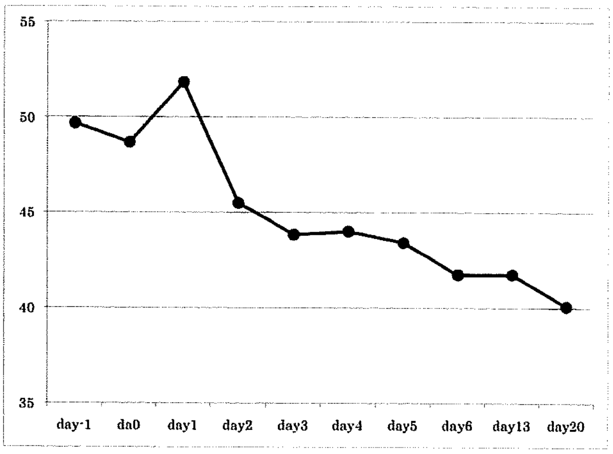

図7 SDS の推移

表4に day-1と day20の間における SF-36の変化を示す。対応のあるt検定の結果、「身体機能」「日常役割機能(身体)」「身体の痛み」「社会生活機能」「心の健康」の下位尺度得点においては有意な変化を認めなかったが、「全体的健康感」「活力」「日常役割機能(精神)」の下位尺度得点において有意な改善($p < 0.05$)を認めた。

	day-1	day20	p値
身体機能	77.0 ± 20.3	87.0 ± 15.8	0.104
日常役割機能(身体)	65.6 ± 28.6	86.3 ± 25.3	0.053
身体の痛み	87.4 ± 21.6	90.2 ± 13.1	0.726
社会生活機能	35.6 ± 16.2	49.7 ± 18.6	0.071
全体的健康感	33.1 ± 14.1	54.4 ± 23.6	0.015
活力	58.8 ± 19.6	78.8 ± 17.7	0.041
日常役割機能(精神)	52.5 ± 15.7	76.7 ± 27.2	0.034
心の健康	43.5 ± 19.6	65.0 ± 22.8	0.094

Values are expressed as mean ± SD

表4 SF-36

平成20年度までに本研究で治療を行った対象者のうち、その後の経過を追うことができた7名の予後を報告する。Case1:全断眠から約2ヶ月後に復職した後、約 8 ヶ月で再燃(約 42 週間維持)。Case2:全断眠後 4 週間で退院し、間もなく再燃(約 4 週間維持)。Case3:退院後すぐに復職し、間もなく再燃(約4週間維持)、Case4:退院後、強いストレス(父親死去、会社倒産の処理)あり再燃(約 7 週間維持)。Case5:全断眠後寛解していたが約 10 ヶ月間休養し、復職後すぐに再燃(約 45 週間維持)。Case6:全断眠後約5週間で再燃(約5週間維持)。Case7:1年以上寛解を維持。

D. 考察

本研究では、薬剤抵抗性、遷延性、反復性、難治性といった特徴を有する大うつ病エピソード患者において、全断眠とそれに続く睡眠位相前進および高照度光療法を併用した治療を行い、他覚的評価、自覚的評価ともに有意な改善を示した。

断眠療法は有効率が高いにも関わらず、回復睡眠後の逆戻りが多いという欠点があると言われているが、本研究では全断眠の後に睡眠位相前進および高照度光療法を併用することで逆戻りを防ぐことができた。HAM-D 得点の改善率 50%以上を Response、50%未満への逆戻りを Relapse と定義すると、Response に達した 9 名のうち Relapse となったのは1名のみであり、最終評価の day20 では8名が Response を維持することができた。

断眠療法を行う際に抗うつ薬や炭酸リチウムを併用することで、断眠療法の効果が維持されやすいことが報告されている。本研究では治療期間中、全対象者が抗うつ薬を服用していたが、それが断眠療法の効果維持に関与していた可能性も考えられる。しかし、対象者間で使用薬剤のコントロールは行っていないため、薬剤の影響を検証することは困難である。

全断眠による改善は断眠直後から現れるという報告が多いが、本研究では、断眠直後(day1)では有意な変化を認めず、睡眠位相前進および高照度光療法を行っている期間に次第に改善していく傾向があり、day-1と比較して有意な改善を認めたのは HAM-D では day2 から、VAS では day3 から、SDS では day5 からであった。睡眠位相前進および高照度光療法は全断眠の効果を維持させるだけでなく、効果を後から増強させる作用もある可能性を示唆している。また、双極性障害に比較して単極性障害では、断眠療法の効果発現が遅

いという報告がある。本研究の対象者は12名中9名が単極性障害であったため、効果発現が遅かったのかもしれない。

SF-36で調査したQOLは、断眠前と比較して最終評価日(day20)で、「全体的健康感」「活力」「日常役割機能(精神)」の下位尺度得点において有意な改善が認められた。これは、うつ状態の改善によってQOLも改善したと考えられるが、本研究の治療では有害事象を伴わなかったこともQOLの改善に寄与していると言えるかもしれない。

研究計画の中での治療効果の評価は全断眠後3週間(day20)までであったが、その後の経過も追えることができた対象者についても報告した。全断眠から4週間で再燃したCaseから1年以上寛解を維持していたCaseまで様々であったが、復職や生活上のストレスに直面することによって再燃しやすい印象を受けた。

本研究において、治療期間中に著しい有害事象は認められず、治療中断例はなかった。したがって、断眠療法、睡眠位相前進、高照度光療法は安全性の高い治療であると言える。

E. 結語

薬剤抵抗性で治療に難渋していた症例が数日以内に改善を示したことから、本研究で行った治療法は臨床で応用していくことに大きな期待を持つことができる。

F. 健康危険情報

特になし

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H. 知的財産権の出願・登録状況

なし

Ⅲ．研究成果の刊行に関する一覧表

雑誌

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Ⅳ.　研究成果の刊行物・別刷

Available online at www.sciencedirect.com

ScienceDirect

General Hospital Psychiatry 32 (2010) 276–283

General Hospital Psychiatry

Sleep-related problems and use of hypnotics in inpatients of acute hospital wards

Minori Enomoto, B.Sc.[a,c], Takako Tsutsui, Ph.D.[b], Sadanori Higashino, Ph.D.[b], Masaaki Otaga, M.S.W.[b], Shigekazu Higuchi, Ph.D.[a], Sayaka Aritake, Ph.D.[a], Akiko Hida, Ph.D.[a], Miyuki Tamura, Ph.D.[a], Masato Matsuura, M.D., Ph.D.[c], Yoshitaka Kaneita, M.D., Ph.D.[d], Kiyohisa Takahashi, M.D., Ph.D.[e], Kazuo Mishima, M.D., Ph.D.[a,*]

[a]*Department of Psychophysiology, National Institute of Mental Health, National Center of Neurology and Psychiatry, Tokyo 187-8553, Japan*
[b]*Department of Social Services, National Institute of Public Health, Ministry of Health, Labour and Welfare, Saitama 351-0197, Japan*
[c]*Section of Biofunctional informatics, Graduate School of Health Care Sciences, Tokyo Medical and Dental University, Tokyo 113-8519, Japan*
[d]*Division of Public Health, Department of Social Medicine, Nihon University School of Medicine, Tokyo 173-8610, Japan*
[e]*Aino University, Osaka 567-0012, Japan*

Received 6 November 2009; accepted 26 January 2010

Abstract

Objective: Although sleep disorders are highly prevalent among patients with physical disorders, only limited information is available about the actual status of sleep-related problems in inpatients of acute hospital wards. We conducted a multicenter cross-sectional observational survey investigating the prevalence of sleep disorders and use of hypnotic-sedative drugs among inpatients of acute wards in 44 general hospitals in Japan.
Method: Questionnaire-, actigraph- and observation-based sleep evaluations were simultaneously performed in 557 adult inpatients [mean age 72.8±12.8 (S.D.) years] of acute wards during a one-month period in July 2007.
Results: Of the 421 patients with data available, 22.3% had at least one of the following sleep disorders: sleep apnea syndrome, restless legs syndrome, periodic limb movement disorder and nocturnal behavior disorder. Similarly, 62.7% had insomnia, 6.9% had severe daytime sleepiness and 12.8% had other sleep-related symptoms. Only 13.8% were free of any sleep-related problem. Although 33.7% of insomnia patients were taking hypnotic-sedative drugs, 65.2% of them complained of residual insomnia symptoms.
Conclusion: The findings obtained in this study have revealed the remarkably high prevalence of sleep-related problems experienced by inpatients of acute hospital wards in Japan. Proper diagnosis of sleep disorders should be made among patients with physical disorders.

Keywords: Sleep disorders; Insomnia; Acute hospital wards; Physical illness; Hypnotic use

1. Introduction

Sleep disorders, including insomnia, sleep apnea syndrome (SAS), restless legs syndrome (RLS) and periodic limb movement disorder (PLMD), are highly prevalent and particularly common in elderly patients with physical disorders. Sleep disorders reduce patients' quality of life (QOL) by causing symptoms such as daytime sleepiness and cognitive impairment and may also exacerbate underlying disorders by inhibiting respiratory, cardiovascular and

* Corresponding author. Tel.: +81 42 346 2014; fax : +81 42 346 2072.
E-mail addresses: minori@ncnp.go.jp (M. Enomoto), tsutsui@niph.go.jp (T. Tsutsui), sadanori@u-shizuoka-ken.ac.jp (S. Higashino), otaga@niph.go.jp (M. Otaga), shige@ncnp.go.jp (S. Higuchi), sayaca@ncnp.go.jp (S. Aritake), hida@ncnp.go.jp (A. Hida), tamuram@ncnp.go.jp (M. Tamura), matsu.mtec@tmd.ac.jp (M. Matsuura), kaneita@med.nihon-u.ac.jp (Y. Kaneita), ktaka@ncnp.go.jp (K. Takahashi), mishima@ncnp.go.jp (K. Mishima).

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doi:10.1016/j.genhosppsych.2010.01.015

metabolic functions. In one study of older patients in a skilled-care geriatric hospital in Japan, the presence of insomnia was associated with a higher risk of mortality during the 2-year follow-up period [1].

The prevalence of these sleep disorders increases with age [2], and the high incidence of physical disorders among the elderly population is a contributing factor. Previous epidemiologic studies have revealed that the prevalence of insomnia among the general population is 10.2–48.0% [3–6], and insomnia frequently occurs in association with chronic pain disorders, respiratory diseases and neurological diseases [7]. SAS, RLS or PLMD also frequently coexists with various physical diseases including hypertension [8], ischemic heart disease [9,10], chronic kidney failure [11], iron-deficiency anemia [12] and neurological diseases such as Parkinson's disease [13]. It is also noteworthy that medications used for the treatment of sleep disorders may worsen physical disorders; for example, most standard hypnotics benzodiazepines cause *sleep apnea* by reducing the muscle tone of the upper respiratory tract during sleep [14].

The fact that physical and sleep disorders can coexist at a high frequency should always be taken into account when making an accurate diagnosis and developing a treatment strategy that provides a favorable risk-benefit balance. Nevertheless, we currently have only limited information about the actual status of sleep-related problems experienced by inpatients of acute hospital wards. Thus, the objectives of the present study were to investigate the breakdown and prevalence of sleep disorders and use of hypnotic-sedative drugs in acute ward inpatients and to identify problems in the clinical practice of sleep medicine.

2. Methods

2.1. Subjects and method

Study subjects who were 20 years of age or more were randomly selected from among the inpatients of acute hospital wards, excluding psychiatric and tuberculosis wards, of 44 general hospitals in Japan. The patients' identities were coded at each hospital ward, and then patients were randomly sampled. The investigation was carried out among 557 subjects [316 males, 241 females; mean age, 72.8±12.8 (S.D.) years; range 22–96 years] who had provided informed consent or whose family member had provided informed consent, simultaneously at all hospitals during a period of 1 month in July 2007. Each patient's primary disorder was classified according to the International Classification of Diseases and Related Health Problems Version 10 (*ICD-10*) (Table 1). The ethics committee at each research site approved the present study.

2.2. Investigation methods

The investigation was conducted over 2 days for each patient to check his or her sleep condition and details of treatment. The investigation consisted of subjective sleep evaluation using a self-administered questionnaire (Table 2), objective sleep evaluation by actigraphy, observational sleep evaluation by nursing staff and a survey of medication use as recorded in the medical records.

The questionnaire was designed to identify the presence of insomnia, SAS, RLS, PLMD, nocturnal behavior disorder (NBD), daytime sleepiness and nocturnal sleep-related symptoms. In the questionnaire, Q1–Q6 were completed by the patients, and Q7 and Q8 were completed by medical staff. Although NBD can be further divided into nocturnal delirium, REM sleep behavior disorder, behavioral and psychological symptoms of dementia and other symptoms, these disorders were not distinguished in view of the primary objective of the present study and technical restrictions.

For objective sleep evaluation, subjects were asked to wear an actigraph [Lifecorder PLUS (LC), Suzuken, Nagoya, Japan] [15] on their waist for two consecutive days for continuous recording of the intensity of activity. Total sleep time (TST; the sum of all sleep time during time in bed), total wake time (TWT; the sum of all wake time during time in bed) and sleep efficiency (SE; the percentage of TST relative to time in bed) were then calculated from the LC data. Time in bed (TIB) was defined as the time during

Table 1
Illness identified in enrolled patients

System organ/disease class	Total 557 (100%)	SAS, RLS, PLMD and NBD 94 (100%)	Insomnia			Good Sleep 63 (100%)
			Improved 31 (100%)	Untreated 175 (100%)	Not-Improved 58 (100%)	
Diseases of the circulatory system	140 (25.1)	20 (21.3)	7 (22.6)	44 (25.1)	9 (15.5)	15 (23.8)
Neoplasms	127 (22.8)	19 (20.2)	5 (16.1)	47 (26.9)	26 (44.8)	8 (12.7)
Diseases of the respiratory system	68 (12.2)	11 (11.7)	3 (9.7)	17 (9.7)	8 (13.8)	9 (14.3)
Diseases of the digestive system	62 (11.1)	13 (13.8)	2 (6.5)	21 (12.0)	7 (12.1)	8 (12.7)
Diseases of the nervous system	45 (8.1)	11 (11.7)	2 (6.5)	9 (5.1)	3 (5.2)	5 (7.9)
Diseases of the genitourinary system	16 (2.9)	4 (4.3)	1 (3.2)	5 (2.9)	1 (1.7)	3 (4.9)
Diseases of the musculoskeletal system and connective tissue	14 (2.5)	2 (2.1)	1 (3.2)	7 (4.0)	0 (0.0)	3 (4.9)
Certain infectious and parasitic diseases	8 (1.4)	0 (0.0)	1 (3.2)	3 (1.7)	1 (1.7)	0 (0.0)
Other diseases	77 (13.8)	14 (14.9)	9 (29.0)	22 (12.6)	3 (5.2)	12 (19.0)

SAS; sleep apnea syndrome, RLS; restless legs syndrome, PLMD; periodic limb movement disorder, NBD; nocturnal behavior disorder.

Table 2
Question items and percentages of respondents in the analyzed 421 inpatients

Items		1)	2)	3)	4)
Q1. How long did it take from light off until you went to sleep? 1) less than 15 minutes 2) 15-29 minutes 3) 30-59 minutes 4) more than 60 minutes		50.4	20.4	14.5	14.7
Q2. How many times did you awake during last night? 1) none 2) 1-2 times 3) 3-4 times 4) more than 5 times		21.4	35.9	24.9	17.8
Q3. What time did you get up this morning (h:min)?		22.6*	77.4		
Q4. Did you get up in the morning unrefreshed or nonrestored? 1) good 2) fair 3) insufficient 4) poor		38.7	37.1	19.2	5.0
Q5. Do you have daytime sleepiness?** 1) none 2)some 3) moderate 4) severe		22.8	22.8	47.5	6.9
Q6. Did you experience any of the following symptoms during last night (completed by a patient)					
Q6-a creeping sensation or restless discomfort in the limbs	1) yes 2) no	5.9	94.1		
Q6-b legs or arms jerk	1) yes 2) no	2.4	97.6		
Q6-c hot flash	1) yes 2) no	4.8	95.2		
Q6-d night sweat	1) yes 2) no	6.9	93.1		
Q6-e palpitation	1) yes 2) no	1.2	98.8		
Q6-f anxiety or panic	1) yes 2) no	1.0	99.0		
Q6-g sleep paralysis	1) yes 2) no	0.0	100.0		
Q6-h nightmare	1) yes 2) no	3.1	96.9		
Q7. Did the patient experience any of the following symptoms during last night (completed by nursing staffs)					
Q7-a loud snoring, or apnea lasting for 10 seconds or longer	1) yes 2) no	10.0	90.0		
Q7-b periodic legs or arms jerk	1) yes 2) no	2.1	97.9		
Q7-c sleep-talking, delirium or abnormal behaviors such as wandering	1) yes 2) no	6.9	93.1		
Q8. Whether or not the patient took any hypnotic-sedative drug(s) for treatment of insomnia within the past one week and the name of the drug(s) if any (completed by nursing staffs) 1) yes 2) no Name of drugs [ ]		27.6	72.4		

* Patients who woke up 30 minutes or earlier than the desired time without falling asleep again (Q3).
** answered at 2 pm.

which patients were supposed to be in bed as specified by each hospital ward, and specifically the time from "lights out" to the time at which patients were expected to wake. Mean TIB was approximately between 9 p.m. and 6 a.m. Observations by the nursing staffs on each of the wards confirmed that the patients were in bed during TIB on the evenings of the study.

For the observational sleep evaluations, several nursing staffs alternated in order to record continuously the subjects' sleep states. Opening and closing of eyes, breathing, movement and any unusual behavior of the subjects were observed and recorded at a distance so as to not disturb the subjects.

2.3. Differential diagnosis of sleep disorders

The diagnostic flow for the patients included in the investigation is shown in Fig. 1. Some of the preselected subjects (n=136) were either excluded from data analyses or could not participate due to reasons such as sudden change in physical condition such as fever, severe dementia, consciousness disturbance due to organic brain damages, need for emergency examination, hospital transfer or discharge or due to missing data on their amount of physical activity. As a result, a total of 421 patients comprised the analysis population [228 males, 193 females; mean age, 72.5±12.6 (S.D.) years; range 22-96 years]. The number of respondents for each question item is shown in Table 2.

Patients were initially examined for the presence of SAS (positive answer to Q7-a), RLS (positive answer to Q6-a), PLMD (positive answer to Q6-b or Q7-b) or NBD (positive answer to Q7-c). Those who were NOT diagnosed with SAS, RLS, PLMD or NBD were subsequently examined for the presence of insomnia. Patients were judged as having insomnia when the subjective sleep investigation indicated the presence of any one of the following:

i. Disturbances of initiating sleep (DIS): Q1, the answer indicates 30 min or more.
ii. Disturbances of maintaining sleep (DMS): Q2, the answer indicates three times or more.
iii. Early morning awakening (EMA): Q3, the answer indicates wake time 30 minutes or earlier than the desired time without falling asleep again.
iv. Non-restorative sleep (NRS): Q4, the answer indicates insufficient or poor sleep.

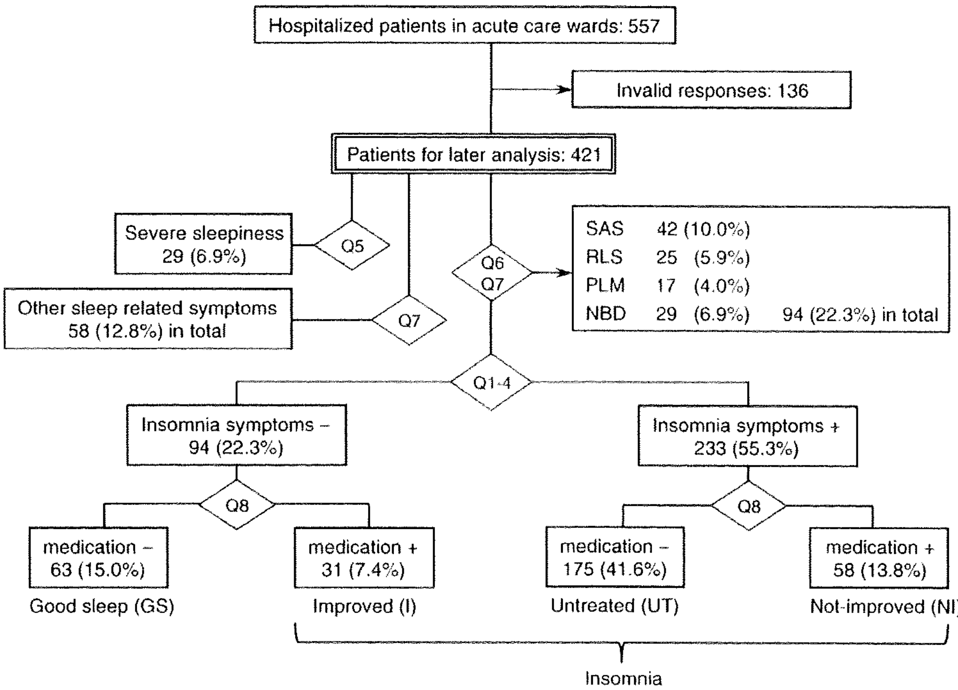

Fig. 1. Diagnostic flow of the subjects in this study. See text and Table 2 for explanation.

The subjects were also divided into the following four groups according to the presence or absence of insomnia and use or not of hypnotic-sedative drugs for insomnia treatment: the good sleep (GS) group consisting of those without insomnia and taking no medication, the improved (I) group consisting of those without insomnia and taking medication (s), the untreated (UT) group consisting of those with insomnia but taking no medication, and the not-improved (NI) group consisting of those with insomnia and taking medication(s). Of these groups, the I, UT and NI groups were grouped together and defined as the insomnia group (Fig. 1).

2.4. Daytime sleepiness

The 421 patients were examined for the presence or absence of daytime sleepiness according to the following criteria: Q5, the answer indicates the presence of moderate or severe sleepiness.

2.5. Sleep-related symptoms

The 421 patients were examined for the presence or absence of other sleep-related symptoms, such as hot flashes in the foot or body (Q6-c), night sweats (Q6-d), palpitations (Q6-e), anxiety and panic (Q6-f), sleep paralysis (Q6-g) and nightmares (Q6-h).

2.6. Statistical analysis

One-way analysis of variance followed by Tukey's multiple comparison tests was used to identify significant differences in sleep parameters (TST, TWT and SE) among the insomnia group and GS group. Sleep parameters were also compared between each sleep disorder group and the GS group using a two-tailed Student's t test. Analysis values are expressed as mean±S.D. Multiple logistic regression analysis was carried out to calculate the odds ratio (OR) and 95% confidence interval (CI) for assessing the association of primary disorders, sleep disorders and use of hypnotic-sedative drugs with severe sleepiness. Presence of severe sleepiness was used as the dependent variable, and primary disorders, sleep disorders and use of hypnotic-sedative drugs were used as independent variables. We performed multiple logistic regression analyses to control for all sociodemographic (sex and age) and other factors. Statistical significance was set at $P<.05$. All analyses were made using SPSS 11.5 for Windows.

3. Results

3.1. Prevalence of sleep disorders

The breakdown of the diagnoses of sleep disorders is shown in Fig. 1. Of the 421 inpatients, 42 (10.0%, M/F=29/13) had SAS, 25 (5.9%, 14/11) had RLS, 17 (4.0%, 11/6) had PLMD and 29 (6.9%, 19/10) had NBD. A total of 94 (22.3%) had at least one of the four sleep disorders. Seventeen patients had two sleep disorders concurrently.

Of the 421 inpatients, 58 (13.8%, NI) and 175 (41.6%, UT) complained of insomnia symptoms. A total of 264 (62.7%), including the NI, UT and I (31, 7.4%) groups were given a diagnosis of insomnia. The most common insomnia

Table 3
Comparison of objective sleep parameters determined by LC in the insomnia and good sleep patients

	SAS n=42	P	RLS n=25	P	PLMD n=17	P	NBD n=29	P	Insomnia						Good sleep n=63
									Untreated n=175	P	Improved n=31	P	Not-improved n=58	P	
TST (min)	367.6±119.2	.06	331.9±117.7	0	354.6±111.5	.01	359.8±126.1	.04	369.2±102.5	.04	400.7±118.4	n.s	399.7±91.0	n.s	409.4±102.4
TWT (min)	172.4±119.2	.05	208.1±117.7	0	185.4±111.5	.01	180.2±126.1	.04	170.3±102.3	.03	139.4±118.4	n.s	140.3±91.0	n.s	129.3±103.3
SE (%)	68.1±22.1	.05	61.5±21.8	0	65.7±20.6	.01	66.6±23.4	.04	68.4±19.0	.03	74.2±21.9	n.s	74.0±16.9	n.s	76.1±19.1

Value are expressed as mean±S.D..
P value vs. Good sleep group.
n.s; not significant.

symptom was DMS (60.1%), followed by DIS (41.2%), EMA (33.9%) and NRS (31.8%). Only 63 (15.0%) were free of the above-mentioned sleep disorders and were assigned to the GS group.

3.2. Objective sleep parameters

Sleep parameters in each sleep disorder group are summarized in Table 3. There were significant differences in TST [F(3,323)=3.24, P=.022], TWT [F(3,323)=3.28, P=.021] and SE [F(3,323)=3.31, P=.020) among the insomnia group and GS group. TST (P=.039) was significantly shorter and TWT (P=.033) and SE (P=.032) were significantly longer in the NI group than in the GS group. Patients with RLS (P<.01) and NBD (P<.05) also presented a significantly shorter TST, significantly longer TWT and significantly lower SE than those in the GS group. A similar tendency was observed for patients with SAS or PLMD (P<.06). On the other hand, we found no significant differences in the sleep parameters between the medicated group (the I or NI group) and the GS group, regardless of whether or not any subjective improvement was observed.

3.3. Daytime sleepiness

Of the 421 inpatients, 229 (54.4%) experienced moderate to severe sleepiness and 29 (6.9%) experienced severe sleepiness. Severe sleepiness was commonly observed in those with sleep disorders; it was most commonly observed in patients with multiple sleep disorders (27.8%, 5/18), followed by those with PLMD (18.2%, 2/11), SAS (17.9%, 5/28) and NBD (17.7%, 3/17). Multiple logistic regression analysis revealed that SAS (adjusted OR=3.78, 95% CI, 1.24–11.53, P<.05) and PLMD (adjusted OR=5.93, 95% CI, 1.50–23.4, P<.05) showed a significantly positive association with the presence of severe sleepiness.

3.4. Other sleep-related symptoms

Of the 421 inpatients, 19 (4.5%, M/F=7/12) had hot flashes, 29 (6.9%, 13/16) had night sweats, 5 (1.2%, 1/4) had palpitations, 4 (1.0%, 2/2) had anxiety or panic and 13 (3.1%, 7/6) had nightmares. None of the patients experienced sleep paralysis.

3.5. Prevalence of use of hypnotic-sedative drugs

Of the 421 inpatients, 116 (27.6%) were taking some kind of hypnotic-sedative drug for the treatment of insomnia symptoms. The breakdown of the prescribed drugs was as follows: benzodiazepine hypnotics including zolpidem and zopiclone accounted for 73.2% (26.1% for ultrashort-acting, 30.6% for short-acting and 16.5% for intermediate-acting), benzodiazepine anxiolytic accounted for 5.8%, antipsychotics accounted for 15.6% and other drugs accounted for 5.2% of all prescribed drugs. In the insomnia group, those receiving medication therapy for insomnia only accounted for 33.7% (the I+NI group). Two thirds of the patients receiving medication therapy (65.2%, corresponding to the NI group) complained of persistent insomnia symptoms. In addition, 36.0% of RLS patients, 29.4% of PLMD patients, 26.2% of SAS patients and 17.2% of NBD patients were taking at least one of the above hypnotic-sedative drugs.

4. Discussion

This is the first multicenter study investigating the prevalence of sleep disorders in inpatients of acute wards in general hospitals. Sleep disorders are extremely common disorders among community residents, and are even more so among patients with underlying physical diseases as in the subjects of the present study. Insomnia, as well as other sleep disorders, while frequently thought to be transitory or secondary to a physical disease, can become prolonged without appropriate treatment in the early stages. Furthermore, chronic sleep disorders can exacerbate lifestyle-related diseases such as hypertension and diabetes, and increase the risk of psychiatric symptoms such as depression and anxiety, not to cause subjective distress [16,17]. Many sleep disorders go undetected and are not appropriately treated in clinical practice. Therefore, this study was conducted to alert practitioners of sleep disorders to this situation, by shedding more light on their current status in general medical practice.

In the present study, we investigated the prevalence of sleep disorders and the use of hypnotic-sedative drugs in 421 inpatients with mean age of 72.5 years by questionnaire-, actigraph- and observation-based sleep evaluations, and have revealed a high prevalence of diverse types of sleep disorders in the study population. SAS, RLS, PLMD, NBD and insomnia, in particular, were highly prevalent (10.0, 5.9, 4.0, 6.9 and 62.7%, respectively). The inpatients also suffered from various sleep-related symptoms (1.0–6.9%, except for sleep paralysis), which are common conditions with physical disorders and which could cause disrupted sleep [18–21]. In fact, the patients with these sleep disorders also showed poor sleep parameters recorded by actigraphy, which objectively indicates that they have poor-quality sleep during the night. Consequently, of the 421 patients, only 13.8% were free of any type of sleep disorder diagnosed, severe daytime sleepiness or sleep-related symptoms, revealing that sleep-related problems are very common clinical problems among inpatients of acute hospital wards.

Due to restrictions on the disclosure of personal information, the only information available regarding the underlying diseases of the patients was the names of the primary diseases according to the major classification of the *ICD-10*. We were thus unable to analyze respective medical conditions that are commonly associated with these sleep disorders, such as chronic pain, cardiovascular diseases, chronic renal failure, hemodialysis and iron deficiency anemia.

The prevalence of SAS and RLS is generally high in elderly people and patients with physical disorders. However, even though the mean age of our patients was high (72.5 years) and they had physical disorders in the exacerbation phase, contrary to our expectations, the prevalence of SAS and RLS was not higher in the study population than in community dwellers of previous studies. For example, the prevalence of SAS in middle-aged to elderly people has been shown to be 9–10% in males and 4–10% in females [22,23], which is comparable to that in the present study population (10% in the entire population, 12.7% in males, 6.7% in females). In the present study, patients were defined as having SAS if they reported loud snoring or apnea lasting for 10 seconds or more, because loud snoring is the most prominent symptom of upper airway resistance syndrome, which is included in the category of SAS [7,24]. Nevertheless, the prevalence of SAS patients including those who snored loudly in the present study was similar to that in the general population. Similarly, a large-scale survey which employed a self-administered questionnaire and used a definition of RLS similar to that in the present study has reported that the prevalence of RLS among Japanese people aged 70 years or more is 4.1% (3.4% in males, 4.6% in females), which is practically identical to that in the present study (5.9% in total, 6.1% in males, 5.7% in females) [25]. Furthermore, the frequency of NBD was as low as 6.9%, despite the occurrence rate of delirium per admission varying between 11 and 42% [26]. The low NBD frequency of the present study compared to that of all previous studies is thought to be because patients with severe physical conditions or with organic brain damages were excluded from the analyses.

In many of the epidemiologic studies on the prevalence of sleep disorders, sleep evaluation is performed during a period of one week to one month. The fact that sleep evaluation in this study was performed on a single night might have held down the prevalence of sleep disorders. However, since the physical status of the inpatients of acute hospital wards can change in a very short period of time and their sleep condition is also subject to change, we assumed that the results obtained from a long investigation period would not properly reflect the actual status of their sleep-related problems. Extension of the duration for determining the presence or absence of sleep disorders may result in a dramatic increase in the prevalence of the sleep disorders in inpatients of acute hospital wards.

Patients with physical disorders, especially with advanced age, are generally vulnerable to insomnia [27–29]. We have found that approximately two thirds (62.7%) of the representative patients in acute wards in Japan are suffering from insomnia. It was confirmed not only from the subjective complaints of patients but also from the objective sleep evaluation that the quality of sleep for patients with insomnia receiving no treatment or who had other sleep disorders was significantly lower than that for patients in the GS group (Table 3). A survey among 1500 community dwellers aged 55–84 years in the United States has demonstrated that the quality of sleep decreases in proportion to an increase in the number of physical disorders suffered [27]. Several studies have also reported a high prevalence (34–69%) of insomnia in outpatients of primary care clinics or regular inpatients with acute or chronic physical disorders [30–33]. The findings of the present study for acute ward inpatients are consistent with those obtained in the previous studies in spite of shorter-term sleep evaluation.

In many cases of sleep disorders, daytime sleepiness often occurs to compensate for low-quality sleep during the night. In the present study, 47.5% of the patients experienced mild or severer sleepiness and 6.9% experienced severe sleepiness, which was particularly high in those with multiple sleep disorders, including SAS, RLS, PLMD and NBD. The results of multiple logistic regression analysis indicated that severe sleepiness is significantly associated with SAS and PLMD, and not with an underlying disease or type of hypnotic-sedative drug.

Only one-third (33.7%) of the patients with insomnia included in the present investigation received treatment for insomnia symptoms. In addition, two-thirds (65.2%) of the patients receiving medication therapy complained of residual insomnia symptoms. The relatively low frequency of patients prescribed hypnotic-sedative drugs in the present study, which is very similar to that reported in the Meissner's study [30], suggests the possibility that physicians are not fully aware of the presence of insomnia in their patients.

The prescribed drugs mainly consisted of benzodiazepine hypnotics including intermediate-acting agents and antipsychotics. Caution should always be exercised when using these hypnotic-sedative drugs in inpatients with physical disorders, especially in elderly patients. This is because elderly patients present a poor risk-benefit balance for hypnotic-sedative drugs due to such reasons as decreased drug metabolizing capacity, increased drug sensitivity, risk of fall and fracture or suppressed mental function, and worsening of underlying diseases induced by medication [34–37].

Moreover, administered hypnotic-sedative drugs may be ineffective or even worsen underlying diseases unless sleep disorders are properly diagnosed. In fact, 23.8% of the patients with SAS were prescribed hypnotic-sedative drugs including benzodiazepines and 36.0% of the patients with RLS were taking hypnotic-sedative drugs other than clonazepam. These results suggest that medications that are not necessarily appropriate for treatment of individual patients' sleep disorders are often selected in actual clinical practice, possibly causing a reduction in the patients' ADL and QOL.

Several limitations should be noted when interpreting the results of the present study. First, as elderly patients aged 65 years or more accounted for a large portion (76.0%) of the 421 inpatients, it is speculated that the high prevalence of sleep-related problems observed in the patients of the present investigation were associated with not only sleep disorders attributable to physical disorders but also age-related changes in sleep property.

Second, one-fourth (24.4%) of the initially enrolled 557 patients were excluded. Patients who were unable to answer questions on the day of the survey because of a change in their physical condition (e.g. fever, consciousness disturbance or need for emergency examination) or those patients with missing data due to interruptions in LC data collection were excluded. Some of these excluded patients might have developed some type of sleep disorder during their stay in hospital.

Third, insomnia defined in the present study is different from insomnia that meets the general criteria of the International Classification of Sleep Disorders, second edition (ICSD-2) [7], because we did not consider the presence or absence of "daytime impairment related to the nighttime sleep difficulty". This investigation item was not included in the present study because it was difficult to determine whether the patients' diverse psychosomatic symptoms observed during the daytime were attributable to insomnia or physical disorders.

Fourth, the questionnaire employed in the present study has not been validated. A set number of items taken from the original were configured so as to reduce the burden on inpatients who were in poor physical condition. Therefore, the questionnaire can only suggest the possibility of certain disorders such as SAS, PLMD and RLS; it does not predict the presence of these disorders with high accuracy. However, the frequency of sleep disorders and the percentage of patients exhibiting symptoms of insomnia found in the present study closely resemble the data of several other studies. This is thought to be indirect evidence that, to a certain degree, the survey items work effectively to detect patients suffering from sleep disorders.

Fifth, the sleep/wake scoring algorithm used for the LC data in the present study has been validated for a sample of healthy young subjects [15], but not for elderly subjects with physical disorders, as in the present study's sample. However, as the results demonstrate, meaningful differences were detected in the sleep parameters calculated with this algorithm for total sleep time, total wake time, and efficiency of sleep between the UT group with insomnia and the GS group. Given this, the clinical application of the LC and sleep/wake scoring algorithm for the subjects of the present study can be considered a sound approach to a certain degree.

5. Conclusion

In the present study, which initially involved 557 inpatients who had been admitted to acute hospital wards in 44 general hospitals, we have revealed an extremely high prevalence of sleep disorders using subjective and objective sleep evaluation scales, and have also indicated several problems in the current practice of sleep medicine. Proper diagnosis of sleep disorders should be made while being aware of the high prevalence of sleep disorders among elderly patients with physical disorders, and a treatment strategy that provides a favorable risk-benefit balance must be developed.

Acknowledgments

This study was supported by a Grant-in-Aid for Cooperative Research from the Ministry of Health, Labor, and Welfare of Japan (H19-kokoro-ippan-013, H20-tyojyu-ippan-001).

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Sleep Deprivation Influences Diurnal Variation of Human Time Perception with Prefrontal Activity Change: A Functional Near-Infrared Spectroscopy Study

Takahiro Soshi[1,2], Kenichi Kuriyama[1,2]*, Sayaka Aritake[1], Minori Enomoto[1], Akiko Hida[1], Miyuki Tamura[1], Yoshiharu Kim[2], Kazuo Mishima[1]

1 Department of Psychophysiology, National Center of Neurology and Psychiatry, National Institute of Mental Health, Tokyo, Japan, 2 Department of Adult Mental Health, National Center of Neurology and Psychiatry, National Institute of Mental Health, Tokyo, Japan

Abstract

Human short-time perception shows diurnal variation. In general, short-time perception fluctuates in parallel with circadian clock parameters, while diurnal variation seems to be modulated by sleep deprivation per se. Functional imaging studies have reported that short-time perception recruits a neural network that includes subcortical structures, as well as cortical areas involving the prefrontal cortex (PFC). It has also been reported that the PFC is vulnerable to sleep deprivation, which has an influence on various cognitive functions. The present study is aimed at elucidating the influence of PFC vulnerability to sleep deprivation on short-time perception, using the optical imaging technique of functional near-infrared spectroscopy. Eighteen participants performed 10-s time production tasks before (at 21:00) and after (at 09:00) experimental nights both in sleep-controlled and sleep-deprived conditions in a 4-day laboratory-based crossover study. Compared to the sleep-controlled condition, one-night sleep deprivation induced a significant reduction in the produced time simultaneous with an increased hemodynamic response in the left PFC at 09:00. These results suggest that activation of the left PFC, which possibly reflects functional compensation under a sleep-deprived condition, is associated with alteration of short-time perception.

Citation: Soshi T, Kuriyama K, Aritake S, Enomoto M, Hida A, et al. (2010) Sleep Deprivation Influences Diurnal Variation of Human Time Perception with Prefrontal Activity Change: A Functional Near-Infrared Spectroscopy Study. PLoS ONE 5(1): e8395. doi:10.1371/journal.pone.0008395

Editor: Alex O. Holcombe, University of Sydney, Australia

Received May 20, 2009; **Accepted** November 30, 2009; **Published** January 1, 2010

Funding: This study was supported by Special Coordination Funds of the Ministry of Education, Culture, Sports, and Technology of Japan and by a Grant-in-Aid for Cooperative Research from the Ministry of Health, Labour, and Welfare of Japan. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: kenichik@ncnp.go.jp

Introduction

Temporal perception is fundamental to environmental adaptation. Developing time management skills enables us not only to avoid life-threatening situations, but also to gain rewards and establish motor and cognitive skills. Higher organisms have at least two endogenous clock systems [1,2]. One of these is a circadian pacemaker located in the suprachiasmatic nucleus of the hypothalamus [3,4] which is driven by a self-sustaining oscillator with a period of about 24 h and provides the time of day as the hour hand of the clock [5]. Another is a stopwatch-like system which perceives brief temporal intervals as the minute hand of the clock [1,6].

Most studies in human time perception refer to the issue that time perception is sensitive to the length of duration perceived, where the perception of a longer interval with a range of several minutes to hours (long-time perception) [7] shows different properties from the perception of a shorter interval with a range of seconds or within a minute (short-time perception), as well as from the perception of a sub-second interval [8–10]. Short-time perception robustly reflects the rate of the stopwatch-like system [8,11,12], being shortened or prolonged when the system "speeds up" or "slows down", respectively [13]. When the stopwatch-like system speeds up, the duration of events may be felt as more extended than the real interval: That may equal to "time expansion", which enables us to deal with more things or to perform more rapidly.

Neural correlates of the stopwatch-like system are suspected to include subcortical (cerebellum and basal ganglia) structures in addition to the right prefrontal cortex (PFC) [8,9,14,15]. A three-stage model of temporal processing proposed by Pouthas et al. [9] comprises a first clock stage in which an endogenous clock system measures primitive timing intervals, a second storage stage in which measuring time is stored in short-term working memory and a third decision stage in which temporal judgment is finally made in reference to short- and long-term temporal memories. A similar model of temporal processing has been proposed by other researchers [16–18], and consensus has almost been reached that the cerebellum and the basal ganglia may contribute to a basic timing process that corresponds to the first stage of the three-stage model [19,20]. The right PFC, on the other hand, is implicated in making judgments with working memory or attentional processes contributing to temporal processing [9,21–23], although some researchers regard right PFC activity as constituting temporal processing per se [24,25].

Biological rhythm studies have reported that short-time perception driven by the stopwatch-like system is not independent of the influence of the circadian pacemaker; short-time perception correlates with circadian markers such as core body temperature and melatonin, showing diurnal variation in consequence [7,13,26–28]. On the other hand, after sleep deprivation, there is less diurnal variation in short-time perception dissociating with endogenous circadian markers [27,29,30]; the biological stopwatch is "sped up" as a result [13].

The present study aims at investigating neural responsibility for attenuation of the diurnal variation in short-time perception after sleep deprivation, utilizing the representative experimental paradigm of the time production (TP) method. The hypothesis is that an attenuated variation of short-time perception is associated with an alteration in PFC activity as a consequence of sleep deprivation. With regard to neural vulnerability to sleep deprivation, the PFC shows complicated hemodynamic or metabolic patterns during cognitive performance after sleep deprivation [31–33]. In this state, the PFC shows hypoactivity during working memory or arithmetic tasks [34,35] but hyperactivity during verbal learning or attention-loaded tasks, as well as verbal working memory tasks [36–38]. Although hemodynamic or metabolic responses to sleep deprivation on various cognitive tasks may be influenced by the task difficulty and weight of contribution from PFC activity [37], the neural vulnerability of the PFC to sleep deprivation must have consistent repercussions on cognitive performance. Taken together, the vulnerability of the PFC to sleep deprivation presumably influences short-time perception.

We utilize the brain imaging method of functional near-infrared spectroscopy (fNIRS) for the experimental purpose. fNIRS is a noninvasive optical imaging technique to measure changes of cerebral blood flow and volume through fluctuations in local glucose and oxygen coupled with neural electric activity [39,40]. It is well suited to sleep deprivation studies because it neither produces high noise levels on scanning nor requires that participants severely restrict their body movement, and thus is unlikely to seriously influence the sleep-deprived condition. It is also suitable for monitoring the participants' condition while they are performing tasks.

Results

Sleep Data

Nocturnal sleep duration on the interval day between the first and the second experiments for two different sleep schedules [sleep-controlled (SC) - sleep-deprived (SD), and SD - SC] was not significantly different [SC-SD (8.01±0.96 h) vs. SD-SC (8.70±1.72 h); $t(1,16) = 1.102$, $p = 0.287$]. Sleep duration between the first and the second TP sessions during the participants' stay in the laboratory also did not differ significantly between the two sleep schedules [SC-SD (6.40±0.18 h) vs. SD-SC (6.63±0.11 h); $t(1,16) = 1.145$, $p = 0.269$].

Time Production Data

Produced time in the SC condition was 11.16±0.27 s on day 1 and 11.60±0.33 s on day 2, and in the SD condition was 11.14±0.24 s on day 1 and 10.94±0.35 s on day 2 (Fig. 1).

A significant interaction of condition × day was obtained [$F(1,16) = 9.888$, $p = 0.006$]. Pair-wise comparisons of two levels within the factor of day in each condition revealed that the produced time on day 2 was significantly longer than that on day 1 in the SC condition [$F(1,17) = 4.575$, $p = 0.047$]. In the SD condition, on the other hand, the produced time on day 2 was not significantly different from that on day 1 [$F(1,17) = 0.753$, $p = 0.398$]. Produced time on day 2 in the SD condition, relative to that in the SC condition, was significantly attenuated [$F(1,17) = 6.123$, $p = 0.024$].

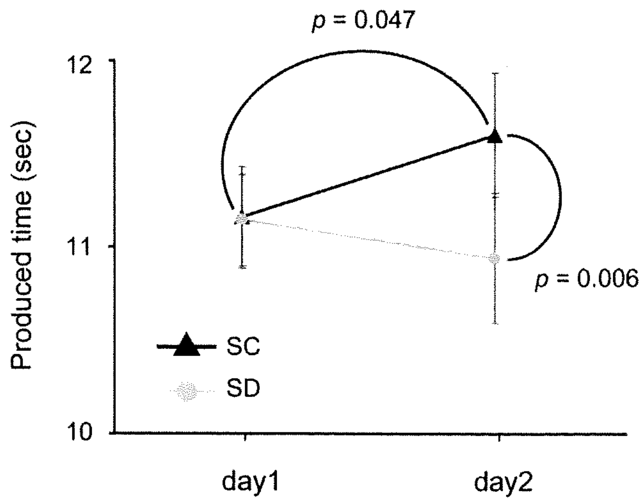

Figure 1. Mean interval variation in SC and SD conditions (n = 18). Black filled triangles with error bars (left: day 1, right: day 2) and the linking line indicate mean produced intervals and the trend of fluctuation in the SC condition, respectively. Gray filled circles with error bars (left: day 1, right: day 2) and the linking line show mean produced intervals and the trend of variation in the SD condition, respectively. Solid curves connecting two markers indicate significant differences ($p < 0.05$).
doi:10.1371/journal.pone.0008395.g001

There was no significant interaction of the between-subject factor of schedule [condition × schedule: $F(1,16) = 0.254$, $p = 0.621$; condition × day × schedule: $F(1,16) = 0.755$, $p = 0.398$]. These findings taken together with those for sleep data indicate that time production performance was not influenced by sleep schedule.

fNIRS Data

We conducted statistical analyses for fNIRS data utilizing mean values of changes in oxygenated hemoglobin (oxy-Hb) concentration. The overall ANOVA for the midline area did not show any significant difference [condition: $F(1,13) = 0.322$, $p = 0.580$; condition × day: $F(1,13) = 1.715$, $p = 0.213$; condition × channel: $F(3,39) = 0.458$, $p = 0.713$; condition × day × channel: $F(3,39) = 1.777$, $p = 0.167$]. The overall ANOVA for the lateral site showed only a significant interaction for condition × day × hemisphere [$F(1,13) = 5.373$, $p = 0.037$], suggesting that PFC activity in the SD condition, compared with that in the SC condition, was more enhanced in the left hemisphere on day 2 (Fig. 2B). Subsequent planed ANOVAs confirmed that there was a significant difference between conditions on day 2 [condition × hemisphere: $F(1,26) = 9.049$, $p = 0.006$], but not on day 1 [condition × hemisphere: $F(1,26) = 0.024$, $p = 0.879$]. Additional ANOVAs showed that the more enhanced PFC activation in the SD condition on day 2 appeared in the left hemisphere [$F(1,52) = 6.142$, $p = 0.017$], but not in the right hemisphere [$F(1,52) = 0.225$, $p = 0.637$].

Enhanced oxy-Hb concentration changes on day 2 in the SD condition, compared with those in the SC condition, were observed in the left anterior PFC (LAPFC) region of interest (ROI) including chs. 17, 21 and 22 (see Fig. 3A). Comparing the mean change in concentration in the SD condition with that in the SC condition, a significant effect was observed in the overall ROI [$t(1,13) = 2.810$, $p = 0.015$ ($p < 0.0375$: adjusted α level under the