off Motor Fluctuation Index was improved postoperatively in both groups ($p < 0.01$). While there was no significant difference in percentage improvement rate of the On-Off Motor Fluctuation Index between the two groups, the postoperative On-Off Motor Fluctuation Index was lower and the preoperative index was higher in the YOPD group as compared with the LOPD group. The results suggested that postsurgical improvement of on-off motor fluctuations showed a tendency to be prominent in patients with YOPD (Table 3).

Multivariate logistic regression analysis revealed preoperative predictive factors that contributed to postoperative improvement of the motor score (UPDRS part 3) in each on- and off-period (Table 4). An increased odds ratio was found in YOPD, but this association was statistically significant only for the on-period score (OR = 7.91; 95% CI, 0.84–48.1; $p < 0.05$). YOPD itself was the predictive factor that contributed to improvement of the total motor ability after STN stimulation during the on-period. A significantly decreased odds ratio was found for duration of disease during the on-period (OR = 0.92; 95% CI, 0.85–0.99; $p < 0.05$). Simple regression analysis revealed that there was a negative correlation between duration of disease and percentage improvement of the motor score (UPDRS part 3)

TABLE 3. Comparison of Preoperative Scores and Postoperative Scores in Patients With YOPD/LOPD

	YOPD (N = 15)			LOPD (N = 113)			
	Preoperative	Postoperative	% improvement	Preoperative	Postoperative	% improvement	p value*
LED (mg/day)	641.0 ± 346.2	498.0 ± 276.6	22†	620.0 ± 316.9	503.4 ± 256.6	19†	NS
UPDRS part 2							
On-period	7.7 ± 5.9	5.5 ± 4.5	28‡	9.9 ± 7.7	7.8 ± 7.4	22†	NS
Off-period	24.5 ± 9.20	7.8 ± 4.20	68†	22.1 ± 8.20	11.6 ± 8.30	47†	<0.05
UPDRS part 3							
On-period	22.8 ± 12.8	12.9 ± 7.30	43†	21.5 ± 13.3	16.6 ± 12.0	23†	<0.05
Off-period	43.6 ± 16.1	16.8 ± 8.10	61†	37.3 ± 13.8	22.1 ± 13.4	41†	<0.01
DSRS	12.9 ± 7.80	3.9 ± 4.3	70†	9.0 ± 6.7	2.3 ± 3.7	74†	NS
On-Off MF index	20.8 ± 15.1	3.9 ± 4.8	81†	15.8 ± 11.6	5.5 ± 7.2	65†	NS

Values are expressed as the means ± SD. *percentage improvements after surgery are compared across the two groups. ‡$p < 0.05$ compared with preoperative scores. †$p < 0.01$ compared with preoperative scores.
DSRS, Dyskinesia Severity Rating Scale; LED, Levodopa equivalent daily dose; LOPD, late-onset PD; MF, motor fluctuation; UPDRS, Unified Parkinson's Disease Rating Scale; YOPD, young-onset PD.

TABLE 4. Presurgical Factors for Postsurgical Improvement of the Total UPDRS Motor Score (part 3) in the On- and Off-Periods

Factors	Odds ratio (95% CI)	p value
On-period		
YOPD vs. LOPD	7.91 (1.30–48.1)	<0.05
Duration of PD	0.91 (0.84–0.99)	<0.05
Age at surgery	0.97 (0.91–1.03)	NS
Sex (male vs. female)	0.92 (0.44–1.90)	NS
Presurgical LED	0.79 (0.35–4.76)	NS
Off-period		
YOPD vs. LOPD	2.14 (0.39–11.7)	NS
Duration of PD	1.01 (0.94–1.09)	NS
Age at surgery	0.95 (0.90–1.01)	NS
Sex (male vs. female)	0.82 (0.40–1.68)	NS
Presurgical LED	0.92 (0.38–6.28)	NS

Multivariate logistic regression analysis showed that YOPD (age at onset <40 years old) significantly increased the odds ratio (OR) and duration of disease significantly decreased the OR for % improvement of the UPDRS part 3 score during the on-period. There was no significant between these factors but multivariate logistic regression analysis showed that YOPD (age at onset <40 years old) increased the odds ratio (OR) for % improvement of the UPDRS part 3 score during the off-period. A significantly decreased odds ratio was found for duration of disease during the on-period.
LED, levodopa equivalent daily dose; LOPD, late-onset PD; PD, Parkinson's disease; UPDRS, Unified Parkinson's Disease Rating Scale; YOPD, young-onset PD.

during the on-period in the LOPD group ($r = -0.28$; $p < 0.01$; Fig. 1) while there was no correlation in the YOPD group ($r = 0.02$; $p = 0.96$; Fig. 1). It appeared that dopa-reactivity in YOPD may be maintained for longer than in LOPD, as the negative correlation between duration of disease and percentage improvement was significant in the LOPD group but not the YOPD group. In the present study, there is great difference between patient's number in YOPD group ($N = 15$) and that of LOPD group ($N = 113$). Thus, with the two groups combined, multivariate logistic regression analysis suggested therefore that duration of disease was a decreasing factor for the percentage improvement of the motor score (UPDRS part 3) during the on-period. Duration of disease was the predictive factor that impeded improvement of the total motor ability after STN stimulation during the on-period in LOPD particularly.

The mean activities of daily living (ADL) score (UPDRS part 2) at six months after surgery in both groups was significantly reduced (YOPD group, on-period, $p < 0.05$; off-period, $p < 0.01$; LOPD group, on-period, $p < 0.01$; off-period, $p < 0.01$; Table 3). The percentage improvement rate of the ADL score (UPDRS part 2) in the off-period was significantly higher in the YOPD group than in the LOPD group ($p < 0.05$), while there was no significant difference between the two groups in the on-period (Table 3).

Changes in Levodopa Equivalent Daily Dose and Dyskinesia

The LED was significantly reduced in both groups (21% reduction in the YOPD group, $p < 0.01$; 19% reduction in the LOPD group, $p < 0.01$; Table 3) at six months after surgery. The severity of peak-dose dyskinesia was significantly improved in both groups (69% improvement of the DSRS score in the YOPD group, $p < 0.01$; 74% improvement of the DSRS score in the LOPD group, $p < 0.01$; Table 3). There were no significant differences in both the percentage reduction of the LED and percentage improvement of the DSRS score between the two groups.

Discussion

Little information is yet available on the effects of STN stimulation in patients with YOPD. Only Krack et al. have

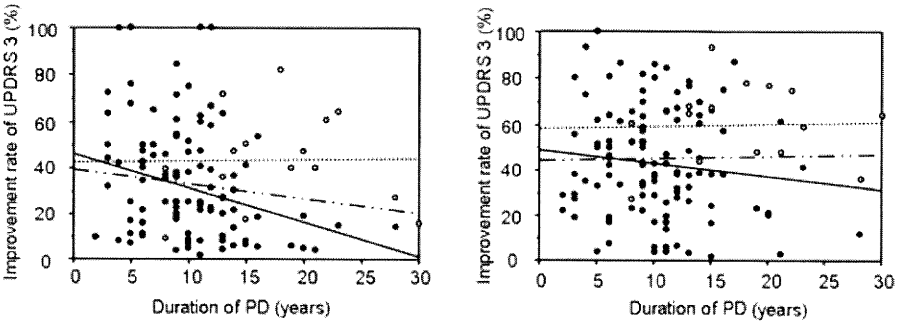

FIGURE 1. Correlations between improvement rate of Unified Parkinson's Disease Rating Scale (UPDRS) 3 and duration of disease during the on-period (left) and off-period (right). Simple regression analysis revealed a significant correlation in the late-onset PD (LOPD) group ($r = -0.28$, $p < 0.01$) but no significant correlation in the young-onset PD (YOPD) group ($r = -0.02$, $p = 0.96$) during the on-period. Open and solid circles represent YOPD patients and LOPD patients, respectively. The dotted and solid lines represent the regression lines for the YOPD group and LOPD group, respectively. The other (dot-dash) lines represent the regression lines for the two groups combined. There are some overlaps of data points. PD, Parkinson's disease.

reported in their comparative study (STN stimulation vs. globus pallidus stimulation) that STN stimulation can clearly ameliorate cardinal motor symptoms in patients with YOPD (15). In agreement with the findings of this earlier investigation by Krack et al. we confirmed that the total motor score (UPDRS part 3) in patients with YOPD could be effectively reduced by STN stimulation. In addition, the results of the present study showed that the impact of STN stimulation tends to be prominent in patients with YOPD rather than in patients with LOPD. Furthermore, the data of multivariate logistic regression analysis supported our assumption that YOPD itself is the best responder to STN stimulation.

We assume that the higher effectiveness of STN stimulation in YOPD patients may be related to the nonsignificant trend toward their high reactivity to levodopa. It is well-known that cardinal motor symptoms in YOPD patients commonly show a higher responsiveness to levodopa in comparison with those in LOPD patients (3–6). It also is evident that the effects of STN stimulation on parkinsonian motor symptoms are similar to those of levodopa (9), so that reactivity to STN stimulation could be greater in patients with YOPD than in patients with LOPD.

Another factor may be related to the characteristics of their unpleasant reactivity toward pharmacotherapy. YOPD patients often experience levodopa-induced motor complications, such as on-off motor fluctuations and dyskinesia, which frequently develop from the introduction of levodopa treatment in a short year (3–6). Although it was not significant, both dopa-induced dyskinesia and on-off motor fluctuations tended to be severe preoperatively in YOPD patients in comparison with LOPD patients in our study. Such motor complications can limit any increases in the levodopa dosage, so that pharmacotherapy is often restrained at a sub-maximal dose in these patients. STN stimulation can complement the potential of levodopa therapy without dopa-induced motor complications in patients taking a restrained dose of medication preoperatively.

Findings indicating that a younger age at surgery and shorter disease duration may be predictive of a better outcome have been reported (13,14). The data of multivariate logistic regression analysis obtained in the present study, showing a longer disease duration to be a negative predictive factor for a good outcome from surgery, supported such a view. However, our results of simple regression analysis suggested that the negative influence of a long duration of disease on postoperative improvement of motor function could be confirmed only in the LOPD group, and not in the YOPD group. One possible explanation for this is a difference in speed of disease progression: A good dopa-response was preserved in YOPD patients despite their longer disease duration. This finding could imply a better long-term outcome of STN stimulation in YOPD patients in comparison with LOPD patients.

It has been suggested that the introduction of levodopa therapy in patients with YOPD should be postponed for as long as possible, since YOPD patients tended to display a significantly higher frequency of both dopa-induced dyskinesia and on-off motor fluctuations, and such motor fluctuations can develop earlier than in LOPD patients (4,5,19–25). Initial single dopa-agonist therapy or combined dopa-agonist/low-dose levodopa therapy can significantly reduce the occurrence of dyskinesia due to subsequent levodopa therapy; however, 6–27% of patients have been reported to suffer from dopa-induced dyskinesia at three to five years after initiation of levodopa therapy (26–31). These findings highlight a remaining problem that many patients may still suffer from motor complications, such as on-off motor fluctuations and dyskinesia, at several years after successful

initial non-levodopa or low-dose levodopa with dopa-agonist therapy when maximal improvement in their motor function is achieved by such therapies in the earlier years. Furthermore, early introduction of levodopa therapy can improve motor function and quality of life to a greater extent than other anti-parkinsonian drugs, so that delayed introduction of levodopa therapy may impose a circumscribed life on some patients because of sub-maximal improvement in their motor function. The results of the present study suggest that YOPD patients with such problems related to pharmacological therapy probably represent good candidates for STN stimulation. Furthermore, early introduction of STN stimulation may preserve a better motor function and quality of life during the prime of their life. Although many authors have reported long-term effectiveness of STN stimulation for PD (32), the situation still remains uncertain in YOPD patients. One important issue to be resolved is therefore the long-term effect of STN stimulation in such patients.

Conclusion

The STN stimulation can reduce the LED, and improve both motor function and its fluctuations in patients with YOPD. These effects in YOPD patients are superior to those in LOPD patients. The present findings suggest that YOPD patients with several problems related to pharmacological therapy are probably good candidates for STN stimulation.

Conflict of Interest

The authors reported no conflict of interest.

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Comments

If they are perceptive, neurosurgeons who implant deep brain stimulation (DBS) systems for the treatment of Parkinson's disease (PD) will have noticed that certain subsets of patients seem to improve more than others. Patients with young-onset Parkinson's disease (YOPD) are often particularly good candidates for surgery. The majority of YOPD patients have a classical presentation of asymmetric tremor, rigidity, and bradykinesia which is highly levodopa-responsive, and they develop medication side effects quite early in the course of treatment compared to those patients whose Parkinson's symptoms occur later in life. In this important manuscript, Otaka et al. provide evidence that convincingly corroborates the clinical perception that YOPD patients respond better to DBS surgery.

Fifteen patients with YOPD who underwent DBS were compared with 113 patients suffering late-onset disease (LOPD) who had DBS procedures done during the same period. Scores on the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS) were significantly improved in both groups, but in the YOPD group the reduction in "off-period" symptoms was 61% as compared to 41% in the LOPD group. In addition, improvement in "on-period" scores was significantly better in the YOPD than the LOPD patients. 41% improvement in the LOPD group is a bit less than in most published studies, which show an average improvement with DBS of approximately 60%. However, despite this modest improvement (or perhaps because of it), the investigators were able to demonstrate a statistically significant advantage of DBS for YOPD over LOPD.

This paper should be required reading for all neurologists and neurosurgeons evaluating patients with PD. The take-home message is that young-onset PD is a surgical disease and that DBS should be considered early, rather than late, in its clinical course.

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CASE REPORT

Effects of Electrode Implantation Angle on Thalamic Stimulation for Treatment of Tremor

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ABSTRACT

Introduction. Chronic thalamic stimulation has been confirmed as an effective treatment for tremor. The optimal target has been commonly accepted to be situated within the ventral thalamus, but a standard trajectory of the deep brain stimulation (DBS) electrode has not yet been established. **Materials and Methods.** A 53-year-old man with an 11-year history of essential tremor was treated by DBS of the thalamus. In this patient, we had a chance to compare the effects of different trajectory angles of the DBS electrode on tremor. **Results.** Intraoperative stimulation with the DBS electrode temporarily inserted at a high angle to the horizontal plane of the anterior commissure–posterior commissure (AC–PC) line to cover only the nucleus ventralis intermedius (Vim) was not effective. In contrast, stimulation with the DBS electrode permanently implanted at a low angle, covering a wide area extending from the nucleus ventralis oralis (Vo) to the Vim, reduced the tremor. **Conclusion.** We report on the case of a patient who showed different effects on tremor depending on the trajectory angle of the DBS electrode to the AC–PC line. The insertion trajectory of the DBS electrode may be an important factor for the treatment of tremor.

KEY WORDS: *Deep brain stimulation, thalamus, tremor.*

Introduction

Deep brain stimulation (DBS) of the thalamus (thalamic DBS) is effective in reducing essential tremor, poststroke tremor, and Parkinsonian tremor (1–10). It is presumed that the optimal target for suppressing tremor with thalamic DBS is the nucleus ventralis intermedius (Vim), which also is the ideal thalamotomy target in the ventral thalamus. This association was derived from empirical observations made during ablation surgery. It was revealed that electrical stimulation was effective in controlling tremor and determined the optimal lesion site prior to radiofrequency ablation (11–13).

Because the electrode for therapeutic DBS (lead 3387; Medtronic, Minneapolis, MN, USA) has four contacts, each

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For more information on author guidelines, an explanation of our peer review process, and conflict of interest informed consent policies, please go to http://www.wiley.com/bw/submit.asp?ref=1094-7159&site=1

1.5 mm long and spaced 1.5 mm apart (the span between the edges of the electrode is 10.5 mm), stimulation with the DBS electrode can cover an area wider than that covered by intraoperative stimulation during ablation surgery. Therapeutic DBS also has advantages over ablation surgery in terms of the reversibility of the treatment (2), the ability to adjust stimulus parameters (14), and fewer adverse effects (15). Moreover, the mechanisms by which DBS and thalamotomy produce effects differ (16,17). Because of this discrepancy, it is necessary to clarify the optimal stimulation site in the thalamus as well as the implantation trajectory of the DBS electrode, which passes through regions of the thalamus for the purpose of tremor control. Therefore, we report a case in which the effects of stimulation of the thalamus on tremor differed depending on the angle of the DBS electrode relative to the anterior commissure–posterior commissure (AC–PC) line.

Case Description

The patient was a 53-year-old, right-handed man with an 11-year history of action tremor in the right upper limb. He had no family history of a similar movement disorder. He underwent several medications previously to reduce the tremors without any noticeable change in his condition. His tremor had gradually worsened over the years and was affecting his activities of daily life; therefore, he was finally referred to our hospital for DBS surgery.

An examination revealed action tremors in the right hand, with no cerebellar signs such as hypotonia or ataxia or any other neurologic abnormalities. Electromyography (EMG) using surface electrodes showed no abnormal discharges at rest and rhythmic burst discharges of 4–5 Hz when performing any action, particularly writing. Magnetic resonance imaging (MRI) of the brain revealed no abnormalities.

He underwent surgery for implantation of a DBS electrode. A Leksell Series G head frame (Elekta Instruments AB; Stockholm, Sweden) was used. A 1-mm-thick section of tissue was used for MRI, and the AC and PC were identified with the aid of specialized software (Leksell SurgiPlan; Elekta Instruments AB). An X-ray indicator (Elekta Instruments AB) also was used to identify the AC and PC on plain X-ray films. A burr hole was made at the level of the coronal suture, approximately 2.5 cm from the midline.

Extracellular single- and multi-unit recordings were obtained using a semimicroelectrode (0.2–0.4 MΩ). Neuronal activity also was fed to an audio speaker. Neural and EMG activities of eight contralateral muscles, including the biceps, triceps, deltoid, wrist extensors, and flexors were displayed on an oscilloscope. Several aspects of neuronal activity were examined such as the relationship between spontaneous activity and tremor, and neuronal activity during somatic sensory stimulation and active movement. Intraoperative audio and oscilloscopic monitoring of tremor frequency and neural activity was performed to detect whether neuronal bursting and tremor frequency had same frequencies. Cells with neuronal activity in response to somatic sensory stimulation, that is, in response to the passive joint movement of the contralateral limbs without a response in skin deformation caused by stimuli, were classified as: 1) deep sensory cells and responding to light touch on the skin of the face and contralateral limbs were classified into 2) cutaneous sensory cells.

The first trajectory of the semimicroelectrode for extracellular unit recording was directed toward the anterior aspect of the PC in the lateral view and at level with the AC–PC line, 17 mm lateral to the midline, with the intention of identifying the anterior border of the nucleus ventrocaudalis (the Vim–Vc border). Physiologic studies were initiated after the electrode had reached 12 mm above the intended target. In this study, the Vim–Vc border was physiologically defined as the most anterior neuron along a length of trajectory in which more than one-half the neurons located posteriorly were either deep or cutaneous sensory neurons (18). The Vim–Vc border was identified as a vertical line approximately 3 mm anterior to the PC, on the basis of the observations made during our initial trajectory assessment (Fig. 1). This identification was consistent with the Vim–Vc border determined on the basis of the Schaltenbrand–Wahren atlas. The second trajectory of the semimicroelectrode was directed toward a position 1 mm anterior to the Vim–Vc border at the level of the AC–PC line, 17 mm lateral to the midline. The target was approached through the burr hole at an angle of 77° to the horizontal plane of the AC–PC line and at an angle of 10° to the sagittal plane. The second trajectory included some deep sensory cells of the wrist and/or the elbow and the tremor-frequency activities were the same as those exhibited at the Vim (Fig. 1). Therefore, on the basis of these classifications, the second trajectory was regarded as the optimal stimulation site. Following this, the first DBS electrode (model 3387; Medtronic, Inc.) was implanted through an identical trajectory using stereotactic instruments and then a test stimulation with the DBS electrode was conducted. These four contacts of the DBS electrode were primarily located in the Vim (Fig. 1a). The stimulation was performed in the bipolar mode, with contact 0 as the cathode (−) and contact 3 as the anode (+). The stimulation generated muscle contraction without having an effect on tremor. It was assumed that the muscle contraction caused the current to spread to the internal capsule. To prevent muscle contraction, a second DBS electrode was introduced more medially through another trajectory at the level of the AC–PC line, 14 mm lateral to the midline, and at the same angle as the first DBS electrode to the horizontal plane of the AC–PC line (Fig. 2). We then conducted a test stimulation in the bipolar mode with the second DBS electrode. The stimulation also did not have an

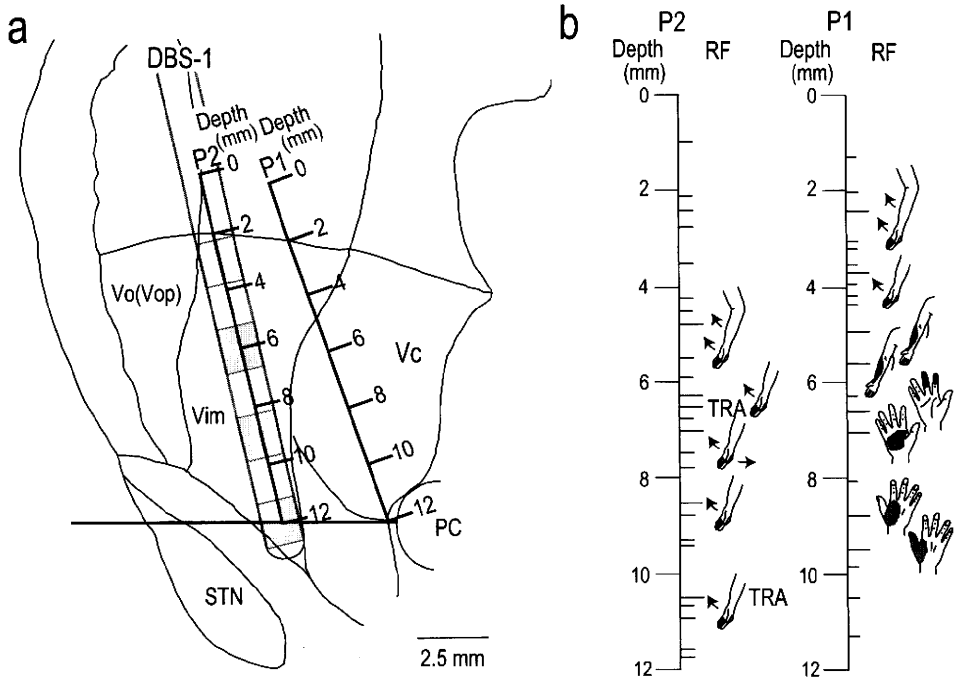

FIGURE 1. Receptive field (RF) maps of trajectories in the region of the ventral thalamus in the described patient. (a) The 17-mm lateral section from the Schaltenbrand–Wahren human brain atlas with the anterior commissure–posterior commissure (AC–PC) length is stretched to fit the coordinates obtained from the patient's stereotactic magnetic resonance imaging. The trajectories used (P1 and P2) are shown by the oblique lines. DBS-1, the first electrode of deep brain stimulation, was temporarily implanted through the same track as P2. (b) Details of the recordings. The labels P1 and P2 indicate sagittal trajectories shown as 1 and 2 on the brain map in a. Locations of neurons are indicated by tick marks to the right of the trajectory. RF maps are shown on the right. The label "TRA" indicates that neuronal activity was subjectively related to tremor, as assessed in the operating room. PC, posterior commissure; STN, subthalamic nucleus; Vc, nucleus ventrocaudalis; Vim, nucleus ventralis intermedius; Vo, nucleus ventralis oralis; Voa, nucleus ventralis oralis anterior; Vop, nucleus ventralis oralis posterior.

effect on tremor. To form another trajectory, a second burr hole was made approximately 3 cm anterior to the coronal suture, approximately 2 cm from the midline. The trajectory was directed toward a position 1 mm anterior to the Vim–Vc border at the level of the AC–PC line, 14 mm lateral to the midline. The target was approached through the burr hole at an angle of 44° to the horizontal plane of the AC–PC line and at an angle of 5° to the sagittal plane. A microthalamotomy effect was observed immediately after implantation of the third DBS electrode and the tremor disappeared completely without electrical stimulation. The microthalamotomy effect indicates that the location in which the third DBS electrode was implanted was the optimal therapeutic site (19,20). Therefore, only adverse effects of stimulation were examined and the third DBS electrode was permanently implanted into the patient.

After the postoperative disappearance of the microthalamotomy effect, stimulation with various combinations of bipolar mode was examined. Stimulation with contact 0 as the cathode (−) and contact 1 as the anode (+) stimulated mainly Vim and had some effect on tremor. However, the strongest effect was produced when contact 0 was the cathode (−) and contact 3 was the anode (+), covering a wide area extending from the nucleus ventralis oralis (Vo) to the Vim (Fig. 2).

Discussion

Ohye and Narabayashi (12) and Nagaseki et al. (11) emphasized that a small area (40 mm^3) that includes movement-related cells is the best site of lesion for thalamotomy to have an effect on tremor. In both studies, the lesions were made within 1 to 2 mm of the Vc, and therefore, did not include the region with cells responding to cutaneous sensory stimuli. It is commonly accepted that the optimal target for chronic thalamic stimulation for treatment for tremor is the Vim, close to the border of the sensory thalamus (Vim–Vc border) (11–13). In the present case, deep sensory cells and cells with tremor-frequency activity were recorded in the second trajectory (Fig. 1). Although the site including these cells is considered the optimal target for tremor control (11,12,21,22), electrical stimulation of this region was not effective in suppressing tremor.