TABLE 2. *Changes in frequency (Hz) of ACC, EMG, and coherence in different postures and with loading of 1 kg*

No.	Frequency (Hz)	Posture 1			Posture 2			Other posture		
			Preload	Load		Preload	Load		Preload	Load
1	ACC	6.5–8.2	7.7	8.6	8.6	8.6	3.3, 9.4			
	EDC	8.5–9.4	8.5	9.8	8.5	8.5	N.D.			
	Coherence	6.2–9.4	7.7	N.D.	8.9	8.9	N.D.			
2	ACC	6.7–9.1	7.6	7.0	6.3–9.1	7.7	9.1			
	EDC	7.7–8.4	10.5, 8.4	9.1	7.7–9.1	7.7	N.D.			
	Coherence	7.7–8.4	7.7	7.7	8.4	7.0	7.7			
3	ACC	6.5–8.4	6.1	8.5, 4.1	9.3					
	EDC	7.7	8.5	N.D.	9.3					
	Coherence	7.0	6.1	N.D.	N.D.					
4	ACC	7.0–8.4	7.0	7.8	3.5–7.8	7.8	3.5	6.1–8.7	3.5	6.7
	EDC	7.9–8.7	7.8	7.8	N.D.	N.D	N.D	8.7	N.D	7.0
	Coherence	7.8–8.7	7.8	7.8	7.8	7.8	N.D	8.7	N.D	3.4
5	ACC	7.4–8.3	7.8	7.9	6.5			3.5	4.1	2.9, 5.2
	EDC	7.8–8.3	7.8	7.9	8.2			N.D	N.D.	N.D.
	Coherence	7.8–8.0	7.9	7.9	6.9–8.0			N.D	N.D.	N.D.
6	ACC	6.4–8.7	8.2	3.5	8.7, 2.9	7.6	5.2	4.1		
	EDC	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.	N.D.		
	Coherence	N.D	8.2	N.D.	8.7	N.D.	N.D.	N.D.		
7	ACC	2.9	2.9	2.9–3.5	3.5–4.6, 8.7	4.6	2.9			
	EDC	9.2	9.9	9.9	8.7	N.D.	9.9			
	Coherence	N.D.	N.D.	8.1–9.9	8.7	N.D.	N.D.			
8	ACC	7.6–8.2			7.0–7.6	7.5	3.5	7.5	7.5	7.6
	EDC	8.2–9.8			7.5	7.5	N.D.	N.D.	N.D.	N.D.
	Coherence	N.D.			7.0	7.5	N.D.	N.D.	N.D.	N.D.

Gray cells means "not done". Dark gray cell in patient numbers indicates that their features are compatible with "mechanical tremor".
ACC, accelerometer; EDC, surface electromyogram of musculus extensor digitorum communis; ND, not detected.

peak at 6.1 Hz appeared in addition to an 8.7 Hz peak in the ACC spectrum. However, both EMG activity and coherence showed a peak only at 8.7 Hz. Figure 2A and B present power spectra of ACC and EMG and their coherence in Case 6. In Posture 1, the tremor peak frequency was 8.7 Hz without associated EMG

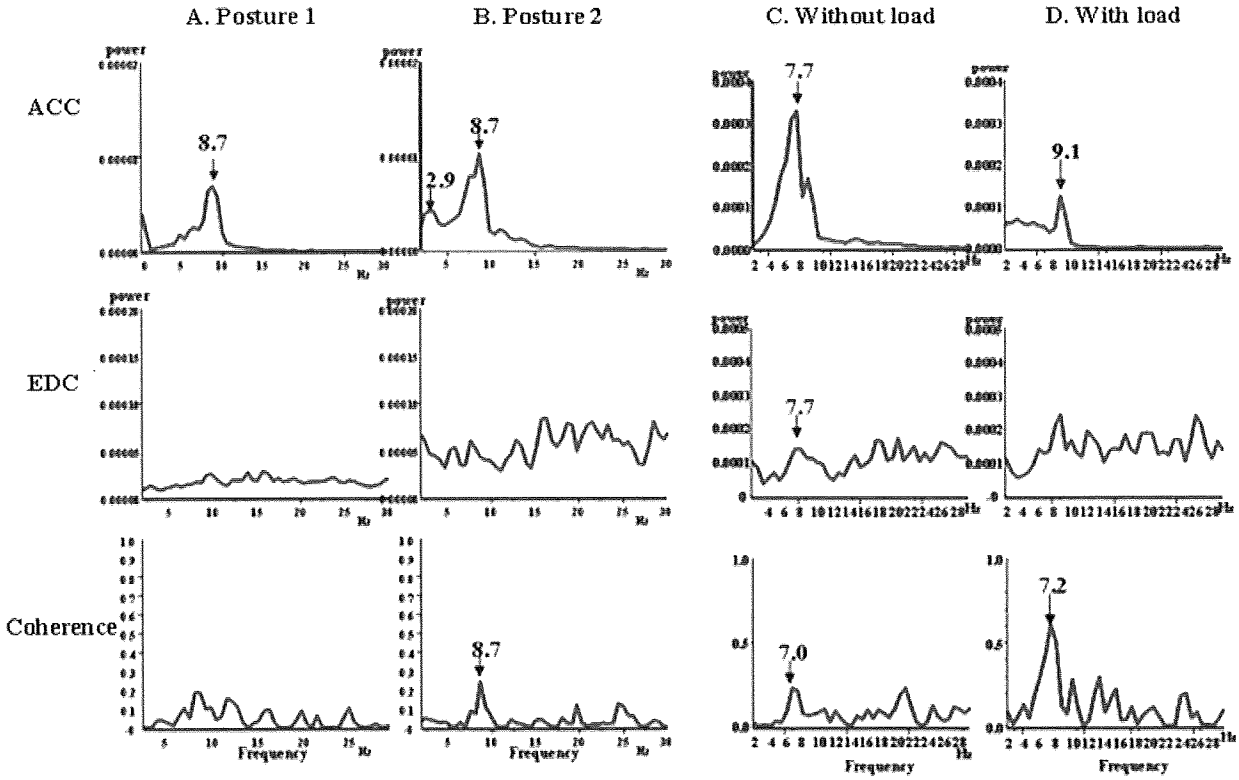

FIG. 2. Power spectra of ACC, EDC EMG, and their coherence in Case 6 (**A** and **B**) and Case 2 (**C** and **D**). A, Posture 1, is holding out the arm; B, Posture 2, is during wrist extension. For Posture 1, the tremor peak frequency was 8.7 Hz. Neither EMG activities nor their coherence exhibited any peak. These results suggest that the tremor is a "mechanical tremor." The ACC power spectrum showed two peaks (2.9 and 8.7 Hz) with no EDC EMG activities when the patient extended the wrist and finger (Posture 2). However, the coherence showed a small peak at 8.7 Hz. (C) Data for a subject holding the hand extended without a weight load and (D) with a load. Without any weight load, all ACC, EDC EMG, and coherence showed peaks at similar frequencies: 7.0–7.7 Hz. The weight load changed the tremor frequency to 9.1 Hz. The EMG spectrum showed no clear peaks, but the coherence had a small peak at 7.2 Hz.

activities (Fig. 2A). Another peak was observed at 2.9 Hz in addition to an original peak at 8.7 Hz in the ACC spectrum (Fig. 2B) when the posture changed from Postures 1 to 2. No EMG activity was associated with a tremor peak in either posture. Nevertheless, a significant coherence was found between ACC and EMG at 8.7 Hz in Posture 2 (Fig. 2B). The results for all patients are presented in Table 2.

The weight load on the hand changed the ACC peak frequency in all patients (Table 2). It reduced the tremor frequency in four patients (Cases 4, 6, 7, and 8), raised the frequency in two (Cases 2 and 5), and added another peak in three (Cases 1, 3, and 6). None of frequency changes induced by weight load was associated with an EMG peak at the same frequency. Figure 2C and D show power spectra of ACC and EMG and their coherence with and without a load in Case 2. The frequency of ACC changed from 7.7 to 9.1 Hz with load. The EMG from EDC showed a 7.7 Hz peak without load and no peaks with load. In six patients, no peak was observed in the EMG power spectrum during loading. In the other two patients, EMG peaks were observed at different frequencies from a peak of ACC frequency.

DISCUSSION

All of our patients with SBMA showed postural tremor in the distal upper limb muscles at a frequency of 6–9 Hz. The tremor frequency of 6–9 Hz was similar to that of essential tremor. We report here, for the first time, that the physiological characteristics of SBMA postural tremor differ from those of the essential tremor, which is considered to be generated by central mechanisms (central tremor). In essential tremor, tremor movement is always associated with EMG grouping activities at the same frequency. It is resistant to external perturbation, such as weight load-

ing.[11] In the patients described herein, some external perturbation affected the tremor frequency; the movement was not always associated with synchronous EMG activities.

In five patients, EMG activities that were significantly coherent with ACC were associated with tremor. The tremor frequency was affected by postural changes. Moreover, imposition of a 1 kg weight load also changed the peak tremor frequency. According to Deuschl et al.[11] these physiological features suggest "reflex tremor," which is mediated through reflex loops between peripheral nerves and the central nervous system such as stretch reflex. Changes in tremor frequency by more than 1 Hz during 1 kg weight loading in some of these patients are also consistent with reflex tremor.[11,12] In the other three of the eight patients (Cases 6–8), the tremor was not associated with EMG activities, which suggests that simple mechanical oscillation might produce tremor movement (mechanical tremor).[11] On the basis of the arguments presented earlier, we conclude that two different mechanisms might contribute to tremor movement generation in SBMA: mechanical oscillation and reflex mechanisms.

Peripheral input changes are important factors in triggering reflex tremor movement. Peripheral nerve involvement is one candidate for peripheral factors to explain reflex tremor in SBMA. Some subclinical sensory system involvement is suggested in SBMA.[13,14] Small sensory nerve action potentials of our patients are consistent with axonal or neuronal damage of the sensory neurons[13,14] even though they had no sensory symptoms. This mild sensory system involvement might partly produce reflex tremor. In patients with some form of peripheral neuropathy, such as IgM demyelinating paraproteinemic neuropathy, postural or action tremor at 3–6 Hz is often observed in the upper limbs.[15–17] Such tremor is often classified as "tremor syndromes in peripheral neuropathy" or "neuropathic tremor."[10] In neuropathic patients, some mistimed peripheral inputs attributable to abnormally prolonged cortical stretch reflexes might induce malfunction of the feed-forward loops caused by disruption of central processing. Such loop malfunction might cause peripheral neuropathic tremor.[10,15,18] A similar mechanism putatively causes tremor in SBMA. In addition, the motor unit discharges synchronizing originally at 6–10 Hz might be responsible for the frequency component of physiological tremor during muscle contraction.[19,20] Muscle spindle feedback reportedly plays an important role in the generation of 6–10 Hz rhythm.[19] This 6–10 Hz motor unit synchronization might occur more easily than in normal subjects in SBMA because the motor units are markedly decreased. This tendency for enhanced synchronization might be another factor generating reflex tremor in SBMA.

Mechanical tremor is a peripheral tremor caused by the simple oscillation of the extremities when the extensor muscles are activated to keep the hands in the outstretched posture to counterbalance gravity.[11] The frequency of mechanical tremor is determined by the resonance frequency of the limb, which is affected by muscle stiffness and the inertia of the oscillating limb. Usually, the resonance frequency is 6–8 Hz in the hands and 25 Hz in the fingers. The frequency observed in our patients is consistent with resonance frequencies of the hand. In SBMA, muscular atrophy and motor unit reduction engender difficulty in maintaining muscle contraction constantly because the muscle activities might not be sufficient to cancel mechanical tremor motion during gravity-defying posture maintenance.

Mechanisms underlying both mechanical and reflex tremor might contribute to physiological tremor (8–12 Hz). In normal subjects, fatigue induces physiological tremor at a similar frequency.[21,22] Similarly, tremor is frequently observed during fatigue in patients with SBMA. Easy fatigability also predisposes SBMA patients to tremor, whether mechanical or reflex tremor. In SBMA, the motor units are enlarged and their number is decreased. Therefore, when patients try to maintain a posture, the firing rate per unit is expected to increase when maintaining the same level of voluntary contraction. Under such conditions, the motor unit might become fatigued quickly and engender easy fatigability. In our patients, the tremor frequency fluctuated from 0.6 to 2.4 Hz during maintenance of a posture. This finding might be compatible with fatigue induction.

Our results suggest that peripheral factors play major roles in generating postural tremor in patients with SBMA, even though the present results cannot completely preclude the possibility that some central factor is also combined in tremor generation.

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反復磁気刺激の治療への応用

武智詩子　魚住武則　辻　貞俊

要旨　rTMSは3発以上規則正しく反復されるTMSと定義されている。rTMSは刺激頻度が1 Hzを越えるものをfast rTMS，1 Hz以下のものをslow rTMSと2種類に区別され，前者ではコイル直下の大脳皮質の興奮性が増大し，後者では大脳皮質の興奮性は低下すると考えられている。これを利用してさまざまな神経・精神疾患の治療に臨床研究が行われている。

パーキンソン病，脊髄小脳変性症，脳梗塞後遺症，ジストニア，てんかん，うつ病，耳鳴り，慢性疼痛などではrTMS治療の有効性を示す報告がみられる。rTMSの最適刺激条件と有効刺激部位が明らかになり，長期的な影響や作用機序の解明など治療法として確立すれば，神経・精神疾患に対する補助的治療法になることが期待できる。

Key Words：transcranial magnetic stimulation, repetitive TMS, Parkinson disease, stroke, depression, chronic pain

はじめに

経頭蓋磁気刺激法（transcranial magnetic stimulation, TMS）は，1985年Barkerら[1]が頭部に磁気刺激を与え，手の筋から誘発電位を記録することに成功し，さまざまな脳機能評価に応用されてきた。1990年代に刺激装置の改良が進み，TMSを連続して用いる反復経頭蓋磁気刺激法（repetitive TMS, rTMS）の方法論が確立した。その後rTMSにより神経活動の抑制，促通が確認されるようになり[2]，rTMSの刺激中だけでなく刺激後にも及ぶ効果を利用して，神経・精神疾患の治療に応用することが考えられるようになった。

rTMSは3発以上規則正しく反復されるTMSと定義されている。rTMSは刺激頻度が1 Hzを越えるものを高頻度rTMS（fast rTMS），1 Hz以下のものを低頻度rTMS（slow rTMS）と2種類に区別され，5 Hz以上のfast rTMSではコイル直下の大脳皮質の興奮性が増大し，slow rTMSでは大脳皮質の興奮性は低下すると考えられている。このため主に大脳皮質興奮性が低下している病態ではfast rTMSが，逆に亢進している病態ではslow rTMSが治療として用いられている。

近年では新しい刺激方法としてtheta-burst stimulation（TBS）が開発された。従来のrTMSより弱い強度（80%収縮時MEP閾値）で高頻度（50 Hz）3連発刺激を5 Hzで繰り返すものであり，より短い刺激時間で効果を持続させることができる[3]。

TMSの安全性については，rTMSでは当初からてんかん発作を誘発する可能性がいわれており[4,5]，現在でもてんかん患者には原則として禁忌である。また，rTMSでは大脳皮質に強いパルス磁場を与えるため，脳動脈瘤クリッピング術後や心臓ペースメーカー埋込術後なども禁忌となる[6]。「日本臨床神経生理学会　磁気刺激法に関する委員会」「磁気刺激法の臨床応用と安全性に関する研究会」が共同で3回にわたり，TMSの安全性に関する全国調査を行い，重篤な副作用が生じていないことを明らかにしている。また現在までの文献的検索でも重篤な副作用はない[7]。

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ここではrTMSを用いた神経・精神疾患の治療の試みについて述べる。

パーキンソン病

パーキンソン病の治療としては主にドパミン製剤やドパミン受容体作動薬等の内服治療が主体であるが，進行期には薬の効き目が不十分になったり，精神症状，運動合併症や心臓弁膜症などの副作用が問題となる。そのような症例で考慮される脳深部刺激（DBS）は侵襲的治療であり，適応とならない症例も多く，更に非運動症状を合併させやすい。

1994年にPascual-Leoneらは，off状態のパーキンソン病患者を対象に手の運動野へfast rTMSを与えると，反応時間が改善することを報告した[8]。その後Ghabraらは5 Hzのr TMSを運動野に与えたが有意な変化は認められないと報告し[9]，運動野に対するfast rTMSの効果については現在のところ疑問視されている。日本ではShimamotoら[10]が両側前頭部に運動閾値の1.1倍の強度で0.2 Hzのslow rTMSを週1回繰り返すことにより著明な症状の改善が認められたと報告している。機序としては前頭部rTMSにより線条体のドパミンレベルが増加すること[11]，GABA受容体を介した抑制機序異常を改善する[12]ということが考えられている。その後も**表1**に示すように運動症状に対するrTMS臨床試験は多く行われている[8〜27]。最近発表された比較対照臨床試験のメタ解析ではfast rTMSでは運動症状に対する有意な効果が認められたが，slowrTMSではほとんど効果がなかったことを報告している[28]。

本邦における多施設共同研究として，2003年には，運動野に対する0.2 Hz rTMSはsham刺激による臨床改善効果と同等であり，placebo効果と変わらないことを明らかにした[13]。続いて2008年に補足運動野を5 Hz週1回800回の刺激を連続8週間行い，UPDRSと自己評価の検討では，sham刺激と比較し運動症状の有意な改善が認められた[15]。他方，パーキンソン病

表1 パーキンソン病に対するrTMS治療

著者	人数	刺激頻度	刺激強度	コイル	刺激回数	刺激部位	治療効果
Paoscual-Lenoneら（1994）[8]	6	5	0.9×rMT	8の字	記載なし	M1	改善
Siebnerら（1999）[15]	12	5	0.9×rMT	8の字	750	M1	改善
Ghabraら（1999）[9]	11	5	0.8〜0.85×rMT	8の字	記載なし	M1	不変
Mallyら（1999）[16]	49	1	0.2×rMT	円形	60回/日×10日	Cz	改善
Mallyら（1999）[17]	10	1	0.34〜0.8×rMT	円形	60回/日×7日	Cz	改善
Tergauら（1999）[18]	7	1, 5, 10, 20	0.9×rMT	円形	1000	Cz	不変
Siebnerら（1999）[19]	10	5	0.9×rMT	8の字	750	M1	改善
Boylanら（2001）[20]	10	10	1.1×rMT	8の字	2000	SMA	増悪
Shimamotoら（2001）[10]	9	0.2	700 V	円形	60回/日×8週	Cz	改善
Sommerら（2002）[21]	11	1	1.2×rMT	8の字	900	M1	改善
Ikeguchiら（2003）[22]	12	0.2	700 V	円形	30回×2/日×2週	F3, F4	改善
Okabeら（2003）※[13]	85	0.2	1.1×rMT	円形	50回/日×8週	Cz	placeboと同等
Lefaucheurら（2004）[23]	12	10	0.8×rMT	8の字	2000	M1	改善
Lefaucheurら（2004）[23]	12	0.5	0.8×rMT	8の字	600	M1	改善
Fregniら（2004）[24]	42	15	1.1×rMT	8の字	200回/日×10日	左DLPC	改善
Boggioら（2005）[25]	25	15	1.1×rMT	8の字	200回/日×10日	左DLPFC	改善
Lomarevら（2006）[26]	18		1.0×rMT	8の字	1200回/日×1日	両側DLPFC	改善
Del Olmoら（2007）[27]	13	10	0.9×rMT	8の字	450回/日×10日	DLPFC	不変
Hamadaら（2008）※[14]	99	5	1.1×rMT	8の字	1000回/日/週×8週	SMA	改善

※厚生労働省班研究，M1：一次運動野，SMA：補足運動野，DLPFC：前頭前野背外側，rMT：resting motor threshold，Cz：国際10-20法に基づく頭蓋頂

は運動症状に加え非運動症状も身体的・社会的活動を妨げる原因となっている。2009年度からは補足運動野10 Hz，1 Hzを刺激条件とし，非運動症状の評価を加えた多施設共同研究が開始されている。パーキンソン病はplacebo効果を受けやすいと言われているがこれまでの報告で明らかな有効性が認められており，今後は刺激部位や強度，頻度といった刺激パラメータをより最適にすることにより，さらに有効な治療法となると期待される。

脊髄小脳変性症

脊髄小脳変性症は，脊髄，小脳に病変の主座をもつ原因不明もしくは遺伝性の変性疾患であり，運動失調を主症状とする。現時点では進行を遅らせる可能性のある内服薬やリハビリテーション以外に有効な治療法がない。

Shimizuら[29]は遺伝性脊髄小脳変性症患者に対して円形コイルを用い，小脳半球への0.2 Hz slow rTMSを30パルス/日，連日の治療法を試みている。この方法により，明らかに歩行障害が改善し，刺激後に小脳半球，橋，被殻の血流が増加したと報告している。

2002年度から全国的な多施設共同研究が行われた。対象患者を皮質性小脳萎縮症と遺伝性脊髄小脳失調症6型（SCA6）に限定し，円形コイルを用いて0.2 Hz のslow rTMSを30パルス/日×15日間与えた。結果は小脳刺激群と対照群はともに症状の改善がみられたが，各群間に有意な差はみられなかった。しかし，SCA6のみの解析では治療開始後4週目から8週目までの間で，運動野刺激が小脳刺激およびsham刺激と比べて有意な小脳症状の軽減効果が認められた。小脳刺激は大脳皮質を刺激する場合と異なって，有効な刺激が到達しているのか簡単に判定できないこともあるが，今後小脳刺激法のさらなる発展が望まれる。さらに病変の主座でない運動野などの刺激の有効性なども含め，多くの異なる刺激パラメータを用いた報告が待たれる。

脳梗塞後遺症

脳梗塞による片麻痺の治療法としてこれまで，筋電バイオフィードバック療法，非麻痺側上肢の拘束療法（constraint-induced therapy），動筋の電気刺激などが報告されているが，回復には限界があり慢性期においては特に困難である[30]。

大脳半球間の左右の運動野は，脳梁を介して互いに抑制関係を呈していると考えられている[31]。リハビリテーションにおいてconstraint-induced therapyが行われるのも，背景として健側の運動野が障害側の運動野の回復に悪影響を及ぼす可能性があることによる。脳

表2　脳梗塞に対するrTMS治療

著者	人数	刺激頻度	刺激強度	コイル	刺激回数	刺激部位	効果
Khedrら（2005）[34]	52	3	1.2 × rMT	8の字	300回/日×10日	非梗塞側大脳半球	あり
Mansurら（2005）[35]	8	1	1.0 × rMT	8の字	600回	非梗塞側運動野	あり
Takeuchiら（2005）[36]	20	3	1.2 × rMT	8の字	1000回	非梗塞側運動野	あり
Boggino ら（2006）[37]	1	1	1.1 × rMT	8の字	1200回×1日		あり
Kimら（2006）[38]	15	10	0.8 × rMT	8の字	160回×1日		あり
Fregniら（2006）[39]	15	1	1.0 × rMT	8の字	1200×5		あり
Talelliら（2007）[40]	6	TBS	0.8 × rMT	8の字	40秒間	iTBS：梗塞側大脳半球	一過性に手の麻痺の改善
						eTBS：非梗塞側大脳半球	なし
Lazzaroら（2008）[41]	12	TBS	0.8 × rMT	8の字	40秒間	iTBS：梗塞側大脳半球	患肢のMEP振幅増加
						eTBS：非梗塞側大脳半球	患肢のMEP振幅増加
Mallyら（2008）[42]	64	1	出力の30%	8の字	200回/日×1週	梗塞側運動野	あり
Kirtonら（2008）[43]	10	1	1.0 × rMT	8の字	1200回×8	非梗塞側運動野	あり
Izumiら（2008）[44]	9	0.1	>100% rMT	8の字	100回×4	梗塞側運動野	あり
Khedrら（2009）[45]	48	3, 10		8の字		梗塞側運動野	あり

TBS：theta burst stimulation, rMT：resting motor threshold

梗塞急性期には，障害側でMEPの振幅が低下し回復過程で増大する。一方健側では振幅が増大し回復過程で低下し，健側半球の興奮性が高くなり，脳梁を介して患側半球に抑制がかかることが知られている[32,33]。これらを根拠としてrTMSの治療応用として1）患側半球運動野の興奮性を上げる，2）健側半球の興奮性を抑制する方法が試されている[34~45]。

Khedrら[34]は急性期脳梗塞患者の健側運動野に3 Hzで300回/日の10日間連続rTMSとsham刺激を行い，rTMS群では臨床症状に改善があり，またMEP振幅も増大を認めたと報告した。最近では，弱刺激・短時間の刺激で長期的な抑制・促通効果を認めるTBSによる麻痺手のMEP振幅の増大が報告されている[40,41]。**表2**に主要な臨床研究を示す。概ね対照群と比較して8-20%の機能改善が一過性ながらも認められているが，今後解明すべき問題点も多い。脳梗塞は他の疾患と異なって病巣の大きさ，障害部位（運動野なのか皮質下・脳幹の錐体路のみかなど）が患者によってさまざまである。したがって個々の症例で機能画像法などを用いてそれらを評価し，患側半球を刺激すべきか健側にすべきか，運動野以外が良いのか判断できるようになればさらに有効性が高まると考えられる。　いずれにしても，リハビリテーションに併用する補助療法として，大きな期待が寄せられている。

ジストニア

ジストニアは筋緊張の異常亢進による不随意運動もしくは姿勢の異常である。局所性ジストニアにはボツリヌス治療が第一選択であり，痙性斜頸では極めて有効である。一方書痙のような動作特異性がある場合には障害されていない運動に関与する筋の筋力低下が治療の問題点となる。このような症例に対しrTMSが試されている。

症候性ジストニアの研究から，ジストニアの病態として基底核や基底核が関与する運動系ループの異常が考えられている[46]。電気生理学的には書痙において運動野の2連発刺激でshort interval intracortical inhibition（SICI）が障害され皮質内抑制が低下していることが示されている[47]。したがって，ジストニア罹患筋に対応する運動皮質を標的にしてslow rTMSを行い運動野を抑制するという試みが行われている。

Siebnerら[48]は書痙患者に対して1 Hzのslow rTMSを30分間与えることにより，筆圧が低下し電気生理学的にも皮質の過剰興奮が減弱したと報告している。島本らは[49]，3例の痙性斜頸患者に対してパーキンソン病に対して行った同じ方法で両側前頭部にslow rTMSを与えたところ，全例で症状の明らかな改善が認められたとしている。またMuraseら[50]が行った刺激部位の検討では，運動野，運動前野，補足運動野を比較すると，前頭前野への0.2 Hz 250回の刺激で症状が改善したと報告している。また低頻度刺激による皮質内抑制効果と末梢神経ブロックなどの他の治療法を組み合わせることでより長期的な治療効果が期待されている。

てんかん

難治性てんかんの定義は，一般に抗てんかん薬で発作が完全に消失しないてんかんであり，てんかん患者の30%を占めるとされている。これらの一部は外科手術で発作が消失するが適応が限られている。薬剤と手術以外のてんかん治療として注目されているのが脳刺激による治療である。刺激法には頭蓋内電極を用いて脳を直接電気刺激する方法とrTMSが研究されている。rTMSは非侵襲的な方法という点で直接電気刺激より優れているといえる[51]。

磁気刺激により脳の抑制系を刺激するとてんかん発作を抑制（予防）できるという発想のもと，多くの研究が報告されている。赤松ら[52]はてんかん重積状態の動物でrTMSを行い，重積状態の改善と優位な死亡率の低下を報告している。これらの成果からrTMSは皮質ネットワークでの興奮性を抑制し，てんかんに対し抗けいれん作用があることが推測される。

Tergauら[53]はてんかん患者9例に対して円形コイルを用いて0.33 Hzのslow rTMSを500パルス/日行い，8例において6~8週にわたって発作頻度や重症度が軽減したと報告している。その後もcortical dysplasiaやcortical myoclonusなどの患者に対しての治療を試みた報告も散見され，中には部分発作重積状態に対してrTMSを行うと発作を止めることが可能であったという報告も認められる[54]。一方Theodoreら[55]は，1 Hzで900回刺激を二度行うプロトコールで有意差がなかったと報告している。

てんかんに対してrTMSを行った臨床研究をメタ解析したreviewが2007年にBeaらにより報告されており[56]，てんかん発作を誘発した副作用は1.4%にすぎず，また38%の症例で50%以上の発作頻度の減少を認め，rTMSの潜在性有効性は肯定できると結論している。

うつ病

うつ病に対して多くの抗うつ薬が開発され治療結果は向上しているが，それでも薬物抵抗性の患者がおおよそ20%存在すると言われている。このような薬物抵抗性の難治性うつ病に対して，古くから電気けいれん療法（electroconvulsive therapy, ECT）が行われてきた。rTMSはECTに比べてはるかに少ない侵襲で大脳皮質を刺激しうる方法であるため，うつ病に対するrTMSに多くの関心が集まり，臨床研究の報告は多い。ヒト・動物での研究でrTMSによりセロトニン，5HIAAの海馬での増加，ドパミン分泌が前頭葉で減少し，線条体・海馬で増加，BDNFの増加が認められることが考えられている[7,57]。

1993年Hoflichら[58]が初めてうつ病に対して低頻度のrTMSを試した。その後さまざまな刺激方法が試みられたが，いずれも円形コイルを用いたslow rTMSで刺激部位をvertexに設定しており刺激部位は広範囲であった。その後SPECTやPETなどの研究から，うつ病の患者では左の前頭前野背外側部（dorsolateral prefrontal cortex; DLPFC）の血流が低下し，回復過程で血流も改善することが示されるようになり，左DLPFCへのfast rTMSが行われるようになった。Georgeら[59]は1995年に安静時運動閾値の80%の刺激で20 Hz 2秒間の刺激を60秒間の間隔をおいて20回行い5日間実施する方法によりうつ状態が改善したと報告した。以来，左DSPFCを刺激部位として行われる高頻度，強刺激のrTMSの有効性の報告は多く，メタ解析の結果が報告されている。メタ解析のほとんどが刺激条件などの違いはあるものの，左前頭前野に対する2週間連日のrTMSは有意な抗うつ効果を有していると結論づけられている。一方でMartinら[60]の報告では効果がないと結論づけられており，rTMSをうつ病の治療として支持する証拠には乏しいと述べているが，検討対象として取り上げられている報告の大半が対照（sham刺激）との比較を行っていないことが大きな理由の1つである。

2008年米食品医薬品局（FDA）は，うつ病の治療に用いるTMS刺激装置を初めて認可した。 臨床試験ではrTMS治療の6週間後，患者の24%にうつ病評価尺度で有意なスコア改善が認められたのに対し，磁気治療を模倣したプラセボ治療を受けた患者で改善がみられたのは12%であった。これは抗うつ薬の単独使用と同等の効果であった[61]。治療費が高いなどまだ問題はあるが今後日本でも普及するものと推測される。

耳鳴り

耳鳴りは難聴をはじめとしたさまざまな耳疾患で認められ，成人の約10%に生じる非常に多い症状である。治療としては原疾患治療が第一であるが，特発性の耳鳴りはしばしば難治であり，約1%ではQOLに悪影響を及ぼしている。耳鳴りのメカニズムについては十分に解明されていないが，SPECTなどの機能画像的研究から，聴覚皮質の過活動との関連が示唆されている。TMSの機序として聴覚皮質の活動性の変化が関連しているといわれている[62]。Plewniaら[63]は，左側頭頭頂部に運動閾値の1.2倍で10 Hz 3秒間の刺激を行い，耳鳴りの改善を報告している。Khedrら[64]は，sham群と比較しrTMSでは明らかに耳鳴り改善を認めるが，1 Hz，10 Hz，25 Hzの刺激頻度間では有意差は認めなかったと報告している。刺激頻度については今後も検討が必要である。また耳鳴りはうつ病と関連があるため，rTMSの耳鳴りに対する効果はうつ症状に対する効果の結果生じている可能性も示唆されている。今後は大規模試験と長期的効果の成績が待たれる。

慢性疼痛

難治性慢性疼痛に対しては，抗てんかん薬，抗うつ薬が試されているがすべての患者に有効とは言い難い。これら各種薬剤に抵抗性の難治性慢性疼痛患者に対して運動野電気刺激療法が1990年代に開発され一部の患者では明らかな疼痛軽減効果が得られ，治療法の一つとして確立された[65]。運動野電気刺激療法は硬膜外に電極を埋め込み1～10 V, 10～100 Hzで刺激す

表3 慢性疼痛に対するrTMS治療

著者	人数	刺激頻度	コイル	刺激回数	刺激部位	治療効果
Migitaら(1995)[68]	2	0.2	円形	200	M1	1人に効果あり
Lefaucheurら(1998)[69]	12	20	8の字	120	M1	あり
Lefaucheurら(2001)[70]	18	0.5, 10	8の字	1000	M1	あり
Lefaucheurら(2001)[71]	14	10	8の字	1000	M1	あり
Reidら(2001)[72]	1	20	NR	1200	PFC	あり
Canaveroら(2002)[73]	9	0.2	8の字, DC	200	M1	3人に効果あり
Rollinkら(2002)[74]	12	20	C, DC	800	M1	なし
Topperら(2003)[75]	2	1, 10	8の字	720, 400	PPC	あり
Lefaucheurら(2004)[76]	60	10	8の字	1000	M1	あり
Plegerら(2004)[77]	10	10	8の字	120	M1	あり
Lefaucheurら(2004)[78]	1	10	8の字	1000	M1	あり
Khedrら(2005)[79]	28	20	8の字	2000	M1	あり
Andre-Obadiaら(2006)[80]	12	1, 20	8の字	1600	M1	5人に効果あり
Hirayamaら(2006)[81]	20	5	8の字	500	M1, S1, PMC, SMA	あり
Johnsonら(2006)[82]	17	20	8の字	500	M1, S1	あり
Lefaucheurら(2006)[83]	36	10	8の字	2000	M1	あり
Lefaucheurら(2008)[84]	46	10, 1	8の字		M1	10Hzで効果あり
Borchardら(2009)[84]	4	10	8の字		PFC	あり

M1：primary motor cortex, S1：primary sensory cortex, PFC：prefrontal cortex, PPC：posterior parietal cortex, PMC：premotor cortex

るものである。その機序としては，痛みの原因となる刺激は太い上行線維を介する他の刺激による入力情報によって抑制されるため，病変部位からより中枢に近い部位で刺激を行うことにより疼痛抑制効果が高いと考えられている。よってより高位である一次運動野が疼痛抑制効果をきたす刺激部位として適している[66]。またGarcia-Larrearら[67]は運動野刺激後の血流分布をPETで評価し，視床腹外側部，視床内側部，前帯状回，島前部，橋上部の血流増加を報告し，運動野と視床の直接的線維連絡に基づくものと考察している。

運動野電気刺激療法では電極を埋め込む外科的手術が必要であるため，1995年により侵襲の少ないrTMSによって運動野刺激を行う方法がMigitaら[68]により行われた。2人の患者に一次運動野に0.2 Hzで200回刺激し1人の患者で効果を見た。その後も一次運動野に対するrTMSの有効性を報告した臨床研究は多く[86]，最近では一次感覚野，運動前野や前頭前野への刺激も試されている（**表3**）[68~85]。一方Rollnikら[74]は20 Hzの運度や刺激で統計学的に有意な効果は認めなかったと報告している。痛みの原因による効果の違いも報告されており，刺激部位と合わせて今後も検討が必要である。

まとめ

神経・精神疾患に対するrTMSによる治療について述べた。前述した疾患以外に，片頭痛や神経因性膀胱[87]，認知機能障害（失語症，半側空間無視，記憶力低下など）にもrTMSは試みられている。rTMS治療はその安全性および簡便性から試みられる疾患は増える一方である。しかしrTMSの治療効果に関する報告は多いが，まだ十分な症例数を対象にして厳密に対照群と比較した研究が少ないこと，また報告によって刺激頻度，刺激強度，刺激回数，刺激間隔等の刺激条件や刺激部位はさまざまであること，長期的な大脳皮質興奮性の変化の確認されていないなどから現在までのところrTMSが重要な治療法として確立されるには至っていない。

rTMSの最適刺激条件と有効刺激部位が明らかにな

り，長期的な影響や作用機序の解明などが確立すれば，薬物治療に加えて神経・精神疾患に対する新たな治療の選択肢になりえる。

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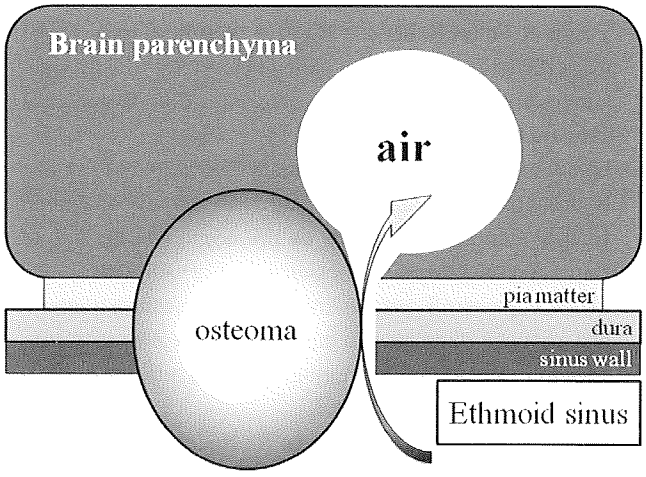

Fig. 3. The suggested mechanism of air influx into the brain parenchyma. The pia mater and dura mater are firmly adherent, owing to the weight of the brain. The air escapes through the dura and pia mater into the brain parenchyma.

the frontal lobe. Consequently we believe that it is not necessary to vent the intraparenchymal air to prevent the recurrence of pneumocephalus.

In this study, we have presented a rare occurrence of intraparenchymal pneumocephalus caused by an ethmoid sinus osteoma. Surgical intervention was beneficial, and the patient was cured. The possibility of an osteoma should be considered, and that an osteoma may occasionally result in intracranial pneumocephalus.

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Long-term suppression of tremor by deep brain stimulation of the ventral intermediate nucleus of the thalamus combined with pallidotomy in hemiparkinsonian patients

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ABSTRACT

Deep brain stimulation (DBS) of the ventral intermediate nucleus of the thalamus (VIM) is a powerful surgical option in the treatment of tremor-predominant Parkinson's disease. However, its therapeutic efficacy depends on the tremor distribution. DBS is highly efficient in relief of distal appendicular tremor but not other types of tremor. Also, it is generally thought that DBS of the VIM has no significant beneficial effects on other motor symptoms of Parkinson's disease. We report two hemiparkinsonian patients, in whom unilateral VIM DBS combined with posteroventral pallidotomy produced long-lasting suppression of not only hand tremor, but also leg or jaw tremor and other motor symptoms.

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1. Introduction

High-frequency deep brain stimulation (DBS) of the ventral intermediate nucleus of the thalamus (VIM) is a promising

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surgical therapy that relieves medically refractory tremor in patients with Parkinson's disease (PD).[1–3] Its therapeutic efficacy, however, depends on the tremor distribution in patients with PD. VIM DBS is highly effective in distal upper limb tremor, but is less effective for tremor of other body structures, such as the lower limbs.[4–8] In addition, the lack of reliable efficacy on other motor symptoms has limited the use of VIM DBS for PD.[3] In this study, we report two patients with PD in whom combined VIM DBS and posteroventral pallidotomy (PVP) synergistically produced long-term suppression of disabling tremor not only in the hand but also in other areas of the body. The treatment also suppressed other motor symptoms.

2. Case report

2.1. Patient 1

A 45-year-old right-handed man, a skilled laboratory technician, noticed tremor of his right arm 5 years earlier. It gradually worsened and spread to his right leg. Because dopaminergic therapy caused gastrointestinal side effects, yet only gave slight improvement of his tremors, he discontinued the medication. Subsequently, his hemiparkinsonian signs worsened and he found it difficult to continue his laboratory work.

On admission, we noted severe tremor of his right hand and leg (both at rest and standing) and mild rigidity of his right upper and lower extremities. The pre-operative scores on the Tremor Rating Scale (TRS)[9] for his upper and lower extremities (Part A, score 5) were 8 and 6, respectively. His Unified Parkinson's Disease Rating Scale (UPDRS) Part III motor score was 10. Pre-operative brain MRI was normal. He was referred for surgery after obtaining prior informed consent from the patient and his family.

A quadripolar DBS electrode (Model 3389; Medtronic, Minneapolis, MN, USA) was implanted in the left VIM with the aid of MRI, third ventriculography, and microelectrode guidance. The optimal target was determined to be 7 mm posterior and 13.5 mm lateral to the midpoint of the anterior commissure–posterior commissure (AC–PC) line, and on the AC–PC line. After the insertion and stimulation of the DBS electrode, his upper, but not lower, limb tremor disappeared.

A left PVP was performed simultaneously according to the method we have previously described.[10] The optimal target for the posteroventral part of the globus pallidus internus (GPi) was determined to be 2 mm anterior and 20 mm lateral to the midpoint of the AC–PC line, and 1 mm dorsal to the third ventricle floor. After creating a test lesion (45 °C, 60 s), a permanent anatomical lesion was made by heating the electrode tip to 72 °C for up to 70 s. The electrode was moved in 2-mm increments in the lateral and dorsal direction, and the lesioning process was repeated to increase the overall size of the lesion.

During the pallidotomy his right leg tremor ceased and disappeared within a few hours. An implantable pulse generator (Soletra; Medtronic) was then placed in the left subclavicular region. The DBS lead implanted in the left VIM and the coagulative lesion made by the left GPi pallidotomy is shown in an MRI 7 days after surgery (Fig. 1).

After extensive trials, we delivered monopolar stimulation using contact 0. The optimal stimulation parameters were a frequency of 160 Hz, pulse-width of 90 μs, and an 1.5 V amplitude. Without stimulation, the TRS score for his upper extremity tremor was 4. His lower extremity tremor remained completely suppressed after surgery. At the 40-month follow-up, the therapeutic benefits remained unchanged. With stimulation, his TRS score was 0, and his UPDRS motor score was 1.

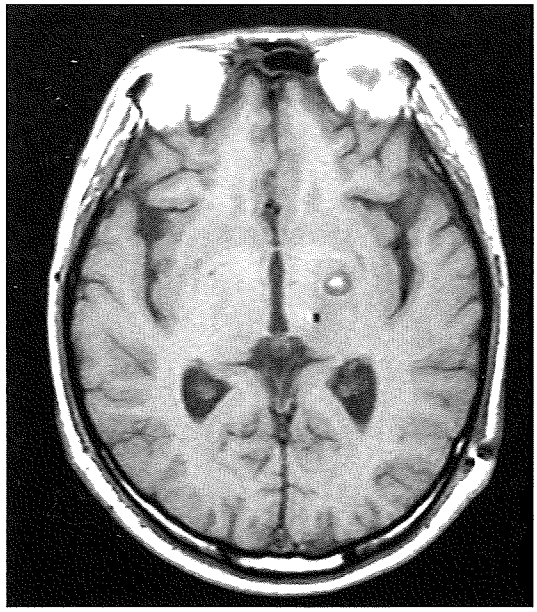

Fig. 1. Patient 1. Axial T1-weighted MRI 7 days after surgery showing the coagulative lesion made by the left globus pallidus internus pallidotomy and the deep brain stimulation lead more posteriorly in the left ventral intermediate nucleus of the thalamus.

2.2. Patient 2

A 70-year-old right-handed farmer noticed tremor of his left hand one year earlier. It gradually worsened and spread to the jaw. Several pharmacological trials produced unsatisfactory results and they were therefore discontinued. On admission, there was no apparent neurological abnormality except for mild rigidity on the left upper and lower extremities and severe parkinsonian tremor of the left hand, arm and jaw. His pre-operative TRS score was 23 and his UPDRS motor score was 13. Pre-operative brain MRI was normal. He was referred for surgery after obtaining prior informed consent from the patient and his family.

The surgery for right VIM DBS and PVP was performed as described above. Intra-operatively, the insertion and stimulation of the DBS electrode produced immediate and complete alleviation of his hand tremor, but not jaw tremor. His jaw tremor ceased and disappeared after the creation of the PVP lesion.

For chronic stimulation, we applied bipolar stimulation using contacts 0 and 2, as cathode and anode, respectively. Stimulus parameters were frequency of 160 Hz, pulse-width of 90 μs, and amplitude of 2.5 V. Without stimulation, the TRS score for his left upper extremity tremor was 4. During stimulation, his TRS score was 0 and his UPDRS motor score was 2. These therapeutic benefits with combined VIM DBS and PVP remained unchanged at the 41-month follow-up after surgery.

3. Discussion

In selected patients with PD, disabling tremor can be the main symptom.[11] Because the patients suffering from tremor-predominant PD often have a benign disease course, unilateral VIM DBS could be considered in those patients in whom other motor fea-

tures are not a source of disability.[3,8,11] Parkinsonian tremor is also effectively treated with thalamic surgery (i.e. thalamotomy and thalamic VIM DBD).[2,3] However, the reversibility, ability to adjust stimulating parameters, and the fewer adverse effects of DBS[2] have led to its popularity and so VIM DBS has replaced thalamotomy for parkinsonian tremor.[3]

A disabling tremor might also be a suitable selection criterion for DBS of the subthalamic nucleus (STN).[11,12] However, this is largely based on results from patients with advanced PD who had undergone bilateral STN DBS while receiving optimal medication.[11,12] It remains unknown whether the tremor-alleviating effects of unilateral STN DBS are comparable to those of VIM DBS in hemiparkinsonian patients. In addition, the therapeutic benefits of VIM DBS are obtained immediately, while tremor control with STN DBS might be delayed and programming is complex.[13]

Many studies have looked at changes in cognitive functions, particularly in aged patients.[13,14] It seems likely that thalamic VIM DBS is currently the most reliable and safe procedure, with respect to cognitive side effects, to control disabling tremor in hemiparkinsonian patients.

The therapeutic efficacy of VIM DBS in suppressing tremors depends upon the distribution of the tremor in the body. VIM DBS is highly effective in distal upper limb tremor, but is less effective for tremor of the lower extremities, proximal limbs, or midline (axial) body structures.[4–8] In addition, VIM DBS is not a reliable treatment with respect to other motor symptoms such as rigidity and akinesia.[3]

In our two patients with unilateral tremor-predominant PD, we therefore carried out PVP in addition to VIM DBS surgery. The combination of VIM DBS and PVP resulted in a long-lasting (over 3 years), marked alleviation of not only hand tremor, but also leg or jaw tremor and other motor symptoms.

Randomized single-blind studies in PD patients have also shown that PVP produced long-term significant reduction of contralateral motor symptoms such as tremor and drug-induced dyskinesias.[15,16] However, PVP for PD has been largely restricted to unilateral procedures because of reports of speech disturbance and worsening cognitive function after bilateral PVP.[3]

In conclusion, similar to our report of a patient with Holmes' tremor,[17] we suggest that unilateral PVP is a useful additional treatment option in hemiparkinsonian patients with disabling tremor who undergo VIM DBS. However, this surgery requiring multiple passes through the brain, may increase the risk of procedural complications such as hemorrhage.[18]

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Brief Reports

Monozygotic Female Twins Discordant for Phenotype of Wilson's Disease

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Abstract: **Wilson's disease (WD) is an autosomal recessive disorder characterized by the functional disruption of the copper-transporting protein adenosine triphosphatase 7B (ATP-ase 7B). The disease is caused by mutations in *ATP7B* gene. It seems that the type of mutation in *ATP7B* only to some degree determines phenotypic manifestation of WD. We examined two pairs of monozygotic twins discordant for WD phenotype. The first set of twins were *ATP7B* compound heterozygotes c.3207C>A (p.H1069Q)/c.1211_1212insA (p.N404Kfs). The index case developed severe liver failure followed by depressive symptoms, dysarthria, and tremor at the age of 36. Her sister remained presymptomatic at diagnosis at the age of 39. The second twins were *ATP7B* c.3207C.A (p.H1069Q) homozygotes. The index case presented with dysarthria and tremor at the age of 26. Her sister remained clinically presymptomatic at diagnosis at the age of 28. We concluded that the phenotypic characteristics of WD are possibly attributable to epigenetic/environmental factors.** © 2009 Movement Disorder Society

Key words: Wilson's disease; *ATP7B*; monozygotic twins; genotype; phenotype

Wilson's disease (WD; OMIM #277900) is an autosomal recessive disorder characterized by the functional disruption of the copper-transporting protein adenosine triphosphatase 7B (ATPase7B; OMIM *606882). This disruption results in the toxic accumulation of copper, mainly in the liver and brain.[1,2] The disease is caused by mutations in *ATP7B* located on chromosome 13 (GC13M051404). The presentation of WD is extremely variable and may be associated with liver disease, with neurological or psychiatric features, or with abnormalities of the blood or kidneys. In general, WD manifests between childhood and young adulthood, and approximately 4% of patients are older than 40 at the onset.[3] It seems that the type of mutation in the *ATP7B* determines the phenotypic manifestation of WD to only a certain degree.[4–7] Twin studies are an important approach in medical genetics, because they help evaluate the relative roles of genetic and nongenetic factors in disease. In particular, the occurrence of monozygotic (MZ) twins that are clinically discordant may be important to determine the etiology of a disease or the pattern of its inheritance.[8–10] We report here on two pairs of MZ twins with WD. In both twin pairs, monozygosity was confirmed by DNA profiling using AmpFLSTR SGM Plus PCR Amplification Kit that amplifies 10 short tandem repeat (STR) loci (D3S1358, VWA, D16S539, D2S1338, D8S1179, D21S11, D18S51, D19S433, TH01, and FGA) and the gender marker Amelogenin. Concordance for all 10 loci predicts monozygosity with greater than 99.98% probability. Despite their monozygosity, the twins had different disease presentations.

TWINS A1 AND A2

This set consisted of female twins born in 1956. Both sisters grew up in the same village, graduated eight school classes, and were working as helpers in the school kitchen. Both sisters got married at the age of 20 and always lived in close neighborhoods. Each of them gave birth to two children. A molecular genetic analysis of *ATP7B* mutations (kindly performed by Department of Gastroenterology, Hepatology and Endocrinology, Charite, Berlin, Germany) revealed that both twins are compound heterozygotes carrying

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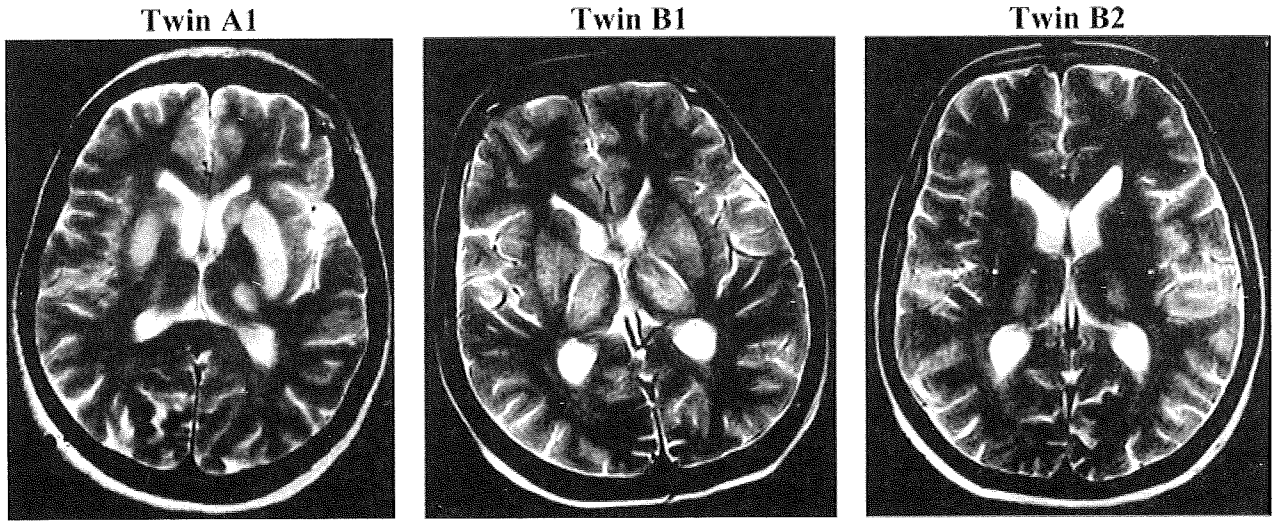

FIG. 1. The brain MRI: hyperintensive areas on T2-weighted images of the basal ganglia and thalami are visible in twin A1, and twins B1 and B2 (changes are more advanced in twin B1 than in B2).

c.3207C>A (p.H1069Q) and the c.1211_1212insA (p.N404Kfs) mutations.

Twin A1 (Index Case)

The first twin was evaluated for WD at our center in 1994, at the age of 38 years. At the age of 7–10 years she had mild jaundice that lasted for a few days. At that time, a local pediatrician diagnosed viral hepatitis without performing any diagnostic tests. The patient was clinically healthy until the age of 35, when she started to complain of fatigue, but did not yet seek medical help. One year later, she was admitted to the local hospital because of jaundice, hemolytic anemia, and liver function decompensation. Positivity for antibodies against hepatitis B (anti-HB) and hepatitis B core antigen (anti-HBc) was detected, but tests for antigens were negative. Liver USG showed areas of increased nonhomogenous echogenicity. Liver biopsy showed the presence of scars and regenerative nodules with inflammatory infiltrates. Liver cirrhosis postviral hepatitis was diagnosed. One year later, she manifested with neuropsychiatric symptoms and was admitted to our hospital. At admission, the woman was hypomimic, and her speech was monotonic, slow. She had moderately increased muscle tonus, positional tremor of the hands and legs; her gait was on a wide base and ataxic. A psychiatrist diagnosed depression. A MRI of the brain revealed hyperintensive areas on T2- and PD-weighted images within the basal ganglia bilaterally, and features of cortical–subcortical brain atrophy (Fig. 1). Kayser-Fleischer (KF) rings were noted bilaterally. The results of routine laboratory investigations and copper metabolism parameters are shown in Table 1.

Twin A2

The second twin was assessed for WD at the age of 39 years. She had no history of the hepatic, neurological, and psychiatric symptoms. She had no KF rings, and a brain MRI and liver CT did not reveal any abnormalities. The twin had decreased serum ceruloplasmin and serum copper, and the results of other routine laboratory tests were within normal limits (Table 1). A serum positivity for anti-HB and anti-HBc antibodies was detected.

TWINS B1 AND B2

This set consisted of female twins born prematurely in 1979 in the 7th month of their fetal life. Both sisters had vocational school education. Neither sister had gotten married; both were living with their parents at the time of WD diagnosis. Both sisters had been working since 18 years of age at a nearby supermarket as physical workers. A molecular genetic analysis of *ATP7B*, performed using PCR-RFLP (polymerase chain reaction-restriction fragment length polymorphism) method (as described in Ref. 11), revealed the homozygous missense mutation c.3207C>A (p.H1069Q) in both twins.

TABLE 1. *Results of laboratory tests at diagnosis, in the twin pairs A and B*

	Twins A		Twins B	
	Twin A1	Twin A2	Twin B1	Twin B2
Biochemical parameters of copper metabolism				
Serum ceruloplasmin (mg/dL) (normal: 25–45)	10.6	11.7	0.0	5.4
Serum copper (μg/dL) (normal: 70–140)	60.0	30.0	26.8	54.7
Copper excretion in urine within 24 hr (μg/24 h) (normal: 0–50)	50.0	69.0	427.0	349.0
Liver function parameters				
Aspartate (IU/L) (normal 0–40)	37.0	19.0	19.0	14.7
Alanine aminotransferases (IU/L) (normal: 0–38)	32.0	38.0	10.0	10.7
Gamma-glutamyl transpeptidase (IU/L) (normal: 8.0–54.0)	70.0	nd	19.0	23.1
Alkaline phosphatase (IU/L) (normal: 35–123)	122.0	87.0	61.0	48.7
Bilirubin (mg/dL) (normal: 0.2–1.2)	1.2	0.9	1.6	2.8
Serum albumin (g/dL) (normal: 3.5–5.3)	3.4	3.4	4.5	4.2
INR (normal: 0.8–1.2)	nd	nd	1.2	1.1
Kidney function parameters				
Urea (mg/dL) (normal: 15.0–39.0)	37.0	25.0	30.0	29.9
Creatinine (mg/dL) (normal: 0.4–1.4)	1.1	0.8	0.7	0.9
Routine hematological parameters				
White blood cells ($\times 10^9$/L) (normal: 4.1–10.9)	7.7	6.7	4.1	3.7
Red blood cells ($\times 10^{12}$/L) (normal: 3.5–5.1)	4.2	4.2	5.1	4.7
Platelets ($\times 10^9$/L) (normal: 140–440)	100	243	128	80

nd, not determined.

Twin B1 (Index Case)

In 2000, the patient had her first hospital admission for lung pneumonia. Then, thrombocytopenia was first diagnosed. In 2005, at the age of 26, she began to experience dizziness, headaches, general weakness, and speech slowness. In 2007, the patient was admitted to our department for diagnostics. A neurological evaluation revealed mild dysarthria; slight paresis of left upper limb; slight ataxia, mainly of the lower limbs; an unstable gait on a wide base; and a loss of balance. She had KF rings. Brain MRI revealed extensive areas of increased signal in T2-weighted images of basal ganglia, thalamus, mesencephalon, pons, and cerebral peduncle, it also detected distinct atrophy of the cerebellum and features of brainstem atrophy (Fig. 1). Liver USG revealed hepatosplenomegaly within the left lobe, multiple hyperechogenic lesions. The patient had abnormal copper metabolism; she also had increased blood bilirubin, leucopenia, and thrombocytopenia (Table 1). Tests for anti-HB and anti-HBc antibodies were negative.

Twin B2

In 2007, the second twin was assessed for WD at our department. She had irregular menstruations and periodically recurrent nose bleeding. A neurological examination did not reveal abnormalities. She had KF rings that were less saturated than in the first twin. Brain MRI revealed increased signal in T2-weighted images of the lenticular ganglia, thalamus, cerebral peduncle, and pons (Fig. 1). Liver USG revealed hepatosplenomegaly. The portal vein was dilated (11.9 mm). Routine laboratory investigations were normal with the exception of increased bilirubin, a decreased leukocyte count, and thrombocytopenia (Table 1). Test results for anti-HB and anti-HBc antibodies were negative.

DISCUSSION

Some prior reports have postulated that *ATP7B* allelic heterogeneity is the most likely basis for the phenotypic variation observed in WD. However, the high ranges for phenotypic presentations were detected among patients with similar genetic defects of *ATP7B*.[4–7] The monozygosity of described twin pairs further suggests that variability in the WD phenotype does not arise solely from allelic *ATP7B* heterogeneity, but is likely to be due to additional factors.[2,12,13]

In the case of our twin pair A, it might be supposed that viral liver impairment during early childhood in Twin A1 may have triggered chronic hepatic inflammation and induced clinical manifestations of a copper-overloaded liver, followed by the development of neurological symptom. However, it should be mentioned that childhood jaundice in twin A1 might be the first symptom of WD and might not be related to viral infection (none diagnostic tests were then performed). It is worth

to mention that in 1993 both sisters were positive for anti-HBs, HBc, and HBe antibodies in the serum. However, the precise determination of the exact time they were infected with hepatitis B virus is difficult. Among other factors that could contribute to liver damage in our symptomatic patients, alcohol and drugs may be considered. However, none of our patients drank alcohol, and none reported drug abuse before diagnosis.

The difference in the clinical phenotype among MZ twins might arise from epigenetic differences, that is, differences in DNA methylation and histone modification.[14,15] Some evidence indicates that relatively small differences in epigenetic patterns can have a large impact on phenotype. However, epigenetic differences are more distinct among MZ twins who are older, have different lifestyles, and have spent less of their lives together, underlying the significant role of environmental factors in translating a common genotype into a different phenotype.[14,15] In the case of the twins we described, both twin pairs were reared together for the entirety of their lives, had similar lifestyles, and similar social and economic levels. So the impact of external factors on differences in epigenetic patterns seems to not be of great importance in this case. However, differences in epigenetic patterns in genetically identical individuals could be explained not only by the influence of external factors, but also by the internal factors.

The precise role of genetic and nongenetic factors in modifying the clinical phenotype of WD is far from apparent. However, the discordance in the phenotype of the siblings described establishes that these factors are important. In the future, defining the interplay among genetic, epigenetic, and environmental influences will possibly be important for determining the extent and age that any given individual with WD will be affected.

Author Roles: Anna Członkowska, MD, PhD: design, conception, execution, critical revision of all or part of the Submitted Publication Material.

Grażyna Gromadzka, PhD: conception, the analysis of genetic and medical data, writing of the first draft, administrative, technical support.

Grzegorz Chabik, MD, PhD: patients' diagnosing and treatment, completeness of medical documentation.

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