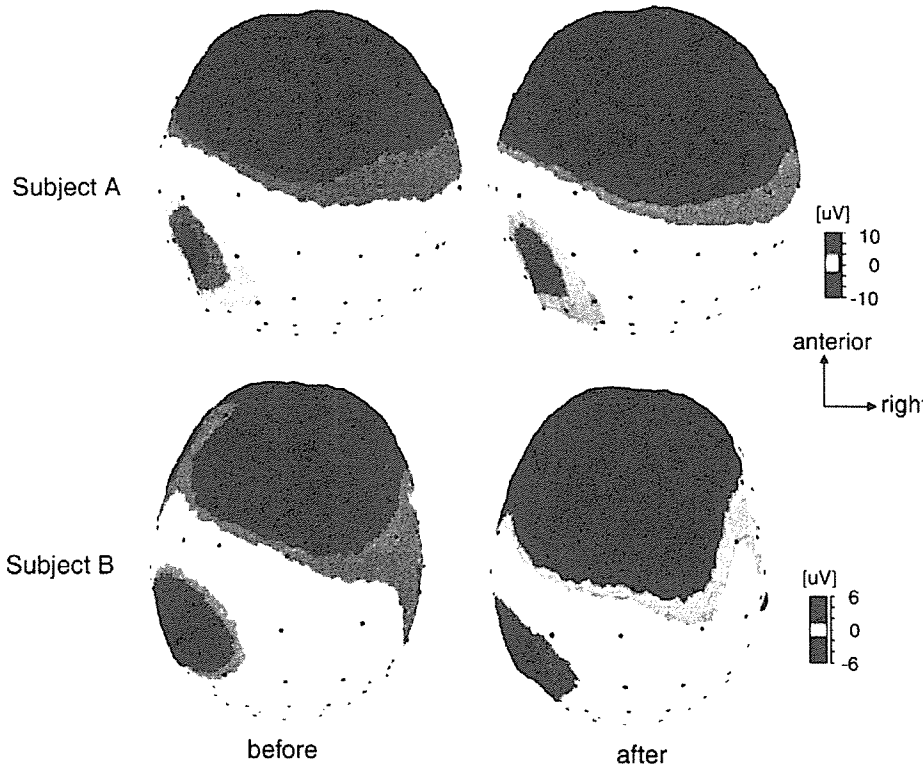

Fig. 4. Topographical SEP mapping using 62-electrode recording in 2 subjects on their realistic heads shape at N30 latency from before (left) to after (right) the application of monophasic 0.2 Hz rTMS over PMC. The amplitude distribution was practically unchanged, whereas the amplitude of the frontal component was clearly increased. Blue–red color scale illustrates the amplitudes, and maximum positivity is coded as red and maximum negativity as blue.

SMA because the extent of the field stimulated by the coil was not exactly defined. If so, SEPs should have changed after stimulation of not only PMC but also MC or SMA. The lack of these changes indicates that amplitude increases of frontal N30 component were elicited by the effects of monophasic 0.2 Hz rTMS over PMC or the more rostral sites such as the prefrontal cortex. Previous studies have reported changes in SEPs following rTMS over MC (Enomoto et al., 2001) or somatosensory cortex (Ragert et al., 2004), whereas no changes were found after rTMS over PMC (Enomoto et al., 2001; Satow et al., 2003). The discrepancy may be due to different stimulation parameters: Enomoto et al. (2001) applied rTMS over PMC at a lower intensity (1.1 times the active motor threshold) and a smaller number (200) of stimuli than those used in this study. Satow et al. (2003) used an intensity (90% RMT) similar to this study and a larger number (900) of stimuli than this study. The most striking difference was the frequency and the total duration of stimulation: these studies used higher frequencies (1 or 0.9 Hz) and shorter total durations (200 and 1000 s) than the present study (0.2 Hz, 1250 s). It is noteworthy that very low-frequency stimulation (0.2 Hz) used in this study and a recent study on dystonia (Murase et al., 2005) produced lasting effects on SEPs, rCBF and clinical symptoms. The previous studies using similar frequencies as a single but not repetitive TMS could be reanalyzed with the view that 0.2 Hz stimulation is repetitive. Finally, it should be noted that the TMS pulses in the present experiments were monophasic rather than the usual biphasic pulses that are employed in higher frequency rTMS. As noted by Tings et al. (2005), biphasic pulses produce effects that may be a combination of effects from two monopolar pulses of different directions. Since these may well be different and even cancel each other, monophasic rTMS appears to be more efficient in generating aftereffects than the usual biphasic rTMS. This may be another reason why the results in the present experiments differ from (and in some respects are more powerful than) those of higher frequency biphasic rTMS. The lack of changes after 1 Hz biphasic stimulation, as shown in the present study, warrants further studies determining whether the frequency or the phase or both are responsible for the cortical effect. If the effect of rTMS over motor cortex on SEPs is orientation selective, it may also account for the absence of effect in the present experiments.

After the application of monophasic very low-frequency rTMS over PMC, rCBF increases were observed most significantly in the left PMC and the prefrontal cortex, the regions under the coil. Although previous study reported decreases of rCBF after low-frequency (1 Hz) rTMS over PMC (Siebner et al., 2003), another study reported increases under the coil (Speer et al., 2003) during the same frequency rTMS over MC or no changes at stimulation site after the same frequency rTMS over MC in healthy subject with artificial pain (Tamura et al., 2004). After less than 1 Hz frequency (0.25 Hz) rTMS at Cz for 2 weeks, rCBF of the stimulus area increased in depressed patients (Peschina et al., 2001). From these studies, although a major hypothesis has been that low-frequency rTMS results in inhibitory physiological changes, imaging studies have yielded inconsistent results. It must, however, be emphasized that increases in inhibitory interneuronal activities could increase rCBF while decreasing cortical excitability. In support of this hypothesis, cortical inhibitory mechanisms as tested with paired-pulse TMS are associated with increase in rCBF, as has

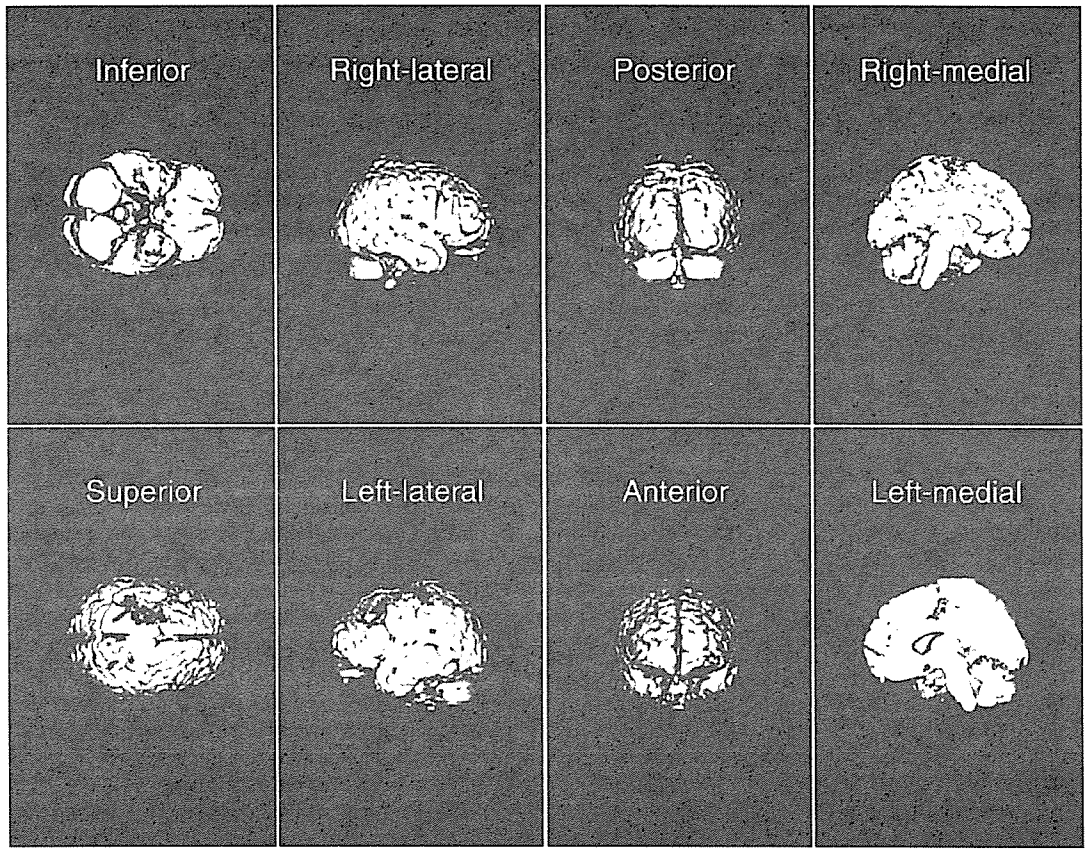

Fig. 5. Parametric statistical rendering maps showing areas of increased blood flow after application of monophasic 0.2 Hz rTMS over PMC compared with before. Regions of increase in the left frontal lobe, including Brodmann areas 9 and 6, correspond to prefrontal cortex and PMC and the right cingulate gyrus (see also Table 2).

been shown in previous study (Strafella and Paus, 2001). Similar rCBF increase was also described using different rTMS frequencies exerting inhibitory and excitatory effect on the cortex (Rounis et al., 2005). Changes in rCBF were also seen in the left middle frontal cortex and right cingulate gyrus, distant from the stimulated site. These areas are connected anatomically and functionally to PMC. Basal ganglia could modulate activities of these areas via PMC, which is the thalamo-cortical projection.

The previous studies showed that the frontal N30 component decreases in amplitude prior to hand movement (Starr and Cohen, 1985; Shimazu et al., 1999) or during motor imagery (Cheron and Borenstein, 1992; Rossini et al., 1997). Although similar gating has also been reported in the parietal P26 components (Starr and Cohen, 1985; Shimazu et al., 1999), the changes of SEPs in this study were observed only in frontal N30 component, not in parietal counterpart (P26 component) after monophasic 0.2 Hz rTMS over PMC. These frontal and parietal components are composed of tangential and radial dipoles. Allison et al. (1991) concluded that N30 is generated in area 3b for its tangential component and in area 1 for its radial component. Other studies have suggested the precentral radial generators of frontal N30 component, especially on SMA (Desmedt and Bourguet, 1985; Cheron and Borenstein, 1992; Mima et al., 1999). If monophasic 0.2 Hz rTMS over PMC was affected on the tangential and/or postcentral radial dipole, the parietal component should also change with the frontal component. In the present study, however, topographic changes in SEP after application of monophasic 0.2 Hz rTMS over PMC were observed only in the frontal component (Fig. 4). Although performed in only two subjects, this study suggested that monophasic 0.2 Hz rTMS over PMC hardly affected the postcentral generator of the tangential and radial component and implies that the increase of frontal N30 component is due to an action on precentral generators

Table 3
Areas of rCBF that increased by rTMS over PMC

Brain region	MNI coordinates			Z-score
	x	y	z	
Left middle frontal gyrus (Brodmann Area 9)	−38	28	38	4.90
Left precentral gyrus (Brodmann area 6)	−16	2	66	4.83
Right limbic lobe cingulate gyrus (Brodmann area 24)	18	−2	42	4.80

The panel shows the MNI coordinates and Z scores of maximal peaks of regions where cerebral blood flow was significantly increased after application of monophasic 0.2 Hz rTMS over PMC compared with before (see also Fig. 5).

of the radial component. The precise location of these precentral generators is not known, particularly since it has been shown that SMA does not receive short-latency somatosensory input directly from peripheral median nerve (Barba et al., 2003). Nevertheless, although the exact generator of N30 component cannot be determined, our findings indicate that PMC is closely linked to the generator of this SEP component.

Parkinson's disease or patients with parkinsonism in parallel with the reduction of Parkinsonian symptoms (Rossini et al., 1995; Pierantozzi et al., 1999). The increase of rCBF in SMA during voluntary movement in Parkinsonian patients was observed only in the "on" condition (Rascol et al., 1992). These studies might suggest that dopaminergic transmission in basal ganglia influenced the increase of frontal N30 component. The anatomical and functional model of basal ganglia comprises dense connections between basal ganglia and PMC (Alexander and Crutcher, 1990), a region of rCBF increasing after application of rTMS in this study.

In a previous study using the same parameters of rTMS as in the present report, Murase et al. (2005) found that rTMS over PMC improved the symptoms of patients with focal writer's cramp. They argued that very low-frequency rTMS reduced the usual overactivity in PMC that is observed in dystonia and that this contributed to the improvement in clinical symptoms. Since patients with hand dystonia have been reported to have enlarged N30 components of the SEP (Reilly et al., 1992), it might also have been expected that the N30 would be reduced by the same intervention.

At first sight, the present results in healthy subjects appear to be the opposite to those expected from the previous report since rTMS over PMC increased rCBF and increased N30. However, as noted above, an increase in blood flow is consistent with an overall reduction in physiological activity if this is caused by an increase in inhibition. Similarly, it is conceivable that an increase in N30 also reflects inhibition rather than facilitation, the opposite to the N30-decreasing effect of motor imagery (Cheron and Borenstein, 1992). As argued by Kujirai et al. (1993), inhibition of neurons may be accompanied by a decrease in membrane resistance, leading to larger current flows during synaptic activation. If so, then an inhibited neuronal population can respond to a given synaptic input with a larger surface SEP than control. Alternatively, it is possible that the enlarged N30 in dystonic patients could respond differently to rTMS than in healthy subjects. However, since Murase et al. (2005) did not examine the behavior of the N30 in their patients, this must await further studies.

In conclusion, the present study demonstrated that application of monophasic 0.2 Hz rTMS over PMC increased the amplitude of frontal N30 component of median SEPs, and this change was associated with increased rCBF of PMC and the prefrontal cortex. Our findings suggest that PMC play a role in central sensorimotor integration by influencing the incoming somatosensory input for motor control.

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NEUROREPORT

Repetitive transcranial magnetic stimulation alters optic flow perception

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Optic flow, the visual motion radiating from the center to side or opposite directions, is used to control human locomotion. Low-frequency repetitive transcranial magnetic stimulation (0.9 Hz, 10 min) was applied to the primary visual cortex (V1) and the extrastriate area (V5/MT) of 12 healthy participants to study effects of repetitive transcranial magnetic stimulation on coherent optic flow perception. Cz stimulation was used as control. Participants were instructed to correctly identify focus for dots with coherent optic flow motion. Ratios of reaction times between V1 and Cz or between V5 and Cz 40 min after repetitive transcranial magnetic stimulation significantly increased. These results suggest the prolonged inhibitory effect of low-frequency repetitive transcranial magnetic stimulation on optic flow perception. Low-frequency repetitive transcranial magnetic stimulation is a useful tool for exploring visuospatial cognition. *NeuroReport* 00:000–000 © 2006 Lippincott Williams & Wilkins.

Keywords: coherent motion perception, optic flow, prolonged effect, repetitive transcranial magnetic stimulation, visual cortex

Introduction

Transcranial magnetic stimulation (TMS) is a noninvasive method used to stimulate the human visual cortex in behaving participants. Single TMS over the occipital cortex induces flash-like light sensation, known as 'phosphenes' [1]. The minimum TMS intensity required to elicit phosphenes is defined as the phosphene threshold (PT). PT was demonstrated to remain temporally stable among participants. Visual imagery tasks decrease PT [2], and PT is lower in methylenedioxymethamphetamine (MDMA) users [3] and migraineurs [4]. Therefore, PT has been suggested to serve as an index of visual cortex excitability [5,6].

Recently, repetitive TMS (rTMS) has been widely used to modulate excitability of the regional cerebral cortex. Previous studies showed that the frequency of rTMS was an important factor. In general, low-frequency (LF) stimuli around 1 Hz reduce cortical excitability, whereas high-frequency (HF) stimuli >5 Hz facilitate excitability. The amplitude of pattern-reversal visual-evoked potentials (VEPs) in the first block and its habituation over sequential blocks decreases after LF-rTMS over the primary visual cortex (V1) in normal individuals [7]. In contrast, HF-rTMS in blind people has been reported to increase reading speed of Braille characters [8]. Several LF-rTMS studies have been previously conducted to investigate functions of the visual cortex. Stimulation of the occipital lobe increases PT [4,6], impairs visual mental imagery [9] and alters contrast detection [10].

Visual information is first carried to V1, and is subsequently processed through parallel pathways consisting of dorsal (spatial vision) and ventral (object vision) streams [11]. The extrastriate area (V5/MT) plays an important role in the dorsal pathway, and contributes to motion perception. The direction of locomotion can be determined from information defined by the optic flow (OF): that of self-motion can be directly perceived from the 'focus of radial outflow' in the OF pattern [12]. V5/MT is also a key structure for perception of OF [13]. In patients with Alzheimer's disease and mild cognitive impairment, OF perception is selectively impaired [14]. Previous studies have shown that motion priming was abolished [15], and motion after-effect duration was reduced [16] with HF-rTMS over V5/MT; however, there have been no studies on effects of LF-rTMS on coherent OF perception. Therefore, we investigated motion perception of OF after LF-rTMS over V1 or V5.

Methods

Participants

Seventeen healthy, right-handed participants (10 men and 7 women; age range, 20–40 years; mean age, 25.1 years) with normal or corrected-to-normal vision participated in the

experiments. All participants gave informed consent to the studies. The study was approved by the Ethics Committee of Kyushu University, and conformed with the tenets of the Declaration of Helsinki.

Phosphene threshold

On the first day of the study, PT and optimal position of TMS were determined. Participants sat on a chair in a dark room, wore a blindfold and a swimming cap with a grid parallel to the medio-sagittal line and the interaural line to capture the accurate repositioning of the coil on the following days. We delivered paired pulse (interstimulus interval, 71 ms) TMS using a Magstim Rapid stimulator (Magstim Co., maximal output 1.6 T) and a figure-of-eight coil (inner diameter, 70 mm) to determine PT. PT was defined as the minimal intensity of the stimulator output to evoke uniform phosphenes in at least two of three consecutive trials.

After dark adaptation for 10 min, PT of the right V1 was measured, which was completed in about 30 min. Subsequent light exposure for 5 min was given to avoid changes of visual cortex excitability owing to prolonged sensory deprivation [17]. After readaptation to darkness, PT of the right V5 was measured. We chose the right hemisphere because of its predominance in motion perception, as seen in VEP or PET studies [18,19]. The order to determine optimal positions and PTs for V1 or V5 was counterbalanced betweenparticipants.

The coil was initially positioned 1 cm laterally and 3 cm above the inion for V1, and 5 cm laterally and 3 cm above the inion for V5. Two participants did not perceive phosphenes until 80% of the stimulator output; they were excluded from the following experiments. If phosphenes were perceived, their optimal position in 1-cm steps, and optimal direction with 45° steps from upward to rightward directions, was determined.

Evaluation of optic flow perception

To assess OF perception, we used a Windows PC (NEC) and the 'presentation' software (neurobehavioral systems). Participants sat 57 cm away from a 15-inch monitor (30 × 22°) in a dark room. On the monitor with a black background, some of the 400 white dots, used as stimulus, were concentrated or expanded from the focus, whereas others move randomly (Fig. 1). Focus was set at 5° left or right from the center of the monitor. Participants were instructed to correctly identify the locations of focus as soon as possible by using computer mouse buttons with their thumbs. Luminance of the white dots was set at 48 cd/m^2, whereas that of the background was set at 0.1 cd/m^2; therefore, the contrast level was 99.6%. Ratios of dots (RODs) with coherent movement of 'concentrating' or 'expanding' varied at 11 steps from 5 to 70% in a random order. Each step consisted of 20 trials (1 session=20 trials × 11 steps). An OF stimulus was shown for 750 ms with an interstimulus interval of 1250 ms. Speed of dot movement was 5°/s. One session was completed in 10 min. Rate of correct choice and reaction time (RT) for each ROD were recorded.

Experimental procedures

Each experiment consisted of three sessions before, immediately after and 40 min after rTMS. rTMS (applied at a rate of 0.9 Hz for 10 min at PT intensity) was focused to Cz (control condition), to the right V1 or V5, on separate days in a counterbalanced order. Participants practiced the motion perception task 1 day before the experiment and performed one practice session before measurement on each experimental day.

Data analysis

We determined the threshold of motion perception (TMP), which was defined as the ROD yielding 81.6% of correct responses according to the Weibull's function (Fig. 2) for each participant. TMPs and mean RTs of V1 or V5 stimulations were standardized against values obtained with Cz stimulation. Effects of rTMS on TMPs and mean RTs were evaluated using two-way repeated measures analysis of variance (ANOVA) with time (before, immediately after and 40 min after rTMS) and site of stimulation (V1/Cz, V5/Cz) as within-subject factors. A post-hoc analysis was performed using a multiple comparison with Bonferroni correction. A P value less than 0.05 was considered significant for all statistical analyses.

Results

Phosphene threshold

Fifteen of 17 participants perceived phosphenes, which tended to be on the contralateral side of rTMS, and most of them were white or light green. Two participants stimulated at V1 and four participants at V5 experienced moving

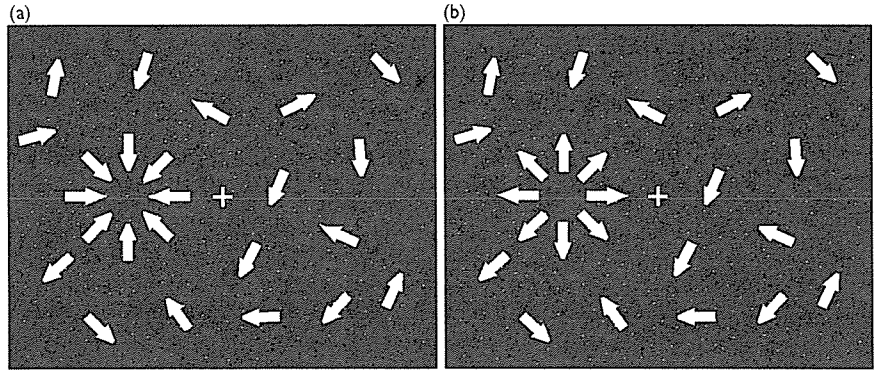

Fig. 1 Optic flow stimuli used in this study. Some of the 400 white dots used as stimulus were concentrated (a) or expanded (b) from the focus point. Participants were instructed to correctly identify locations of the focus that was left or right of the fixation point (cross).

phosphenes. Two of 15 participants conflicted with the schedule and one participant felt discomfort during rTMS; so, only the remaining 12 participants participated in the following rTMS experiments. Mean PTs were 58.9% for V1 and 57.5% for V5, respectively. Optimal direction of the handle of the magnetic coil was mostly rightward for V1, but rightward or oblique for V5.

Effect of repetitive transcranial magnetic stimulation on optic flow perception

Mean RTs at all levels of ROD and TMP for each stimulus site (V1/Cz, V5/Cz) are shown in Fig. 3. No significant temporal changes in RTs and TMPs were seen. We assumed that RTs could change mostly around TMP. Thus, we arbitrarily divided mean RTs into three subgroups: mean RTs around the threshold, subthreshold and suprathreshold (Fig. 4). Mean RT at threshold was calculated by averaging RTs at four ROD levels around TMP. Two-way ANOVA revealed a significant temporal increase in RT [$F(2,22)=4.943$; $P=0.017$], but neither a significant effect of stimulus site (V1/Cz vs. V5/Cz) nor a significant interaction between time and stimulus site was found. Multiple comparisons between time points revealed a significant decrease in RT between before rTMS and 40 min after rTMS ($P=0.023$). These results indicated that RTs for V1 and V5 stimulations increased 40 min after rTMS compared with Cz stimulation.

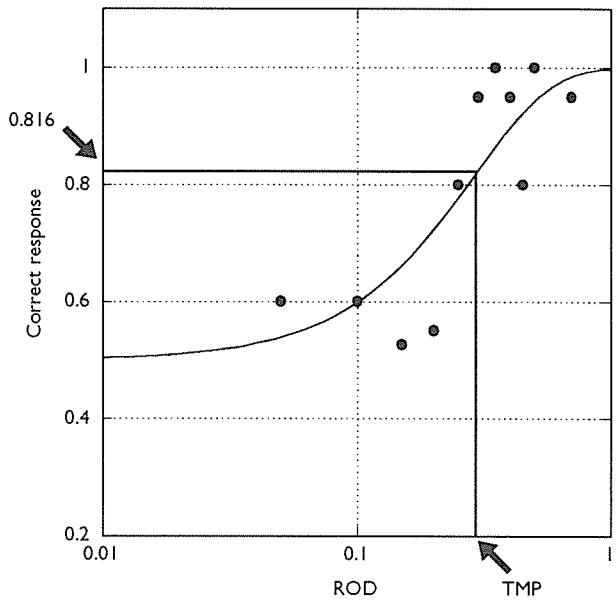

Fig. 2 Determination of the threshold of motion perception (TMP). TMP of a session (arrow) for each participant was defined as the ratio of dots (RODs) with coherent movement in stimuli yielding 81.6% of correct responses plotted according to the Weibull's function. The curve was fitted for 11 steps of ROD (filled dots). The correct response for each step was calculated for 20 trials.

Discussion

In this study, LF-rTMS over V1 or V5 inhibited OF perception, which lasted as long as 40 min as assessed by RT. We determined PT by paired TMS because of the difficulty in evoking phosphenes using single TMS in a preliminary study. Paired TMS reduced PTs as reported previously [1]. As we used rTMS with a single pulse, the intensity of rTMS was relatively low compared with paired pulse rTMS. Despite the subthreshold rTMS, we demonstrated an inhibitory effect of LF-rTMS on the visual cortex. This result was in good agreement with the results of previous studies showing that subthreshold LF-rTMS inhibited functions of the motor or visual cortex [6,20].

Significant differences were found in RTs but not in TMPs. This implied that RT might be more sensitive to cognitive changes than accuracy rate in rTMS studies [15]. So, how does RT really reflect motion perception? RT consists of visual perceptual and postperceptual (including motor response) processings; however, decision timing is not easy to specify. A recent magnetoencephalographic study [21] showed that accumulated activities in extrastriate areas identified the plausible timing of motion perception that was 150–200 ms before participants manually reacted to stimulation. Therefore, effects of LF-rTMS in our study may result from a decrease in rate or number of firing neurons in visual areas.

We also observed a significant inhibitory effect after 40 min rather than immediately after rTMS. In contrast,

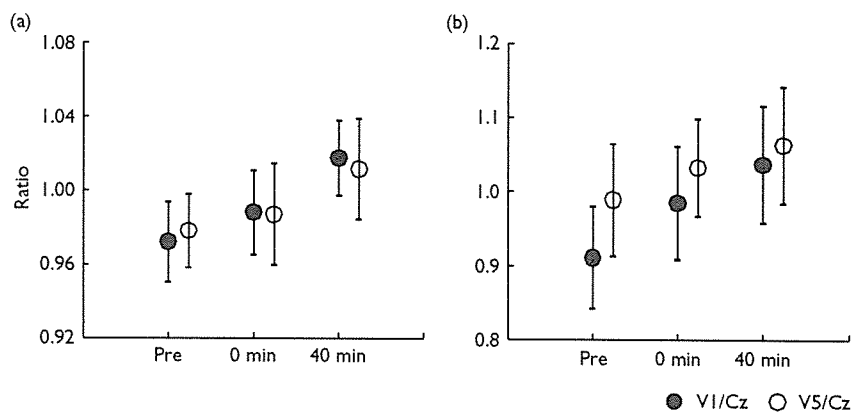

Fig. 3 Performance of motion perception: reaction time (RT) (a) and threshold of motion perception (TMP) (b). Mean RTs and TMPs of V1 or V5 stimulations were standardized against values for Cz stimulation. RTs and TMPs tended to be prolonged with time, but did not reach significant levels. Error bars indicate standard errors of means. Pre, before repetitive transcranial magnetic stimulation (rTMS); 0 min, immediately after rTMS; 40 min, 40 min after rTMS.

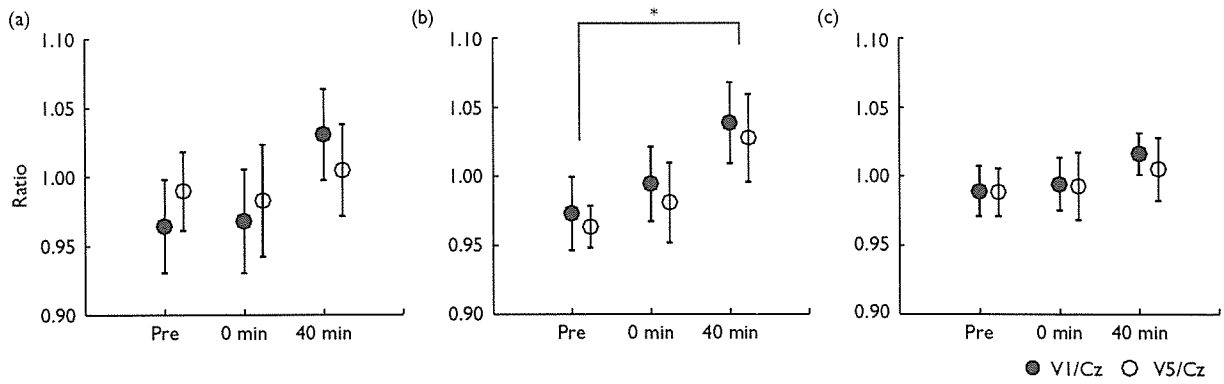

Fig. 4 Classification of reaction times into three groups: subthreshold (a), threshold (b) four steps around threshold of motion perception) and supra-threshold (c). Reaction times to the threshold level show clear changes compared with other groups, indicating a significant increase at 40 min after repetitive transcranial magnetic stimulation over V1 or V5. Error bars indicate standard errors of means.

many rTMS studies revealed an immediate effect that lasted for a short period [7,20]. The mechanism of rTMS remains largely unclear, but the prolonged effect in our study may be related to long-term depression caused by synaptic changes or cell excitability changes [22].

OF is a stimulus related to motion perception and is important for locomotion or navigation [12]. A previous PETstudy [19] showed that V3 and other areas in addition to V5 and V1 were activated by OF. We demonstrated that rTMS over V1 or V5 could modulate OF perception in similar manners, indicating that both V1 and V5 were important for OF perception. It is well known that visual information is processed step by step from V1 to V5/MT, and spreads to higher cortical areas. V1 and V5 stimulations may differentially affect OF perception. In fact, motion after-effect and visual motion priming were also disrupted by rTMS over V5 and not over V1 or posterior parietal cortices [15,16]. When single TMS was applied to V1 after V5, but not before V5, there was a marked decrease in quantity, and a change in quality of phosphenes elicited by V5 stimulation [23]. In addition, double-pulse TMS over V1 or V5/MT during a coherent motion task showed double dissociation in critical time windows, in which critical periods of V1 both preceded and followed that of V5/MT [24]. Although V5/MT obtains visual information through V1 feed-forward activity, back-projections from V5/MT to V1 are also critical for awareness of motion [23,24]. Thus, V1 and V5/MT differentially contribute to motion perception in a time-dependent manner. Although previous studies used single or paired TMS, LF-rTMS may result in modulation of motion perception through V1 as well as V5/MT.

OF is disturbed in patients with Alzheimer's disease and mild cognitive impairment [14], and VEPs to OF in Alzheimer's disease have also been reported to be impaired [25]. Subthreshold LF-rTMS over V1 or V5 in healthy participants can mimic visuospatial disturbance of such diseases as virtual brain lesions, as shown in this study.

Conclusion

LF-rTMS over V1 or V5 altered OF perception until 40 min after stimulation. This prolonged effect probably resulted from long-term depression. Therefore, LF-rTMS can be a useful tool for exploring visuospatial cognition.

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All authors declare that they had no conflicts of interest.

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A distinct subgroup of chronic inflammatory demyelinating polyneuropathy with CNS demyelination and a favorable response to immunotherapy

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Abstract

To explore subclinical central nervous system (CNS) involvement in chronic inflammatory demyelinating polyneuropathy (CIDP), we recorded somatosensory evoked potentials (SEPs) and motor evoked potentials (MEPs) using transcranial magnetic stimulation, to measure central sensory conduction time (CSCT) and central motor conduction time (CMCT) and examined brain and spinal cord MRI in patients with probable CIDP based on the American Academy of Neurology AIDS Task Force criteria. Eighteen patients with probable CIDP (12 males and 6 females; mean age at examination±SD, 45.8±17.0 years; range, 17–72) were included in the study. Of the 13 patients who underwent SEPs, one had prolonged CSCT (8%) and of the 13 who underwent MEPs, four had abnormal CMCT (31%). Cranial MRI revealed five of 18 patients had abnormal scans, only one of which showed multiple ovoid periventricular lesions suggestive of demyelination while none showed any intramedullary lesion on spinal cord MRI. Thus, 6 of the 18 patients were considered to have subclinical demyelinative CNS involvement which had lower disability on Global Neurological Disability Score (GNDS) ($p=0.0061$), a male preponderance (0.0537) and a larger compound muscle action potential (CMAP) amplitude in the median nerve ($p=0.005$) than those without. The decrease of GNDS with immunologic therapies was nearly significant in the former ($p=0.0556$) but not in the latter. The results of the present study suggest that subclinical CNS involvement in CIDP is not uncommon in Japanese patients and that CIDP with subclinical CNS involvement is more demyelinative thus responsive to immunotherapies while those without have more axonal damage and less responsive to immunotherapies.

Keywords: Chronic inflammatory demyelinating polyneuropathy; Motor evoked potentials; Somatosensory evoked potentials; Central nervous system

1. Introduction

Chronic inflammatory demyelinating polyneuropathy (CIDP) is considered to be an autoimmune disorder of the peripheral nervous system (PNS). Although peripheral myelin is targeted by an autoimmune attack, central nervous system (CNS) involvement has been suggested in a fraction of CIDP patients with the presence of subclinical electrophysiologic and magnetic resonance imaging (MRI) abnormalities.

In two large series, CNS involvement was clinically observed in 5% and 8% of patients, respectively [1,2]. In the electrophysiological study by Ormerod et al. [3], six of 18 patients (33%) had unilateral or bilateral abnormalities in central motor conduction time (CMCT) on motor evoked potentials (MEPs). On brain MRI, a third to a half of CIDP patients have been reported to have brain lesions [3–6] whereas demyelinating lesions with typical appearance of multiple sclerosis (MS) are uncommon; for example, two of

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26 patients (8%) in the series of Hawke et al. [6]. As non-specific brain lesions are frequently encountered on MRI, the electrophysiological methods may be more suitable for detecting demyelinative CNS lesions in CIDP. Therefore, the present study was undertaken firstly to explore subclinical CNS involvement in CIDP patients without clinically overt CNS signs, by electrophysiological methods such as MEPs and somatosensory evoked potentials (SEPs), and by brain and spinal cord MRI. Moreover, it was recently shown that in CIDP patients, treatment response to intravenous immunoglobulin (IVIg) administration was in part determined by degree of peripheral axonal involvement with poor response in those with greater axonal damage [7]. However, it is unknown whether CIDP patients with subclinical CNS involvement respond to immunotherapies well or not. Thus, secondly, we aimed to clarify the difference between patients with subclinical CNS involvement and those without.

2. Subjects and methods

2.1. Subjects

Eighteen consecutive patients with probable CIDP (12 males and six females; mean age at examination±SD, 45.8±7.0 years; range, 17–72) based on the criteria of the American Academy of Neurology AIDS Task Force were included [8]. The demographic features of the patients are described in Table 1. The mean age of onset was 40.5±20.7 years (mean±SD; range 17–72 years). The duration of disease ranged from 2 months to 36 years (mean±SD=5.8±10.9 years). Seven presented with weakness while eleven with combined weakness and sensory impairment. At some stage in the clinical course, all of the patients showed distal limb weakness while sensory disturbance was present in 15. None of the patients had clinical signs of CNS involvement. The clinical courses were chronic progressive in 10 patients, relapsing–remitting in three, and monophasic in five. For the assessment of neuropathy, the Global Neurological Disability Score (GNDS) was used to initially assess the motor neurological disability, sensory loss and areflexia on a scale of 1 to 15 [9]. The GNDS scores before treatment were 12.5±3.0 (mean±SD, range: 6–15). On nerve conduction studies, motor nerve conduction velocities (MCV) were all reduced in all patients in at least more than one nerve. Sensory nerve conduction velocities (SCV) were normal in 5/18, unevoked in 7/18 and reduced in 6/18 in the median nerve and normal in 4/18, unevoked in 8/18 and reduced in 4/18 in the sural nerve. Protein levels in the cerebrospinal fluid (CSF) were elevated in 13 of 17 examined (>40 mg/dl) while none had CSF pleocytosis. All but one patient were subjected to immunotherapies and a 2-point decrease in the GNDS score was considered to be effective. Seven of 17 patients (41.1%) responded to immunotherapies; high-dose corticosteroids (prednisolone 40–60 mg/day with gradual taper) were effective in two of four patients who received it, IVIg was effective in three of five patients, and plasma exchange (PE) was effective in two of five. Three patients who received PE and IVIg showed no

Table 1
Demographic features of patients with CIDP

Patient No.	Sex	Age at onset (year)	Age at exam. (year)	Duration (months or years)	GNDS at peak	CSF cell/protein (/μl, mg/dl)	Clinical course	Response to immunotherapies	Clinical symptoms		Evoked potentials			
									Predominant symptoms	Symmetrical involvement	MEP abnormality		SEP abnormality	
											CNS	PNS	CNS	PNS
1	M	58	65	8y	15	3/217	R	IVIg: +	motor>sensory	+	−	+	ND	
2	M	28	28	1y	11	5/100	CP	IVIg: +	motor>>sensory	+	+	+	−	+
3	F	58	59	4m	15	0/33	CP	IVIg: +	motor>sensory	+	−	+	−	−
4	M	17	17	1y	15	1/58	CP	PE: −	motor	+	−	+	ND	
5	M	47	52	5y	15	1/34	CP	IVIg, PE: −	motor>sensory	+	−	+	ND	
6	F	51	52	1y	11	3/178	CP	PE: −	motor>sensory	+	−	+	−	−
7	M	31	32	11m	9	0/320	CP	IVIg, PE: −	motor>sensory	+	−	+	−	−
8	F	48	52	5y	15	1/55	CP	PE: +	motor>sensory	−	−	+	−	−
9	M	12	18	6y	15	0/266	CP	PE: −	motor>sensory	+	−	−	ND	
10	M	11	45	34y	9	0/67	R	CS: +	motor	+	−	+	+	−
11	M	66	67	1y	15	3/290	CP	CS: −	motor>sensory	+	ND		−	−
12	M	36	42	6y	6	3/62	R	IVIg, PE: −	motor>sensory	+	+	+	−	+
13	M	69	69	2m	13	1/57	M	PE: +	motor>sensory	+	+	+	ND	
14	F	26	26	2m	11	1/157	M	CS: +	motor	+	ND		−	+
15	M	46	46	2m	15	2/127	M	CS: −	motor>sensory	+	ND		−	−
16	M	1	37	36y	8	2/27	CP	IVIg: −	motor>sensory	+	+	+	−	+
17	M	46	46	2m	13	ND	CP	ND	motor=sensory	+	ND		−	+
18	F	72	72	2m	15	1/28	CP	IVIg: −	motor>sensory	−	ND		−	−

M: male; F: female; m: months; y: years; CSF: cerebrospinal fluid; R: relapsing–remitting; M: monophasic; CP: chronic progressive; ND: not done; GNDS: Global Neurological Disability Score.
Response to immunotherapies given.
IVIg: intravenous immunoglobulin (IVIg), PE: plasma exchange (PE), CS: corticosteroids.
+: effective (2 or >2-point decrease in GNDS scores), −: no change (<2-point decrease in GNDS scores).

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significant improvement. One patient did not undergo any treatment.

2.2. Somatosensory evoked potential recording

The SEPs were obtained by stimulating the median nerve at the wrist and the posterior tibial nerve at the ankle with frequencies of 5 Hz and 2 Hz respectively [10]. Recording electrodes were placed over Erb's point, seventh cervical vertebra, and C3′ or C4′ over the somatosensory cortex; for the lower extremities, the electrodes were placed over the 12th thoracic vertebra and Cz′. Fz was used as the reference of all electrodes. The amplifier used was a Neuropack 8 (Nihon kohden) with a bandpass of 5–2000 Hz and averaged at 500 for the uppers and 350 for the lowers. At least two trials were superimposed to establish reproducibility. The peak latencies of the responses were measured: N9 (Erb), N13 (C7) and N20 (sensory cortex) for median nerve SEPs and N20 (Th12) and P37 (sensory cortex) for tibial nerve SEPs. Central sensory conduction time (CSCT) was calculated as N20–N13 for the upper extremities while P37–N20 for the lower extremities. The normal values for SEPs in our laboratory are as follows: for the upper extremities, for median nerve stimulation, the mean for N13–N20 is 5.89 with an upper limit of 7.33 ms, while for the lower extremities, with posterior tibial nerve stimulation, the mean for N20–P37 is 16.88 ms with an upper limit of 21.83 ms, while for peroneal nerve stimulation, the mean for N13–P28 is 14.5 ms with an upper limit of 20.08 ms [10]. Latencies exceeding the mean+3SD from the established normal values for SEPs were considered abnormal.

2.3. Motor evoked potential recordings

Magnetic stimuli were applied to the motor cortex and the seventh cervical vertebra using an eight-shaped coil for the upper extremities while a double cone coil was used for stimulating the motor cortex for the lower extremities, and the lumbar root (L4) was elicited by the eight-shaped coil [11]. The target muscles were the abductor pollicis brevis for the hands and the abductor hallucis for the legs. The stimulator used was an SMN-1200 (Nihon kohden) with a stimulus intensity of 65% of stimulator output for the upper extremity and lumbar, and 90% was used for the vertex. The amplifier was a Neuropack 8 (Nihon kohden) and the bandpass of 50–3000 Hz. We assessed MEP latencies and amplitudes (qualitatively) and calculated the central motor conduction time (CMCT): CMCT=CML−PML (CML: cortical motor latency; PML: peripheral motor latency). Normal values: the normal mean central conduction used in our laboratory for the thenar muscle central conduction is 8.61 ms with an upper limit of 10.67 ms while for the plantar muscle the mean central conduction time is 16.94 ms with an upper limit of 21.04 ms [10]. Latencies exceeding the mean+3SD from the established normal values for MEPs were considered abnormal.

2.4. Magnetic resonance imaging

MRI was performed using 1.5 T units, Magnetom Vision and Symphony (Siemens Medical Systems, Erlangen, Germany) as described previously [12]. The typical imaging parameters for brain MRI were: axial T2-weighted turbo spin-echo imaging using TR/TE=2800/90 ms, flip angle=180°; axial turbo-FLAIR imaging using TI/TR/TE=2200/9000/110 ms, flip angle=180°; and sagittal and axial precontrast and axial and coronal postcontrast T1-weighted spin-echo imaging using TR/TE range=400–460/12–17 ms, flip angle range=80–90°. One excitation, with a matrix of 256×256, a slice thickness of 5 mm, and a slice gap of 2.5 mm was used for all brain studies. Gadopentetate dimeglumine at 0.1 mmol/kg body weight was administered intravenously for contrast-enhanced studies. The typical imaging parameters for the spinal cord were as follows: sagittal T2-weighted turbo spin-echo imaging using TR/TE range=2500–2800/90–116 ms, flip angle=180°, number of excitations=3–4; sagittal T1-weighted spin-echo imaging using TR/TE range=400–440/11–12 ms, flip angle range=90–170°, number of excitations=2–3; axial T2-weighted turbo spin-echo imaging using TR/TE range=3200–5360/99–116 ms, flip angle=180°, number of excitations=3–4; axial T1-weighted spin-echo imaging using TR/TE range=400–440/12 ms, flip angle range=90–170°, number of excitations=2. For sagittal imaging, a matrix of 256×256 or 512×512, a slice thickness of 4 mm and a slice gap of 0.4 mm were used, and for axial imaging, a matrix of 256×256 or 512×512, a slice thickness of 5 mm, and a slice gap range of 1.5–5 mm were used. Both brain and spinal cord MRI's were taken at the time of illness and were independently evaluated by two of the authors, one of whom (T. Yoshiura) is a neuroradiologist who was unaware of the diagnoses.

2.5. Statistical analysis

Statistical analyses were performed using the Mann–Whitney *U* test to determine significant differences in age at onset, duration of disease and CSF protein levels between the two groups and the differences in GNDS scores between those with CNS involvement and those without and between before and after treatment. Fisher's exact probability test was used for sex ratio and clinical course. The p values of <0.05 were considered to be significant.

3. Results

3.1. Electrophysiological findings

Five of the 13 patients who underwent SEPs had peripheral nerve involvement, one (Patient No. 10 in Table 1) having prolonged CSCT (8%). This patient had bilateral lower extremity involvement (peroneals) with CSCTs of 22.72 ms on the right and 23.52 ms on the left. Another patient (Patient No. 15) had unevoked N13 but prolonged N20 on median

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nerve SEPs bilaterally and was not regarded as having definite CNS involvement, though the possibility of CNS involvement was not fully ruled out. Of the 52 limbs examined, 12 (23%) showed prolonged latencies (compared with the normal values previously mentioned) for Erb (N9), and the seventh cervical vertebrae (N13) for the upper extremities and fourth lumbar vertebrae (N17) and twelfth thoracic vertebrae (N20) for the lower extremities with posterior tibial nerve stimulation. Of the 13 patients who underwent MEP, 12 showed peripheral involvement and four had abnormal CMCT (31%) (Table 1). Three of these four patients had unilateral involvement (left upper extremity with a CMCT of 10.8 ms, right lower extremity with a CMCT of 23.5 ms and left lower extremity with a CMCT of 39.6 ms) while one patient had bilateral lower extremity involvement with CMCT of 26.6 ms on the right and 28.4 ms on the left. Five additional patients showed unevoked MEPs at cervical or lumbar stimulation but prolonged latency of MEPs at cortical stimulation, and were not considered to have definite CNS involvement, though the possibility of CNS involvement was not completely excluded. Of the 52 limbs examined, 31 (60%) showed prolonged latencies with Erb, cervical or lumbar stimulation as compared with normal values.

3.2. Magnetic resonance imaging findings

On brain MRI, five of 18 patients had an abnormal MRI scan; of these, four were aged 50 years or older. One patient (Patient No. 13 in Table 1, 69 years old) with abnormal CMCT, showed punctate T2 prolonged lesions in the cerebral white matter on MRI, which were considered to be non-specific. In the other three patients without CMCT or CSCT abnormalities, one (Patient No. 3, 59 years old) showed T2 prolonged lesions in the right putamen and caudate nucleus suggestive of old small infarcts while the other two (Patients No. 6, 52 years old and No. 8, 52 years old) had tiny spots of T2 prolonged lesions in the white matter on cranial MRI, which were also considered non-specific. Patient No. 17, a 46-year-old male, on fluid-attenuated inversion recovery (FLAIR) imaging, showed multiple ovoid lesions of increased signal intensity in the corpus callosum bilaterally, and in the left parietal and occipital lobes which appeared MS-like (Fig. 1).

3.3. Clinical characteristics of patients with subclinical CNS involvement

For comparison of clinical features, we divided the patients by electrophysiologic and MRI findings into two groups, those with and those without subclinical CNS involvement; patients were regarded as having subclinical

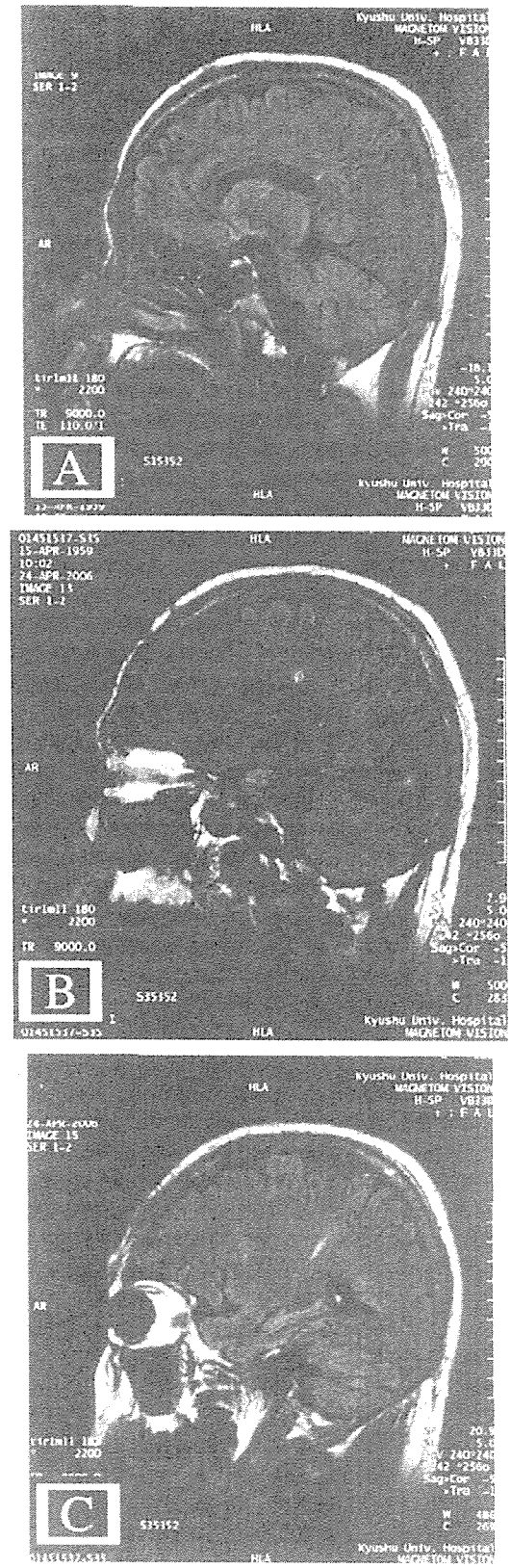

Fig. 1. Brain MRI of Patient No. 17. Sagittal fluid-attenuated inversion recovery (FLAIR) images (TR=9000 ms, TE=110 ms) of a 46-year-old male demonstrating multiple ovoid lesions of increased signal intensity in the corpus callosum, bilaterally, and in the left parietal and occipital lobes which appeared MS-like. [A] to [C]: right to left side of the patient.

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demyelinative CNS involvement if they had prolonged CMCT or CSCT or MRI lesions suggestive of CNS demyelination (MS-like ovoid lesions). Based on the electrophysiological and MRI findings, six were considered to have subclinical demyelinative CNS involvement (Patient Nos. 2, 10, 12, 13, 16 and 17) and the other 11 were not. As shown in Table 2, the patients with subclinical CNS involvement showed a tendency of male preponderance ($p=0.0537$) and significantly lower GNDS scores before treatment ($p=0.0061$), as compared with those without CNS involvement. Most patients (83%) without CNS involvement showed a chronic progressive course while half of those with subclinical CNS involvement had either a relapsing–remitting or a monophasic course. In addition, the patients with subclinical CNS involvement had lower CSF protein levels than those without, but this was not statistically significant. In the peripheral nerve conduction study, CMAP amplitude in the median nerve was significantly larger in the patients with subclinical CNS involvement than those without ($p=0.005$). In addition, in half of CIDP patients without CNS involvement, tibial nerve CMAPs were unevoked while only one of six CIDP with subclinical CNS involvement were. Patients with subclinical CNS involvement showed a nearly significant decrease of GNDS scores after immunotherapy ($p=0.0556$) while the decrease of GNDS scores was not significant in those without CNS involvement (Table 2). GNDS scores after treatment were also significantly lower in the patients with subclinical CNS involvement than in those without ($p=0.0365$).

Table 2
Comparison of clinical findings between patients with subclinical CNS involvement by EP or MRI and those without

	CIDP with subclinical CNS involvement by EP or MRI ($n=6$)	CIDP without CNS involvement ($n=12$)
Male:female	6:0	6:6
Age at onset (mean±SD, years)	31.8±24.5	44.4±19.1
Duration of disease (range, median)	2m–34y 3.5y	2m–36y 1y
Clinical course/onset		
Chronic progressive	3 (50%)	10 (83%)
Relapsing–remitting	2	1
Monophasic	1	1
GNDS before treatment	9.4±2.7*	13.8±2.2
GNDS after treatment	5.8±1.8*	11.1±4.6
CSF protein	62.6±26.1	146.9±107.5
Median nerve		
MCV, m/s	34.7±13.5	29.8±14.2
DL, ms	6.6±3.0	7.6±3.8
CMAP, mV	15.4±7.0*	5.8±3.2
Unevoked	0/6	0/12
Tibial nerve		
MCV, m/s	35.7±5.2	29.5±10.4
DL, ms	5.6±2.5	11.6±6.9
CMAP, mV	5.9±4.7	4.3±6.2
Unevoked	1/6	6/12

GNDS: Global Neurological Disability Score; CSF: cerebrospinal fluid; MCV: motor nerve conduction velocity; DL: distal latency; CMAP: compound muscle action potential. One patient from the CNS involvement group declined to have a lumbar puncture and also did not receive any immunotherapeutic intervention.
* $p<0.05$.

4. Discussion

The present study revealed subclinical CNS involvement suggestive of demyelination in Japanese patients with CIDP by combined electrophysiological and neuroimaging studies. We further described the distinct clinical features between those with and those without subclinical CNS involvement; CIDP patients with subclinical CNS involvement had lower disability and a more favorable response to immunological treatment than those without.

Although the frequent occurrence of peripheral conduction abnormalities in CIDP patients may well decrease the detection rate of CNS abnormality by EP, in the present study, about 30% of the CIDP patients demonstrated prolongation in either CMCT or CSCT, suggesting the presence of simultaneous CNS demyelination. The frequency of CNS abnormalities on EP in the present study is compatible with that reported in the previous studies [3,13]. However, though Mendell et al. [4] reported that approximately 40% of CIDP patients had MS-like periventricular, subcortical and brainstem lesions on MRI in their selected patient series, MS-like periventricular ovoid lesions were seen in only one patient in our series. Our findings are in accord with the report of Feasby et al. [5] that typical MS-like lesions are uncommon in CIDP. Our results are also compatible with those of Pakalnis et al. [13], who concluded that with a combined EP and MRI study, EP is more sensitive than MRI in detecting CNS demyelination in CIDP. Therefore, we consider that subclinical CNS involvement is not infrequent on EPs while typical MS-like lesions suggestive of demyelination on MRI are exceptional in Japanese patients. It is suggested that a combined peripheral and central nervous system demyelination is not rare, but the nature and mechanism of CNS demyelination in CIDP is probably distinct from those in MS.

Neither characteristic clinical features nor response to immunotherapies has yet to be described in CIDP patients with subclinical CNS involvement. In our series, although the number of patients is limited, it was shown that those with subclinical CNS involvement had a milder disease, and chronic progressive disease was less frequent compared with those without CNS involvement, and showed a favorable response to immunotherapies. Although therapeutic modalities were not controlled in the present study, it has been shown that IVIg, PE and corticosteroids have essentially the same efficacy in CIDP [14,15]. In previous studies, axonal loss, as shown by a decrease in CMAP or nerve biopsy, was correlated with a significantly poor response to immunotherapies such as IVIg [1,7]. In the present study, CMAP amplitudes in median nerve were significantly larger in CIDP patients with subclinical CNS involvement than those

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without, while in the tibial nerve, unevoked response was more frequent in the latter than in the former. These findings, although seen in a small number of patients and a generalized conclusion should be drawn with caution, are still suggestive that CIDP patients without CNS involvement suffer more severe axonal pathology than those with subclinical CNS involvement. The high frequency of chronic progressive course in those without CNS involvement may also contribute to more severe axonal damage [7]. Such difference in pathology may in part explain the difference in treatment response between the two subgroups; CIDP with subclinical CNS involvement is more demyelinative and thus responsive to immunotherapies while CIDP without CNS involvement is more axonal and less responsive to such therapies. Fee and Fleming [16] reported that IVIg resolved CNS demyelinative lesions in a case of CIDP. Thus, subclinical CNS lesions are also likely to be caused by the same immune mechanism as that involved in PNS demyelination in this condition.

The presence of a combined central and peripheral inflammatory demyelinating neuropathy has long been proposed in the literature [3,4,6]. The results of our study support such a notion. Whether CIDP with subclinical CNS demyelination is distinct from CIDP without CNS involvement in etiology and mechanism remains to be elucidated, the combined use of MEP/SEP and brain MRI may help identify a subgroup of CIDP patients with combined central and peripheral demyelination. Future immunological and pathological studies in a larger group of patients and controlled therapeutic trials on this specific subgroup of CIDP patients are called for to further clarify the mechanisms behind this debilitating disease of the human nervous system.

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Fusako Yokochi

Lateral flexion in Parkinson's disease and Pisa syndrome

Abstract Various types of abnormal posture are observed in Parkinson's disease (PD). Lateral flexion is very common and frequent among them. The clinical characteristics of lateral flexion in PD vary and are classified into two types, the chronic and subchronic types. The chronic type of lateral flexion in PD appears subclinically and worsens, which is related to the laterality of parkinsonian symptoms and the progression of the disease. The subchronic type of lateral flexion in PD develops subacutely and worsens rapidly in several months. An atypical and rare type of tonic truncal dystonia, Pisa syndrome, may be induced following the intake of neuroleptics. The clinical features of the subchronic type of lateral flexion in PD are similar to those of Pisa syndrome. Differences between lateral flexion in PD and Pisa syndrome are described.

Key words Parkinson's disease · lateral flexion posture · Pisa syndrome · dopamine agonist · oblique sign

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Introduction

An abnormal posture is a very common symptom of Parkinson's disease (PD). Parkinsonian posture is characterized by a flexed posture of the trunk and extremities, as described in an essay written by Dr. James Parkinson. Abnormal postures in PD are observed in the entire body, namely, flexion to the anterior, lateral or anterolateral parts of the trunk, neck flexion, flexion of the extremities, and abnormal postures of the hands, fingers and toes such as thalamic hand or hammer toe. The abnormal posture presented in this paper is limited to lateral flexion, which I describe on the basis of published reports and my clinical observation. Lateral flexion is a very common clinical observation, but there are few published reports on this abnormal posture. There was no specific name for this symptom, but recently, the term Pisa syndrome has sometimes been used for a similar symptom in PD. The term Pisa syndrome was originally used to refer to a symptom caused by psychiatric drugs, which I describe later.

Lateral flexion in Parkinson's disease

In 1975, Duvoisin and Marsden described lateral flexion as the scoliosis of parkinsonism [1, 2], characterized by a lateral deviation of the spine and a corresponding tendency to lean to one side. They analyzed the relationship between the direction of postural deviation and the laterality of symptoms in 20 nonoperated patients with parkinsonism. Sixteen patients had scoliosis contralateral to the side of initial symptoms, three patients had ipsilateral scoliosis and one patient had no scoliosis. The direction of postural deviation correlated significantly with the initial and major symptoms of parkinsonism, and the concavity of scoliosis was contralateral to the side of initial and major symptoms. They did not discuss the effects of antiparkinsonian drugs on abnormal postures.

Duvoisin and Marsden reported a very high frequency (95%) of lateral flexion in PD. To confirm the frequency and awareness of lateral flexion in PD, patients with PD were analyzed. Fifteen consecutive patients, consisting of nine women and six men with a mean age of 66.6(7.7) years and a mean illness duration of 14.3(8.0) years, examined in the outpatient clinic par-

ticipated in the study. There were four patients at Hohen-Yahr stage II, nine at stage III, and two at stage IV. All of the patients were treated with antiparkinsonian drugs and not operated on. The two types of posture on standing viewed from the back were photographed for each patient. One was the patient's natural posture and the other was the posture after correction by a neurologist. Each patient was asked whether he/she felt that he/she was leaning in the corrected posture. Twelve of the fifteen patients (80%) had lateral flexion. All of the patients felt that they were leaning toward the contralateral side following the correction of their posture. Only four of the twelve patients who had abnormal postures had simple lateral flexion and the remaining eight patients had a combination of lateral flexion and forward flexion. Therefore, the abnormal postures of almost all parkinsonian patients are complex, not only for lateral flexion, but also for forward flexion. Almost all of the patients were not themselves aware of their abnormal postures.

Furukawa reported the oblique sign (naname sign) of PD, which means the leaning of the trunk on sitting, an oblique supine posture on lying down, or an indeterminate posture in many situations [3]. Patients with the oblique sign keep their postures indeterminate. Apparently, it is difficult to maintain this posture. Furukawa studied the awareness of the oblique sign in patients with PD in terms of the position of the trunk using a chair that changed the angle of the body from the supine to the sitting position [4]. The patients were instructed to determine whether they were in the vertical or horizontal position without a visual guide. Under the condition that the position was changed from supine (horizontal: 180 degrees) to sitting (vertical: 90 degrees), he/she had to determine the position in which he/she felt the angle was 90 degrees. Control subjects felt that they were in a vertical position in the range of 110–100 degrees, but parkinsonian patients with the oblique sign felt that they were in a vertical position at a more obtuse angle than the control subject. Under the condition that the position was changed from sitting to supine, control subjects felt that they were in a horizontal position in the range of 155–160 degrees, whereas parkinsonian patients with the oblique sign felt that they were in a horizontal position at smaller angles, at which the position was similar to a half-sitting position. This study showed that the judgment of vertical and horizontal positions was affected in patients with PD.

The disturbance in awareness of an abnormal position of the body in patients with PD might involve a disturbance in body schema or body image. Body schema means the image of one's own body in space [5]. All of the moment-to-moment postural changes are memorized one by one and the postural change in progress is compared with a posture memorized previously and the determined position is recognized as the body image in normal subjects. However, it is hypothesized that patients with PD memorize an abnormal body image, resulting in chronic and progressive disturbance in posture. It was suggested that the abnormal position of the body in space and the disturbance in its awareness in PD result from the disorders in the memory of the body image. In a study to determine the relationship between body size and the width of a door shown on a screen, the ability to determine body position in space was found to be disturbed in patients with hemiparkinsonism [6]. The disturbance in the ability to determine body position in space in PD appears not only as a result of a progressive abnormal posture, but also as a disorder caused by PD [7].

Pisa syndrome

Pisa syndrome is an atypical acute or tardive dystonia called pleurothotonus or drug-induced pleurothotonus, which is a very rare adverse event associated with neuroleptic treatment. The typical clinical feature is tonic truncal dystonia with a slight backward rotation without dystonia in other parts of the body. Ekbom et al. [8] reported a new dystonic syndrome associated with butyrophenone therapy. An acute syndrome in three elderly women with presenile dementia appeared as a side effect of treatment with methylperone or haloperidol. In each patient, a tonic flexion of the trunk to one side was observed. A slight rotation of the trunk in the sagittal plane was noted. The rotation was enhanced with walking and the patients tended to turn in a direction opposite to their intended path. The symptoms were reversible and were improved by anticholinergic drugs.

The prevalence of Pisa syndrome in a psychogeriatric population over a five-year period was analyzed by Yassa et al. [9], which was 8.3%, with 9.3% in women and 6.4% in men. In a multicenter drug safety surveillance project [10], Pisa syndrome was observed in 17 among 45,000 psychiatric patients and the prevalence was 0.04%. Risk factors were a history of previous treatment with conventional neuroleptics, female gender, old age, and organic brain disorders.

Drugs reported to induce Pisa syndrome are typical and atypical antipsychotics, tricyclic antidepressants, selective serotonin reuptake inhibitors, cholinesterase inhibitors, antiemetics, lithium carbonate, benzodiazepines and tiapride [11]. Suzuki et al. [12] studied the clinical characteristics of 24 patients with drug-induced Pisa syndrome, which included responders and nonresponders to anticholinergic drugs. However, no significant differences in gender, age, psychiatric diagnosis, direction of extrapyramidal symptoms, or organic brain changes were noted between the responders and nonresponders.

Generally, Pisa syndrome is treated with anticholin-

ergic drugs or the reduction of the dose of neuroleptics. The significant improvement in the symptoms of Pisa syndrome following the withdrawal of antipsychotic drugs differentiates this syndrome from tardive dystonia.

It is suggested that a cholinegic-dopaminergic imbalance, or the interactions among noradrenaline, serotonin and dopamine are involved in the development of drug-induced Pisa syndrome [13].

Is abnormal posture in Parkinson's disease similar to Pisa Syndrome?

An abnormal posture observed in PD is caused not only by the worsening of the disease or the distribution of symptoms, but also by antiparkinsonian drugs. The administration of a dopamine agonist sometimes induces abnormal postures such as the drop neck, forward flexion or lateral flexion of the body. The development of Pisa syndrome in a patient with PD during treatment with Pergolide [14] or Pramipexole [15] was reported. One patient had been treated with Pergolide for more than one year before developing Pisa syndrome, which was improved and reversed by only the withdrawal of Pergolide. On the other hand, Pisa syndrome induced by Pramipexole showed no improvement following the withdrawal of this dopaminergic medication for one week. I have encountered patients who developed this syndrome during the administration of another dopamine agonist. This suggests that these symptoms are not characteristically induced by a particular dopamine agonist.

In the advanced stage of PD, the stiffness of the trunk and neck worsens gradually. In this stage or in patients treated with antiparkinsonian drugs, rigidity in extremities is attenuated, but rigidity in the trunk, which is difficult to treat with antiparkinsonian drugs, is severe. The distribution of symptoms in PD varies in each patient; but generally, neck and trunk stiffness becomes severe in the advanced stage. Trunk stiffness is caused by rigidity and deformities in the spine, and by many other factors. Rigidity is a characteristic feature of abnormal postures in PD. On the other hand, Pisa syndrome induced by neuroleptics is characterized not by trunk rigidity, but by dystonia in trunk muscles.

Abnormal postures with lateral flexion in PD are classified into two types on the basis of the pattern of appearance: chronic and subchronic. The chronic type of lateral flexion in PD appears subclinically and worsens gradually; such worsening is related to the progression of the disease. The subchronic type of lateral flexion in PD is observed in cases reported by Cannas et al. [14] and Gambarin et al. [15] and seems to show similar symptoms with those of Pisa syndrome. The severity of this lateral flexion progresses in a few months and this abnormal posture becomes marked. The administration of a dopamine agonist sometimes causes truncal dystonia as reported previously [14, 15]. In a patient with the subchronic type of lateral flexion, the asymmetry of the paraspinal muscles is prominent, as shown in the figure. The volume of the paraspinal muscles contralateral to the side of lateral flexion is larger than that of those ipsilateral to the side of this abnormal posture and this pathological enlargement of the muscles might be a sign caused by dystonia. This finding indicates that this postural abnormality in patients with PD have a component of dystonia in addition to that of rigidity. The initial development of lateral flexion is subclinical, but its progression is rapid. This type of lateral flexion has a neurological condition similar to one of the neurological conditions of Pisa syndrome. Anticholinergic drugs do not improve this type of lateral flexion in PD. There is no doubt that Pisa syndrome and the subchronic type of lateral flexion in PD are not the same owing to the existence of truncal rigidity in PD. Neuroleptics have a function of acting on neurotransmitters in the brain, and antiparkinsonian drugs do as well. In a study of rats with hemiparkinsonism induced by a unilateral injection of 6-hydroxydopamine into the ventralis tegmenti, a strong

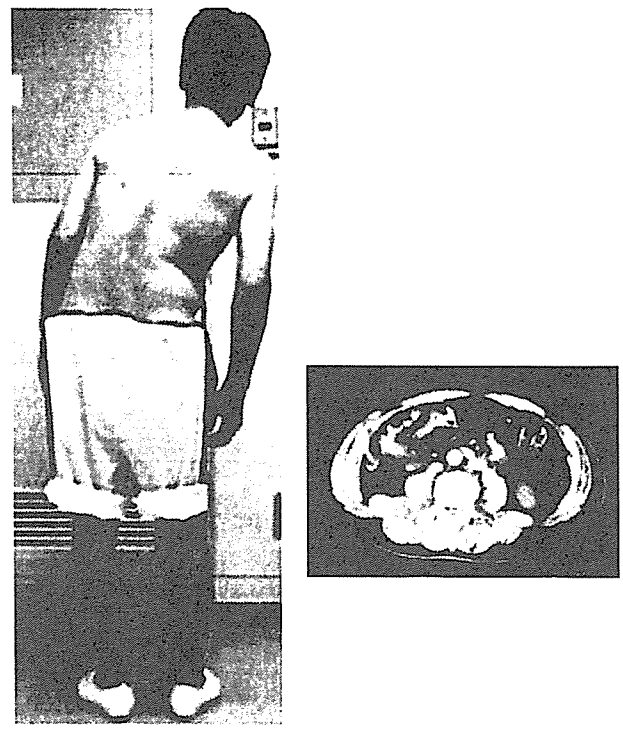

Fig. 1 Subchronic type of lateral flexion similar to Pisa syndrome. Sixty-year-old patient with PD and illness duration of seven years. Lateral flexion to the right and forward developed 1 year ago. His medication was 300 mg of levodopa/DCI, 150 mg of amantadine and 1.5 mg of pramipexole. A computed tomographic image shows a larger volume of the left paraspinal muscle than that of the right paraspinal muscle, which was contralateral to the lateral flexion

ipsilateral deviation and a scoliosis-like skeletal deformity were observed, and the severity of this scoliosis was closely related to a decrease in extracellular striatal dopamine level measured by microdialysis [16]. The term Pisa syndrome should not be indiscriminately used for all cases of lateral flexion in PD, and the type of lateral flexion in PD should be carefully observed.

Treatment of lateral flexion in Parkinson's disease

Lateral flexion in PD is a difficult symptom to treat with antiparkinsonian drugs. Preventing the development and progression of lateral flexion is the most important aim, which is difficult to realize. To treat the subchronic type of lateral flexion, it should be determined whether drugs lead to the development of this type of lateral flexion. A dopamine agonist administered before the development of lateral flexion should be discontinued or the dopamine agonist may need to be changed. Deep brain stimulation can effectively treat abnormal postures including lateral flexion and forward flexion. However, if lateral flexion induces deformities in the spine, it is impossible to treat deformities in the spine by deep brain stimulation. The decision to treat by deep brain stimulation must be made before abnormal posture becomes irreversible.

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Effect of deep brain stimulation on FOG

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Abstract

The freezing of gait (FOG) phenomenon is a common symptom in patients with advanced Parkinson's disease (PD), but it is very difficult or almost impossible to treat this condition with antiparkinsonian drugs. FOG is an interesting symptom for neurologists in many aspects. It is observed in both phases of on and off during the wearing-off phenomenon and under specific conditions such as being in a narrow space and not in an open space, and can be improved by external cues, so-called kinesie paradoxale. From these observations, it is supposed that FOG is not only a motor symptom but a symptom generated by the arousal system.

Surgical therapy for PD has been performed to improve symptoms that are resistant to drug therapy since the mid-20th century. Recently, deep brain stimulation (DBS) has been performed and has shown great effects on parkinsonian symptoms. DBS of the subthalamic nucleus in particular markedly improves FOG. The clinical outcomes of subthalamic DBS are the focus of discussion in this paper.

Keywords: Gait; Freezing; Deep brain stimulation; Parkinson's disease; Finger tapping test

1. Introduction

Freezing of gait (FOG) phenomenon is a common symptom in patients with advanced Parkinson's disease (PD); however, it remains very difficult or almost impossible to treat using antiparkinsonian or other drugs. FOG is an interesting symptom for neurologists in some aspects. FOG is observed in both on and off phases during the wearing-off phenomenon, and under specific conditions, such as being in a narrow, not an open space, and is improved by external cues. This is the so-called kinesie paradoxale. Clinically, FOG is similiar, however, the mechanism involved remains unclear.

Surgical therapy for PD has been performed since the mid-20th century to alleviate parkinsonian symptoms which are resistant to drug therapy. Recently, deep brain stimulation (DBS) has been performed and has shown an improved effect on parkinsonian symptoms. The DBS of the subthalamic nucleus, in particular, markedly improved FOG. The DBS of the thalamus or the internal part of the pallidum showed no effects on improving FOG.

Several possible characteristics of FOG have been considered. Electromyographical examination has shown abnormal activities and difficulty in the initiation of stepping in muscles of the lower extremities in patients with FOG [1]. Disorders in the reciprocal innervation in leg muscles have also been reported [2]. These findings are the result of the freezing phenomenon. It remains difficult to study the mechanism of FOG, however, we considered and examined several factors such as kinesie paradoxale, balance disorders and disturbance of rhythm formation [3] observed in FOG.

2. Materials and methods

2.1. Effects of subthalamic DBS

The outcome of subthalamic DBS was studied in eight patients with PD treated with bilateral DBS. Eight patients (three males and five females) with an average

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