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False-positive cases in multiple sleep latency test by accumulated sleep debt

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Abstract

Purpose: Multiple sleep latency test (MSLT) is performed as objective assessment of sleepiness, on the following day after polysomnography (PSG). In most clinics, patients are required to stay for 2 days. However, if patients have chronic sleep debt before the examination, even if they get adequate nocturnal sleep during the initial PSG, their sleep debt would not be fully resolved, affecting MSLT results. This may lead to improper administration of psycho-stimulant medication. To clarify the sleep debt for the patients who showed short sleep latencies, we compared the mean sleep latencies of MSLTs.

Methods: Twelve hypersomnolent males, who underwent MSLTs (1st MSLT with 1 night and 2nd MSLT with more than 3 nights), were enrolled. We selected these cases based on the longer total sleep time on PSG night compared to the mean total sleep time on pre-examination sleep logs and shortened sleep latencies on PSG. To evaluate the effect of the sleep debt for the patients who showed short sleep latencies, we extended their hospitalization or re-hospitalized them.

Results: The mean sleep latency of 1st MSLT was 5.8 minutes and that of 2nd was 13.9 minutes ($P < .001$). Among these 12 cases, 5 cases altered from short to normal sleep latencies at the 2nd MSLT. These 5 cases were prevented from over-diagnoses by the extension of evaluations.

Conclusions: The sleep debt may produce false-positive results when patients are examined by standard PSG and MSLT. Accumulation of sleep debt will cause shortened sleep latencies in the following nights. Patients should be advised to extend their hospitalization before PSG and MSLT to reduce the chronic sleep debt for accurate diagnosis of hypersomnia.

1 | INTRODUCTION

Multiple sleep latency test (MSLT) is considered as an objective assessment of sleepiness. It is performed on the following day after polysomnography (PSG). In most clinics and hospitals, patients are required to stay for two days. However, if patients have chronic sleep debt, the accumulation of insufficient sleep may affect MSLT results. Even if they get adequate nocturnal sleep during the initial PSG (at least ≥6 hours were required), their sleep debt would not be fully resolved.[1,2,3]

Primarily, we examined these cases using standard PSG and MSLT procedure; however, their diagnoses based on such MSLT results were doubtful compared with sleep logs and other symptoms. In order to evaluate the effect of the sleep debt for the patients that showed short sleep latencies, we performed additional MSLT evaluations: the initial MSLT following the first PSG and the second MSLT for more than 3 nights in the hospital. It is necessary to be careful for a diagnosis of central hypersomnia, since it may lead to medication of psycho-stimulants, such as modafinil and methylphenidate.

2 | METHODS

This study was performed as a retrospective chart review. Twelve males (31.8 ± 14.2 years) who performed MSLTs twice were enrolled in this study. They complained of hypersomnolence and were evaluated in our hospital from 2004 to 2012. We previously have been performing PSG and MSLT in 2 days following the standardized protocol. Since some patients showed inconsistent results between MSLT and sleep logs, they were hospitalized for extended period (n = 5) or re-hospitalized (n = 7) to evaluate sleep logs and other symptoms for much more accurate diagnoses. We used the following 4 inclusion criteria for selecting patients to perform the 2nd MSLT. Those who met three of the four criteria were enrolled for this study. (a) The mean total sleep time on pre-examination sleep log was less than 6 hours per night; (b) total sleep time on PSG was extended to more than 7.5 hours; (c) PSG showed sleep efficiency more than 85%; and (d) irregular sleep-wake patterns with more than two naps were observed on sleep logs 2 weeks before admission. We compared the mean sleep latencies of 1st and 2nd MSLTs in these cases. These patients showed over 11/24 points in Epworth sleepiness scale before the 1st MSLT. Representative case 6 is presented in "Results" section.

All patients need to show short mean sleep latency, less than 8 or 10 minutes (in the cases who complained of severe hypersomnolence subjectively). Exclusion criteria are as follows: apnea-hypopnea index (AHI) >15; periodic limb movements in sleep >15, and subjects who did not agree with 2nd MSLT.

The re-hospitalization intervals of patients were distributed 1-2 months for 1st and 2nd MSLTs. The 2 patients with narcolepsy were hospitalized for 1 week drug holiday at 2nd MSLTs with about 1-2 year interval of initial PSG/MSLT for diagnosis. Subsequently, all the 2nd MSLT were performed with more than 3 nights with an instruction to take sufficient sleep. Physicians asked on a scale of 0-3 (0 = would never doze, 1 = slight chance of dozing, 2 = moderate chance of dozing, 3 = high chance of dozing), if the patients dozed off while (a) sitting and reading, (b) watching TV, (c) sitting still in a public place, (d) lying down to rest in the afternoon when the circumstances allow, (e) sitting and talking to someone, (f) sitting quietly after lunch without having drunk alcohol, and checked patients' sleep logs every other day in order to determine the timing of 2nd MSLT. Patients with less than or equal to 10 points were included for the 2nd MSLT. PSGs were not performed in the most cases before 2nd MSLTs, but nocturnal sleep time was recorded by their sleep logs. From the sleep logs, we looked for (a) regular sleep-wake pattern and (b) short naps less than or equal to once with total sleep time more than 7 hours to evaluate for the 2nd MSLT execution criteria.

The patients with physical comorbidities were allowed to continue their medications, such as for hypertension and hyperlipidemia, while all the medications regarding mental and sleep disorders were ceased for 1 week prior to PSG at the1st MSLTs. PSG was started at 21:00 and stopped at 6:00 when the patient was awakened. Some particular subjects with delayed sleep phase syndrome (DSPS), who were taking a melatonin agonist, ramelteon, were allowed to continue their medication before the 2nd MSLT evaluation. These patients carried out their routines (meals: 7:00, 12:00 and 18:00; and nocturnal sleep period: 21:00 to 6:00) according to the schedule of the hospital.

The ICSD-2 criteria were used for diagnosis. Briefly, <8 minutes mean sleep latency was required for the diagnosis of central hypersomnia and additional 2 or more sleep-onset REM sleep periods (SOREMPs) were required for the diagnosis of narcolepsy. The ethics committee of Akita University approved this study (No.768). Statistical analyses were performed using SPSS ver.24 (IBM) and R2.8.1. Significance level was $P < .05$.

3 | RESULT

The data of PSG are shown in Table 1. Their mean total sleep time was 428.5 minutes, and sleep efficiency was 87.8%. Percentages of each sleep stage were normal without sleep-disordered breathing (AHI: 4.9 ± 7.7). In Figure 1A, the plots show mean sleep latencies of MSLT in each patient following the nights in the hospital. MSLT was conducted twice per patient. The longer the hospitalized period, the patients showed longer mean sleep latencies (Spearman's correlation, $r = .77$, $P = .00002$). Subsequently, we compared mean sleep latency obtained from MSLT between the 1st night and ≥3 nights in hospitalization (Figure 1B). The mean sleep latency of 1st MSLT was 5.8 minutes and that of 2nd was 13.9 minutes ($P < .001$).

Representative case 6 was a 16 years old male (Table 2). After entering high school, bedtime on weekdays remained extremely irregular, from 23:30 to 3:30. In addition, it often took about 1 hour to fall asleep after bedtime. There was no mid-awakening. His mother woke him around 7:00; however, he did not feel well rested. Nighttime sleep duration ranged from 3 to 7 hours. His daytime sleepiness was

severe. The weekends sleep time ranged from 4 to 14 hours. There was no cataplexy, hypnogogic hallucination, or sleep paralysis. His snoring was mild. This irregular sleep pattern continued for half a year until the hospital admission.

The patient wore actiwatch for 3 weeks until the time of admission to the hospital. He was often awake until early in the morning and showed a decrease in activity during the day. PSG was performed on the day of admission to the hospital. The sleep latency was 1 minute, and SOREMP was observed. Total sleep time was about 10 hours without sleep apnea, and the sleep efficiency was 96.6%. In the 1st MSLT, his mean sleep latency was 4.9 minutes and two SOREMPs were observed during four naps. Based on the criteria of MSLT, he was considered as narcoleptic patient. After being admitted to the hospital, he adjusted smoothly to regular sleep-wake schedule, going to bed by 21:00, and waking up at 6 or 7:00. The subjective daytime sleepiness disappeared 3-4 days after the admission. On the sixth day of hospitalization, mean sleep latency was normalized to 13.6 minutes on the 2nd MSLT and no SOREMPs were observed.

TABLE 1 Baseline characteristics of PSG

n = 12, male: 12	Mean ± SD
Age (year)	32.3 ± 14.1
PSG data	
Total sleep time (min)	426.6 ± 94.6
Sleep efficiency (%)	86.9 ± 11.1
Stage N1 (%)	15.3 ± 10.5
Stage N2 (%)	56.0 ± 2.9
Stage N3 (%)	11.4 ± 7.1
Stage REM (%)	15.7 ± 6.4
Wake time after sleep onset (WASO, min)	32.6 ± 54.1
Sleep latency (min)	21.9 ± 23.9
REM latency (min)	86.8 ± 16.5
AHI, event/h	4.7 ± 7.9
Arousal index (ARI, event/h)	15.9 ± 7.1
SpO_2 mean (%)	96.2 ± 1.6

Note: Conventional PSG variables were shown. Their mean total sleep time was 426.6 min and sleep efficiency was 86.9%. Percentages of each sleep stage were normal. WASO was 32.6 min and sleep latency was 21.9 min. Mean AHI (4.7/h) and SpO_2 (96.2%) were normal. PSG was evaluated every 20 seconds.

Abbreviations: AHI, Apnea-hypopnea index; PSG, polysomnography.

As seen in the 1st MSLT of the Table 2, eight patients were considered as central hypersomnia (mean sleep latency: 3.9 minutes) due to short sleep latency (≤8 minutes) while 4 cases were not (mean sleep latency: 9.2 minutes) (Figure 2). Among these eight hypersomnia patients, only two were finally diagnosed as central hypersomnia after 2nd MSLT (mean sleep latency: 7.7 minutes). For the other six subjects, they were not diagnosed as central hypersomnia patients in the second MSLT evaluations (mean sleep latency: 15 minutes), but rather other sleep disorders. The other 4 cases were examined during the 2nd MSLTs, and all cases had >8 minutes sleep latencies (mean sleep latency: 15.6 minutes). As for the number of SOREMPs in the 1st MSLTs, 4 out of 8 cases with ≤8 minutes had ≥2 of SOREMPs. One out of 4 cases with mean sleep latencies (8-10 minutes) showed 2 or more SOREMPs during MSLT. All the cases that were not diagnosed as narcolepsy showed 0-1 SOREMP in the 2nd MSLT. Although the number of REM periods decreased, the REM latencies were not changed as much (Table 2). The appearance of REM sleep occurred more in the morning session during the 1st MSLT, while in the 2nd MSLT, REM sleep in the morning decreased by 75%.

Throughout the 1st and 2nd MSLTs, two cases were diagnosed as central hypersomnia (narcolepsy) and 10 cases did not show

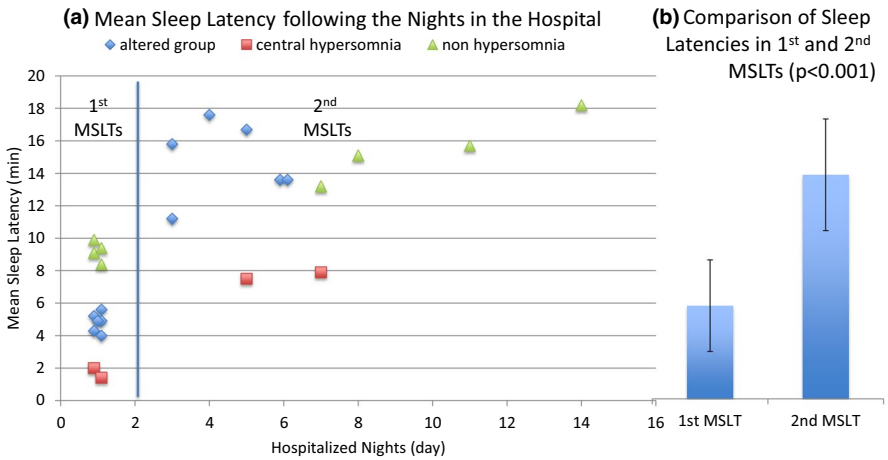

FIGURE 1 Mean sleep latency and the nights in the hospital. A, Mean sleep latency following the nights in the hospital. The plots show mean sleep latencies of MSLT in each patient following nights in the hospital. The number of patients was 11, and MSLT was conducted twice per patient. The longer the hospitalized period, the patients showed longer mean sleep latencies (Spearman's correlation, $r = .77$, $P = .00002$). Diamond plots mean altered group. Square plots mean central hypersomnia group. Triangle plots mean nonhypersomnia group. Vertical line at day 2 separates the examined dates of 1st MSLTs and 2nd MSLTs. B, Comparison of mean sleep latency obtained from MSLT between 1st MSLTs and 2nd MSLTs. We compared mean sleep latency obtained from MSLT between 1 night and ≥3 nights in hospitalization. The mean sleep latency of 1st MSLT was 6.4 minutes and that with 2nd was 14.8 minutes (Mann-Whitney *U* test, $P < .001$)

TABLE 2 Demographic data and results of the 1st and 2nd MSLTs

	No	Age	Gender	BMI	Initial diagnosis	Corrected diagnosis	Sleep Latency in 1st MSLT (m)	Sleep Latency in 2nd MSLT (m)	Delta of sleep latency (m)	Number of SOREMPs in 1st MSLT	Number of SOREMPs in 2nd MSLT	REM Latency in 1st MSLT (m)	REM Latency in 2nd MSLT (m)
Altered group	1	20	M	22.8	Idiopathic hypersomnia (IHS)	Insufficient sleep syndrome (ISS)	4.3	11.2	6.9	2	1	3.8	3.3
	2	21	M	23.3	narcolepsy	ISS	5.6	13.6	8	4	0	5.5	–
	3	53	M	24.3	IHS	Delayed sleep phase syndrome (DSPS)	4	16.7	12.7	1	0	8.3	–
	4	14	M	22.1	Narcolepsy	Irregular sleep hygine	4.9	15.8	10.9	4	1	5.7	6.7
	5	38	M	25.4	IHS	ISS	5.2	17.6	12.4	0	0	–	–
	6*	16	M	24.1	Narcolepsy	Irregular sleep hygine	4.9	13.6	8.7	2	0	4.8	–
	Mean	27.0		23.7			4.8	14.8	9.9	2.2	0.3	5.6	5.0
	SD	15.3		1.2			0.6	2.4	2.4	1.6	0.5	1.7	2.4
Central hypersomia	7	58	M	23.7	Narcolepsy	Narcolepsy	2	7.9	5.9	4	2	0.9	2
	8	36	M	25.1	Narcolepsy	Narcolepsy	1.4	7.5	6.1	3	2	2.2	4.1
	Mean	47.0		24.4			1.7	7.7	6.0	3.5	2.0	1.6	3.1
	SD	15.6		1.0			0.4	0.3	0.1	0.7	0.0	0.9	1.5
Nonhypersomnia	9	39	M	24.5	DSPS	DSPS	8.4	15.1	6.7	0	0	–	–
	10	22	M	23.6	Long sleeper	Long sleeper	9.1	15.7	6.6	0	0	–	–
	11	35	M	22.9	ISS	ISS	9.4	13.2	3.8	2	0	3.25	–
	12	36	M	23.1	ISS	ISS	9.9	18.2	8.3	0	0	–	–
	Mean	33.0		23.5			9.2	15.6	6.4	0.5	0.0	3.3	–
	SD	7.5		0.7			0.6	2.1	1.9	1.0	0.0	–	–
Total	Mean	32.3		23.7			5.8	13.8	8.1	2.0	0.5	4.3	4.1
	SD	14.1		1.0			2.8	3.5	2.8	1.8	0.8	2.3	2.0

Abbreviation: MSLT, multiple sleep latency test.

*This is a representative case described in the Results section.

Twelve male subjects were divided into 3 groups: altered, central hypersomnia and non-hypersomnia groups. All 3 groups display extended sleep latencies from the 1st MSLT; however without significant differences among the delta of each groups (Steel-Dwass, $p>0.05$). There were no significant differences in age among the groups (Steel-Dwass, $p>0.05$). No correlation between the age and mSL was observed using multivariate regression analysis ($p>0.05$). MSLT was evaluated every 20 seconds

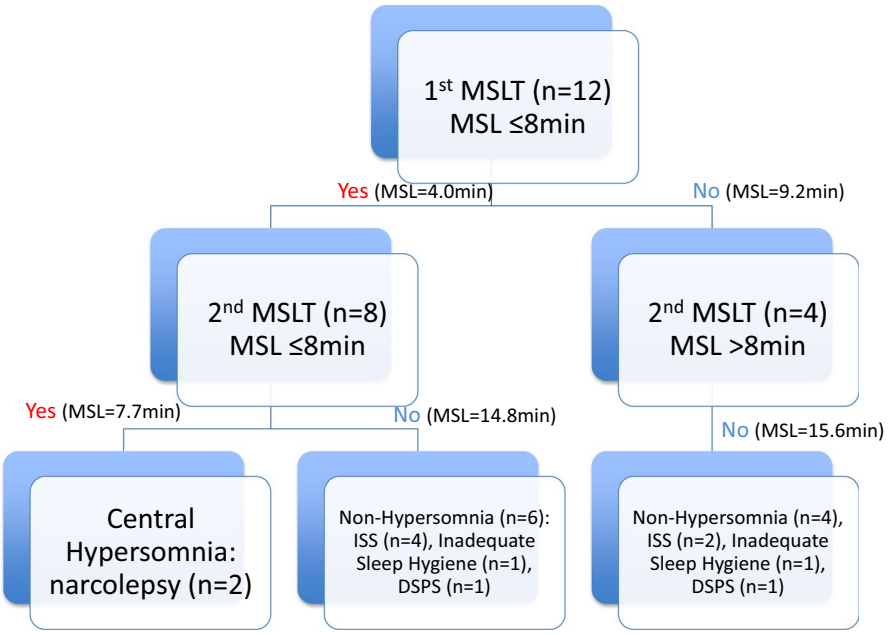

FIGURE 2 Algorithm used to identify central hypersomnia by 1st and 2nd MSLTs. Eleven patients were examined MSLTs twice. In 1st MSLT, 7 patients were diagnosed as central hypersomnia (mean sleep latency: 3.9 minutes) due to short sleep latency (≤8 minutes) and 4 cases were not (mean sleep latency: 9.2 minutes). Above 7 patients were examined during 2nd MSLTs; among those, 2 patients were diagnosed as central hypersomnia (mean sleep latency: 7.7 minutes), while the remaining 5 cases were not (mean sleep latency: 15 minutes) but diagnosed as ISS (n = 3), inadequate sleep hygiene (n = 1), and DSPS (n = 1). The other 4 cases were examined 2nd MSLTs, and all cases had >8 minutes sleep latencies again (mean sleep latency: 15.6 minutes). They were diagnosed as ISS (n = 2), inadequate sleep hygiene (n = 1), and DSPS (n = 1) for their initial hypersomnolence symptoms

consistent excessive sleepiness based on MSLT results. From them, six cases altered from short to normal sleep latencies (diamond plots in Figure 1A) at the 2nd MSLTs. According to ICSD-2 criteria, the other 4 cases that had >8 minutes sleep latencies repeatedly (triangle plots in Figure 1A) were diagnosed as insufficient sleep syndrome (ISS) (n = 2), inadequate sleep hygiene (n = 1), and DSPS (n = 1) due to their initial hypersomnolence symptoms and the results of PSG and MSLT.

We compared MSLT results between 1 night and ≥3 nights hospitalizations (Figure 3). The percentage for central hypersomnia by 1st MSLT with 1 night was 66.7% (8/12), due to their short sleep latencies (≤8 minutes) (Figure 3A). 16.7% (2/12) of the patients were diagnosed as central hypersomnia, by 2nd MSLT with ≥3 nights (Figure 3B). Consequently, 50% (6/12) of patients were recognized as false positive in the 1st MSLTs.

4 | DISCUSSION

In the representative case, excessive daytime sleepiness was present in the past medical history. In addition, MSLT showed shortened sleep latency and multiple SOREMPs. On the basis of this finding alone, this case would be diagnosed as narcolepsy without cataplexy. However, MSLT results should be judged with caution when sleep duration is irregular or short nocturnal sleep is present.

Resolving chronic sleep debt is not adequately calibrated by routine MSLT which is known to be affected by sleep deficit accumulation. Therefore, in this study, it was possible to investigate the effects of chronic sleep debt by re-evaluating MSLT. Although these re-examined subjects were recognized as doubtful cases, 50% (6/12 cases) of patients were recognized as false positive in the 1st MSLT.

As reported previously, if patients have chronic sleep debt, the accumulation of their sleep insufficiencies may affect MSLT results.[1,2,3] Our cases often showed short sleep latency and appearance of SOREMPs, especially in the morning session of 1st MSLT. Even if they got adequate nocturnal sleep during the PSG as same as our study, their sleep debt would not be fully recovered. Especially, it is necessary to be careful for a diagnosis of central hypersomnia which leads to medication of psycho-stimulants.

The final diagnosis of 6 cases with altered sleep latencies from short to normal (≤8 to 15 minutes) was ISS (n = 4), inadequate sleep hygiene (n = 1), and DSPS (n = 1). Social, academic, and employment demands may prohibit sufficient sleep to maintain daytime alertness for these subjects.[1,2,3] From prevalent society demands, circadian dysregulation and sleep hygiene problem are often misconstrued as excessive daytime sleepiness from currently suggested MSLT guidelines. At the end of the PSG prior to MSLTs, forced awakening due to protocol will also induce patients who are chronically sleep deprived, and those with DSPS to masquerade as patients with narcolepsy or idiopathic hypersomnia as shown in our 1st MSLTs.[1,2] Since accumulation of insufficient sleep time induces the shortening of mean sleep latencies in MSLT, the extension of hospitalization would be one of methods for producing enough nocturnal sleep time, as reported previously.[1]

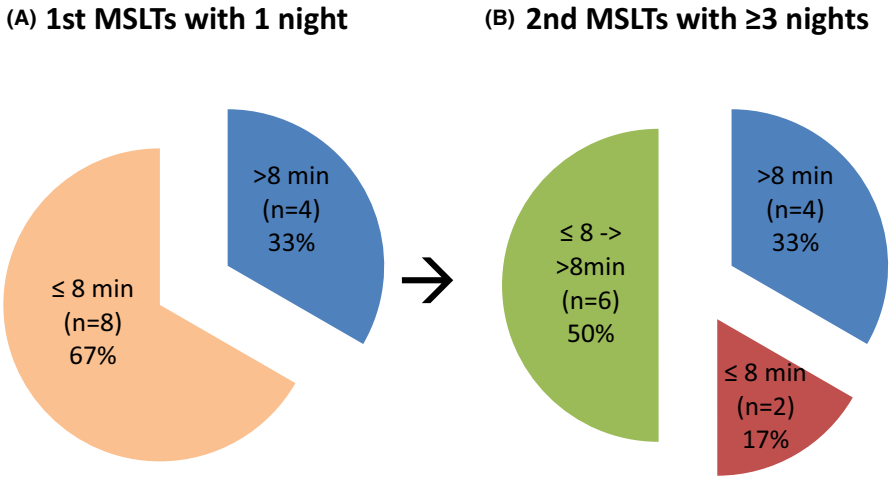

FIGURE 3 The comparison of MSLT with 1 night and ≥3 nights in hospitalization. A, 64% cases were diagnosed as central hypersomnia by 1st MSLT. B, 18% cases were diagnosed as central hypersomnia by 2nd MSLT. We compared MSLT results between 1 night and ≥3 nights hospitalizations (Figure 3). The percentage for central hypersomnia by 1st MSLT with 1 night was 64% (7/11), due to their short sleep latencies (≤8 minutes) (A). 18% (2/11) of the patients were diagnosed as central hypersomnia, by 2nd MSLT with ≥3 nights (B). Consequently, 46% (5/11) of patients were recognized as false positive in the 1st MSLTs

Unexpectedly, mean sleep latencies of two cases with narcolepsy were 1.7 minutes in the 1st and 7.7 minutes in the 2nd MSLTs. CSF measurement of orexin A confirmed that these two narcolepsy cases were orexin deficient. It was reported that the 1st and the 2nd MSLT results with standard procedure were often changed in the subjects with narcolepsy type 2 (=narcolepsy without cataplexy) but not with type 1 (=narcolepsy with cataplexy).[3,4,5,6] Mean sleep latencies of these 2 cases were still <8 minutes. If their sleep latencies were more than 8 minutes, false-negative results would be made. Even for the cases with narcolepsy or idiopathic hypersomnia, their sleep latencies would be extended to more than 8 minutes the longer the hospitalization. Although the comparisons of MSLTs were reported,[3,4,5,6] these studies employed 2 days standard PSG and MSLT procedure with several years interval. On the other hand, our study was conducted to compare MSLTs with 1 night and more than 3 nights.

For the two narcoleptic patients, we conducted the second MSLT on the fifth and on the seventh day of the hospitalization. Surprisingly, they both showed extended mean sleep latency in the 2nd MSLT. It could be possible that when the first MSLT was employed, the sleep latency was not very accurate due to insufficient accommodation and/or acclimatization for these patients. These two patients reacted very well to the medication; their daily life and nighttime schedules became much more regular. Their regular daily and nighttime schedule continued after re-hospitalization despite a week-long drug holidays. This could partly explain the extension of sleep latency in the 2nd MSLT. Further evaluation of these narcolepsy cases would be needed for the established regulation of wakefulness with prolonged hospitalizations.

4.1 | Limitation

Since no patients were resolved of their sleepiness within 2 nights, there were no cases of two nights before MSLT in this study. We suppose that the two nights group will show intermediate values between 1 night group and ≥3 nights group. Although the mean sleep latencies were extended by the hospitalization, at least 3 nights before MSLTs would be recommended for excluding the false-positive results from our evaluations.

5 | CONCLUSION

Sleep latencies of 1 night group were shorter than those of more than 3 nights group. This may produce false-positive results at diagnosis when patients are examined by standard PSG and MSLT procedures in 2 days. It is thought that the insufficient sleep affects parameters of MSLT, especially short sleep latencies. Therefore, we need to consider the durations of hospitalization before PSG and MSLT procedures for the patients who are suspected of having disorders regarding sleep debt.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHORS' CONTRIBUTION

Data analysis concept and design: Kizawa, Hosokawa, Takahashi, Kanbayashi, and Sakurai; data interpretation: Hosokawa, Nishijima, Takahashi, and Ono; drafting of manuscript: Kizawa, Shimizu, Han, Kanbayashi, and Kondo. All authors approved the manuscript for submission.

ETHICAL STATEMENT

Approval of the research protocol by an Institutional Reviewer Board: The Ethical Committees of Akita University school of medicine approved this study.

INFORMED CONSENT

The informed consents were obtained from the patients.

Registry and the Registration Number of the study: n/a.

Animal studies: N/a.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy and ethical restrictions. The IRB did not grant the deposit of raw data in a publicly accessible data archive or repository at the time of approval since the procedure was not included in the study protocol or informed consent document.

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