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PERIODIC LIMB MOVEMENT DISORDER IN NEUROLEPTIC-INDUCED AKATHISIA

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INDEXING WORDS

periodic limb movements; akathisia; clonazepam

SYNOPSIS

We recorded all-night polysomnograms of four schizophrenic patients with neuroleptic-induced akathisia (NIA) before and during treatment with clonazepam. Also, four non-akathitic schizophrenic patients were recorded all-night polysomnograms as control subjects. Daily treatment with 1.5 to 3 mg clonazepam improved subjective complaints of all the 4 patients with NIA. Three of 4 patients with NIA exhibited periodic limb movements (PLM) on bilateral legs, but none of 4 control subjects showed PLM. Total number of PLM and PLM per hour decreased during clonazepam treatment. Moreover, mean inter-movement intervals of PLM of 3 patients were prolonged on bilateral legs. NIA might change its feature as PLM during night sleep.

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INTRODUCTION

Neuroleptic-induced akathisia (NIA) is a frequent side effect of pharmacotherapy for psychosis. Akathisia is diagnosed only by inquiring about symptoms and by observing motor restlessness in patients, as there are no specific laboratory findings. Restless legs syndrome (RLS) is characterized by severe dysesthesia and motor restlessness resembling NIA. RLS is frequently associated with periodic limb movements (PLM),[1,6] which is characterized stereotyped dorsi-flexion movements at the ankle joint and flexion movements at the knee and hip joints. They usually repeat at regular 20 to 40 sec intervals during non-rapid eye movement (NREM) sleep, and originally called nocturnal myoclonus.[4,33] Clonazepam has been reported as effective to treat RLS.[2,14,21] These features of RLS led us to examine whether patients with NIA have PLMD or not, and whether clonazepam also improves NIA or not. In the present study, we treated patients with NIA with clonazepam and quantified periodic limb movements (PLM) in polysomnographic findings.

SUBJECTS AND METHODS

Four patients with schizophrenic disorder receiving neuroleptics and antiparkinsonian drugs were diagnosed as acute neuroleptic-induced akathisia at the clinic of psychiatry of Ehime University Hospital (Table I). These patients with NIA, 2 males and 2 females (mean age; 41 years), met DSM-III-R (Diagnostic and Statistical Manual of Mental Disorders, 3rd ed., Revised) criteria for schizophrenic disorder and had been treated with oral neuroleptics and antiparkinsonian drugs for a mean duration of 3 months. Patients with dystonia, dyskinesia, parkinsonism or other physical disorders were excluded. To compare patients with NIA, we selected 4 patients with schizophrenic disorder who also met DSM-III-R criteria, and had been taking with oral neuroleptics and antiparkinsonian drugs for a mean duration of 3 months without NIA. They were 2 males and 2 females (mean age; 39 years) without other extrapyramidal symptoms such as dystonia or dyskinesia. No significant difference in age, sex, and duration of neuroleptic treatment was observed between NIA and non-NIA groups.

All NIA patients and their control subjects underwent conventional all-night recording including the electroencephalography using the standard recording techniques (electrodes pairs used: C_3 - A_2, C_4 - A_1, O_1 - A_2, O_2 - A_1), electrooculography (left and right outer canthus), mentalis electromyogram, respiration (nasal air flow), electrocardiogram, and limbs electromyograms (surface electrodes placed on both tibialis anterior and extensor hallucis longus muscles). One PLM was counted when one leg movement resulted in at least one-half of the amplitude of maximal ankle dorsiflexion, either unilateral muscle or simultaneously bilateral muscle.[4] Additionally, a PLM was scored only when it occurred as a part of a series of five or more consecutive movements lasting 0.5 to 5.0 sec, with an inter-movement interval of 5 to 90 sec.[6] A PLM index (number of PLM per hour of sleep) greater than 5 was considered pathological.[6]

Table I. Profiles of NIA patients and non-NIA control subjects.

NIA Case	Age	Sex	Neuroleptics	(mg/day)	Antiparkinsonian Drugs	(mg/day)
1	37	female	chlorpromazine	100	biperiden	1
			haloperidol	1.5	promethazine	80
2	41	male	chlorpromazine	25	profenamine	60
			sultopride	300	promethazine	12.5
			zotepine	150		
3	42	female	chlorpromazine	12.5	biperiden	2
			haloperidol	3	promethazine	25
					trihexyphenidyl	4
4	43	male	chlorpromazine	25	biperiden	3
			haloperidol	6		
non-NIA control						
1	33	male	chlorpromazine	50	biperiden	3
			haloperidol	3		
2	36	female	haloperidol	3	biperiden	3
			bromperidol	3	promethazine	12.5
3	41	male	haloperidol	3	biperiden	3
			sulpiride	300		
4	45	female	chlorpromazine	120	biperiden	3
			haloperidol	3	promethazine	75

Sleep stages were determined in 10 sec epoch, according to the standardized manual.[28]

Four patients with NIA were treated with oral clonazepam at a dose of 1.5 mg daily without changing the dose of neuroleptics and antiparkinsonian drugs. The effectiveness was evaluated according to complaints of the patients and objective observations using the Clinical Assessment for Akathisia designed by Yagi.[34] The dosage of clonazepam was adjusted in 0.5 mg steps to 4 mg daily. Before and during clonazepam treatment, all NIA patients underwent the all-night recordings. We compared their PLM characteristics quantitatively before and during treatment. Control subject also underwent an all-night recording. Informed consent was obtained from all patients and controls.

RESULTS

Therapeutic response

All 4 patients with NIA resolved their symptoms within 8 days from the start of treatment.

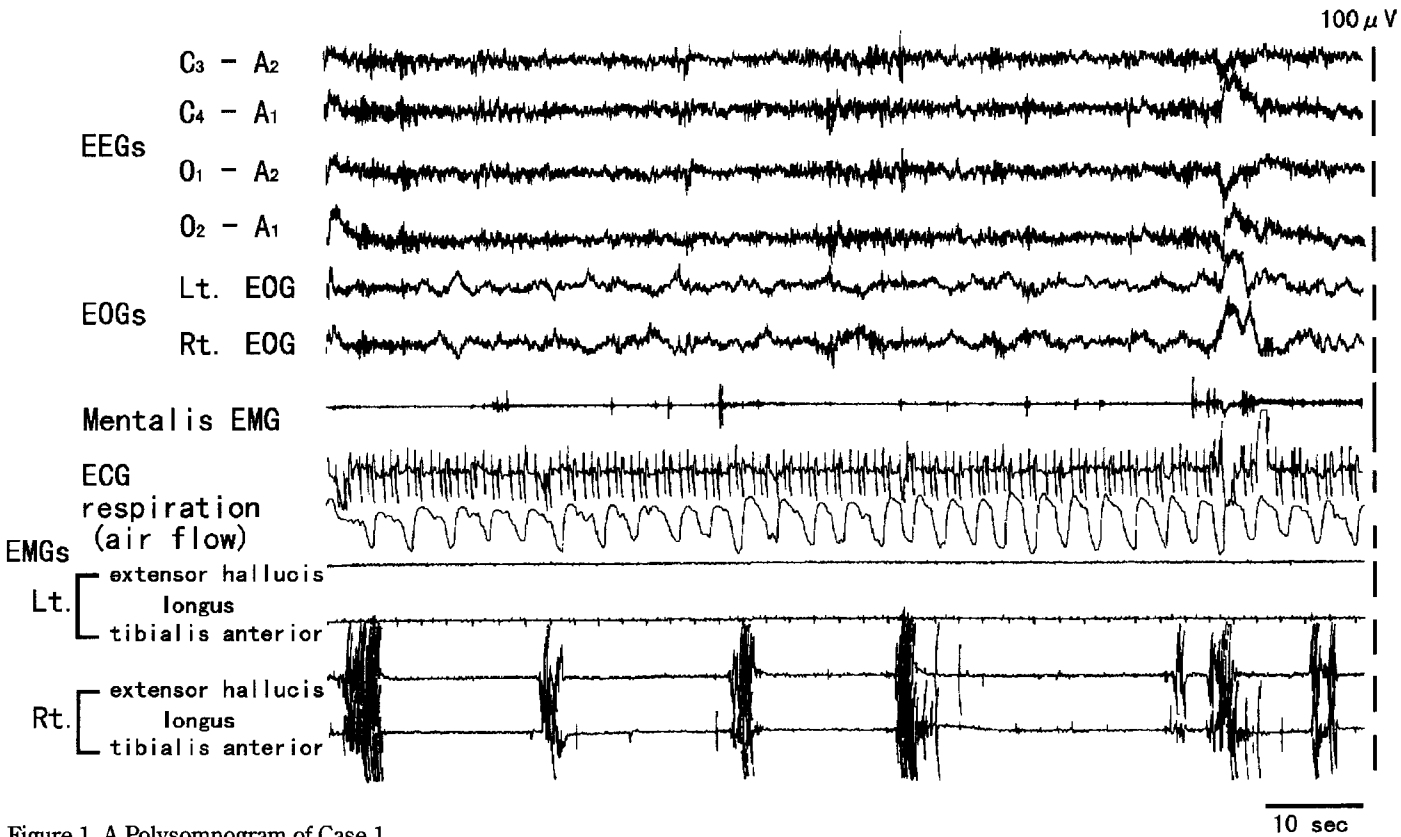

Figure 1. A Polysomnogram of Case 1.

A 37 year-old female, who had insomnia due to neuroleptic-induced akathisia, showed periodic limb movements (PLM) on the polysomnogram. Periodic muscle discharges were observed on right tibialis anterior muscle and extensor hallucis longus muscle in this part. Inter-movement interval was about 20 sec with duration of 3 to 4 sec.

The effective dosage of clonazepam ranged from 1.5 to 3 mg daily (two patients received 1.5 mg, one 2.5 mg, and one 3 mg). No serious side effects were observed.

Polysomnographic findings

A case example (NIA Case 1)

Figure 1 shows the all-night polysomnogram of Case 1 with NIA. Periodic muscular discharges of PLM appeared in the EMGs recorded from right anterior tibialis and extensor hallucis longus muscles. The intervals between discharges were about 20 sec with durations of 3 to 4 sec. Soon after the onset of some discharges, arousal responses appeared in the mentalis EMG and EEG.

Total number of PLM

Table II shows changes in total number of PLM found in patients with NIA before and during clonazepam treatment. We observed PLM in three out of 4 patients. Clonazepam decreased their total number of PLM bilaterally. In details, PLM mainly appeared in light sleep (sleep stages 1 and 2) and also decreased in the same stages. Case 4, the mildest one according to the Clinical Assessment for Akathisia,[34] did not show any PLM before and during treatment. None of non-NIA controls showed any PLM.

Number of PLM per hour and Inter-movement Interval

The number of PLM per hour decreased on each side during clonazepam treatment (Table II). Additionally, mean inter-movement interval was prolonged in 3 patients who showed PLM.

DISCUSSION

Antiparkinsonian drugs such as biperiden and trihexyphenidyl have been reported of value in treating NIA, though the drugs such as propranolol[16] and clonazepam[11,12,29] have been reported effective. We first reported the usefulness of clonazepam in 21 patients with NIA.[11] Sandyk reported a successful treatment of a NIA patient using baclofen and clonazepam in 1985.[29] Clonazepam is known to increase waking threshold, muscle relaxation, making stage 2 sleep longer, and shortening sleep stages 3, 4 and REM.[25] In the present study, clonazepam was effective to ameliorate symptoms of NIA, but the basic mechanism of NIA is not still fully clarified. We have reported that patients with NIA had significantly lower serum iron concentrations than non-NIA patients,[13] together with effectiveness of iron treatment in NIA patients.[15]

Table II. PLM of NIA patients.

Case	left right	total number of PLM		number of PLM per hour		mean interval of PLM (sec)	
		before	during	before	during	before	during
1	left	143	27	81	5	32.1	47.5
	right	132	20	76	4	35.0	48.1
2	left	62	9	8.5	1	32.4	45.2
	right	133	26	18.3	4	27.8	43.8
3	left	17	0	1.7	0	49.1	(-)
	right	40	2	4.0	0.2	46.5	60.3
4	left	0	0	0	0	(-)	(-)
	right	0	0	0	0	(-)	(-)

As mentioned first, restless legs syndrome (RLS) is frequently associated with PLM.[1,6] The symptoms of RLS are resemble to those of NIA, but few investigations have been performed on PLM in NIA. Lipinski et al. have reported that eight of nine patients with NIA exhibit 10 to 40 sec bursts of increased muscle tone before sleep onset on all-night polysomnography,[17] and we also detected PLM in a patient with NIA on all-night polysomnogram.[24]

Mitchell first described periodic limb movement disorder (PLMD) as a specific sleep disorder.[20] He noted a similarity to "sleep jerks" on falling asleep and suggested a possible relationship to "foot fidgets." Symonds considered it epileptic myoclonus[30] and named "nocturnal myoclonus",[9] but Lugaresi et al. recorded polysomnograms and found no epileptic activity on EEGs.[18] Since the pattern and length of these movements differed from those of true myoclonus,[19] the term periodic movements in sleep (PMS) had been used.[4,25] Later, PMS have been termed PLMD by the International Classification of Sleep Disorders (ICSD).[1] PLM has been found in various sleep-wake disorders. Coleman et al. have reported 53% of healthy elderly individuals have PLM by polysomnography.[5] Several drugs such as clonazepam,[26] baclofen,[7] and opiates[10] have been reported as useful in treating PLMD.

Montplaisir et al.[23] have reported that PLM may result from reduced dopaminergic activity in Central Nervous System, possibly resulting from decreased sensitivity of postsynaptic receptors. They found that L-DOPA was an effective drug for PLM. A previous study reported higher levels of free dopamine and homovanillic acid in the CSF of a patient with PLM.[22] Decreased serotonin activity was found to be involved in non-periodic myoclonus in humans[31] but 5-hydroxytryptophan has not been found effective in treating PLM.[8] Clonazepam reduces serotonin utilization,[27] and effects on dopamine neurotransmission.[32]

We found that clonazepam significantly decreased PLM and resulted in electrophysiologi-

cal improvement for NIA. As degree of symptoms of NIA and PLM changed parallel, NIA might change its feature as PLM during night sleep.

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