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SCIENTIFIC INVESTIGATIONS

A Longitudinal Follow-Up Study on Multiple Sleep Latency Test and Body Mass Index of Patients With Narcolepsy Type 1 in Korea

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Study Objectives: Narcolepsy is a chronic disorder with numerous adverse long-term consequences including increased obesity, high mortality rates, and decreased quality of life. With emerging attention to the long-term course of the disorder and importance of accurate diagnosis, the diagnostic stability of the Multiple Sleep Latency Test (MSLT)—the mostly frequently used test to identify narcolepsy—is often challenged.

Methods: In this study, we compared the baseline and follow-up demographic characteristics and body mass index (BMI) of patients with narcolepsy type 1. Moreover, MSLT results from repeated tests conducted on 48 patients with narcolepsy type 1 were compared, with mean follow-up of approximately 10 years.

Results: BMI from the baseline to the follow-up visit was significantly increased in the participants. There were no significantly different parameter changes in MSLT results.

Conclusions: MSLT has good test-retest validity in patients with narcolepsy type 1. Close surveillance for the detection and management of obesity is warranted in clinical settings.

Keywords: Multiple Sleep Latency Test, narcolepsy, obesity

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INTRODUCTION

Narcolepsy is well known for its chronic course, with a pentad of symptoms: excessive daytime sleepiness, cataplexy, hypnagogic hallucination, sleep paralysis, and nighttime sleep disturbances.[1,2] One epidemiological study demonstrated an increase of mortality rates as high as 1.5-fold in patients with narcolepsy when compared with those without narcolepsy,[3] and frequent incidences of the comorbidities from obesity, diabetes mellitus, sleep apnea, and lower back pain have been discovered after the diagnosis of narcolepsy.[4] Moreover, patients with narcolepsy suffer from diverse psychiatric comorbidities, including major depressive disorder and social anxiety disorder, further complicating the prognosis of the disease.[5] With the aforementioned adverse long-term consequences, early diagnosis of the disorder and effective management of comorbidities have become important issues discussed in recent narcolepsy research.

In attempts to promote the need for early diagnosis and intervention for patients with narcolepsy, diagnostic modalities for the diagnosis in patients with narcolepsy have been investigated and reevaluated to test diagnostic validity in clinical settings. The most frequently reported diagnostic modality has been the Multiple Sleep Latency Test (MSLT), with its test-retest validity frequently challenged as to question its current role as a main diagnostic tool to diagnose narcolepsy.[6,7] Despite increasing propositions against test-retest reliability of MSLT, limitations of previous studies should be considered, including small number of participants and short interval of follow-up.[6,8] Moreover, despite its clinical significance, studies on long-term changes in MSLT parameters of patients with narcolepsy are still scarce, especially with respect to narcolepsy types.

Meanwhile, among the aforementioned comorbidities of narcolepsy, obesity and its relationship with narcolepsy pathology has emerged as a major research interest. A symptomatology study conducted during a 10-year period in China reported weight gain as one of the four prominent symptoms of patients with narcolepsy.[9] Higher insulin sensitivity and reduced lipolysis were purported culprits of frequent obesity in patients with narcolepsy in one study, but the number of participants was too small to generalize the results.[10] Problems of obesity in pediatric patients have been frequently reported, with subsequent exposure to risks of sleep apnea and poor sleep efficiency.[11,12]

BRIEF SUMMARY

Current Knowledge/Study Rationale: The study was conducted to evaluate the long-term clinical course of patients with narcolepsy type 1. Obesity and validity of the Multiple Sleep Latency Test used to diagnose narcolepsy are key issues discussed in the current study.

Study Impact: This study will help clinicians understand the long-term course of patients with narcolepsy type 1 and further clinicians' focus on crucial issues such as obesity and the diagnostic validity of the Multiple Sleep Latency Test when treating patients with narcolepsy in clinical settings.

Table 1—Demographic characteristics of the participants (n = 48).

Age at baseline (mean ± SD)	29.79 ± 14.69
Sex (male, %)	58
Follow up duration (mean ± SD) (years)	8.15 ± 3.03
Prescription of modafinil (%)	96
Prescription of modafinil+methylphenidate (%)	33
Prescription of modafinil+venlafaxine (%)	79
Prescription of modafinil+methylphenidate+venlafaxine(%)	33

SD = standard deviation.

To unravel a link between obesity and narcolepsy pathology, longitudinal studies are imperative. However, the longitudinal course of change in body mass index (BMI) and basal metabolic rate (BMR) of patients with narcolepsy remain obscure until now. More evidence-based studies are needed to discover the relationship between obesity and narcolepsy, with accumulation of longitudinal study results.

Due to a relatively low prevalence rate when compared with other mental health disorders in Korea, narcolepsy has not received the governmental attention it deserves. A proper epidemiological study has not been conducted. One epidemiological study on Korean adolescents in whom narcolepsy type 1 has been diagnosed proposed a prevalence rate estimate of 0.015%, but it is hard to generalize the result to the entire Korean population.[13] Recently, because of the Korean governmental insurance regulations that require follow-up MSLT to ensure the maintenance of governmental insurance support for rare diseases, patients with narcolepsy went through follow-up MSLT to continue receiving the benefit.

In the current study, we compared the baseline and follow-up BMI, as well as results from MSLT in a group of Korean patients with narcolepsy type 1. This group of patients visited our clinic on a regular basis for nearly a decade, taking medications for the management of narcolepsy symptoms. We hypothesize that there would be clinically meaningful changes in the BMI and MSLT parameters of participants measured during the baseline and follow-up visits.

METHODS

Participants and Patient Evaluation

A chart review was conducted on 48 patients with narcolepsy type 1 who visited the sleep clinic of St. Vincent's Hospital, the Catholic University of Korea. They all went through MSLT twice with an interval of almost 10 years. At their baseline, all the participants were drug-naive, and a diagnosis of narcolepsy with cataplexy was made using the International Classification of Sleep Disorders, Second Edition[14] for the first time (please note that the updated terminology "narcolepsy type 1" is used throughout this article in place of "narcolepsy with cataplexy"). Confirmation on the presence of cataplexy was completed by a sleep specialist. Patients with any history of medical disorder associated with excessive daytime sleepiness were excluded.

Table 2—Comparison of BMI between baseline and follow-up (n = 26).

BMI (mean ± SD)	Baseline	Follow-up	Sig.
Female (n = 9)	25.99 ± 2.53	29.33 ± 5.13	.042*
Male (n = 17)	26.40 ± 3.67	29.63 ± 4.90	.001*

* = P < .05. BMI = body mass index, SD = standard deviation, Sig. = significance.

Every participant was drug-free for 7 to 10 days before the follow-up MSLT. They were asked to stop prescribed medications or over-the-counter drugs they were taking to control for their narcolepsy symptoms during the drug-free interval. This study was conducted after approval by the Institutional Review Board of the St. Vincent's Hospital, the Catholic University of Korea. MSLT was conducted in each patient during their baseline visit and the second visit.

Statistical Analysis

Demographic data from the patients were collected and demonstrated with descriptive statistics, and subsequently, baseline and follow-up BMI, and sleep parameters from MSLT were compared with paired t test to observe the longitudinal therapeutic effects of narcolepsy medication. Wilcoxon signed-rank tests were performed with regard to changes in BMI between baseline and follow-up data, and these statistical analyses were conducted only on 26 participants (9 of them female and 17 of them male) who had complete baseline and follow-up BMI data. An α value of .05 was used for all tests.

RESULTS

A total of 48 patients participated in the study, and the demographic characteristics of participants are shown in **Table 1**. Mean age of the participants at baseline were 29.79 ± 14.69 years, and 58% of them were male. An average follow-up duration was 8.15 ± 3.03 years. Ninety-six percent of participants were on modafinil to control their excessive daytime sleepiness. Only 33% of them were coprescribed methylphenidate, whereas 79% of the participants were coprescribed venlafaxine to control their episodes of cataplexy.

There was a statistically significant increase in BMI from 25.99 ± 2.53 to 29.33 ± 5.13 for females and from 26.40 ± 3.67 to 29.63 ± 4.90 for males. There was no statistical difference between baseline and follow-up mean sleep latency acquired from two instances of the MSLT (P = .875), and also, there was no statistical difference between frequency of sleep onset rapid eye movement period (SOREMP) (P = .281). Results are summarized in **Table 2** and **Table 3**.

DISCUSSION

To our knowledge, this is one of the few longitudinal, retrospective studies with BMI and sleep parameters attained from MSLT

during the baseline and follow-up visits in patients with narcolepsy type 1. A strength of this study is that the average follow-up duration (almost 10 years) for each participant was longer than in previous studies. Moreover, there are several clinically meaningful implications that could be derived from our study results.

First, BMI was significantly increased in the participants from the baseline to the follow-up visit. The relationship between narcolepsy type 1 and obesity has become a major research topic, because obesity significantly affects quality of life in individuals with narcolepsy.[12] Our results are concordant with previous results, where BMI increase independent of time and narcolepsy type was observed.[15] Moreover, a Chinese study on children with narcolepsy type 1 demonstrated some meaningful results, with a steep increase of BMI and a decrease in basal metabolic rate in the early follow-up period.[16] The authors suggested some possible underlying compensatory mechanisms involved in the trajectory of illness course of patients with narcolepsy type 1 with regard to BMI increase, with stabilization of BMI and BMR over time.[16] Such stabilization seems to be evident in different age groups as well, with reduced BMI in older narcolepsy groups reported in one recent study.[17] The underlying mechanisms for the aforementioned stabilization patterns should be supported by more evidence-based research.

Interestingly, our participants, both female and male, were obese at baseline and follow-up. Currently, in the Korean population, obesity is defined as a BMI $\geq$ 25 kg/m^2.[18] According to a recent report by the Korean Agency for Technology and Standards, the mean BMI in 2004 for females and males in a 25- to 29-year age group was 21.6 and 23.6, respectively.[19] As for a 30- to 34-year age group in 2004, mean BMI for females and males was 22.1 and 24.4, respectively.[19] We have also explored the mean BMI of the Korean population in 2015 for comparisons with our participants. Mean BMI for females and males in a 25- to 29-year age group in 2015 was 21.5 and 24.5, respectively.[19] As for a 30- to 34-year age group in 2015, mean BMI for females and males was 22.1 and 25.3, respectively.[19] It is significant in that participants, even with consideration for their mean age, presented with high BMI at the time of their narcolepsy diagnosis. Hypocretin (orexin) has been a major mediating factor studied to link obesity and narcolepsy,[20] and its deficiency has been implicated as a cause for decreasing energy expenditure, thus resulting in obesity.[20] Hypocretin is also reported to be involved in promoting motivated behaviors,[21] and therefore, hypocretin deficiency can lead to physical inactivity due to lack of motivation, which can lead to obesity. In addition to orexin, decreased sympathetic activity[22] and sleep deprivation[23] also have been proposed as reasons for decreased metabolic rate in patients with narcolepsy. The aforementioned findings could explain presentation of high BMI at baseline and significant increases of BMI in our patients during the follow-up visit. Obesity may be a comorbidity in the trajectory of narcolepsy and also a discrete symptom that could represent the pathology of narcolepsy.

Second, longitudinal changes were absent in MSLT variables including MSL and frequency of SOREMP. Multiple sleep latency alone measures the degree of excessive daytime sleepiness, and thus produces problems of false-positive test results in patients with insufficient sleep syndrome or obstructive sleep apnea.[24] According to study results from a Wisconsin sleep cohort, the MSLT was affected by chronic sleep deprivation and shift work.[8] Thus, diagnostic value and test-retest validity of MSLT in patients complaining of hypersomnia have been challenged.[6,7] However, our results are somewhat different from the aforementioned results questioning test-retest validity of MSLT. Absence of changes in MSLT parameters in our study indicated that MSLT was effective in diagnosis of narcolepsy type 1 in the same patient group when repeated after nearly 10 years. Indeed, high diagnostic stability of MSLT in patients with narcolepsy type 1 has been reported, with sensitivity and specificity over 90% reported in one study.[25] High repeatability of the test has been demonstrated in patients with narcolepsy type 1 in another study by Folkerts et al.[26] However, such reliability of the test was significantly reduced in a narcolepsy type 2 and idiopathic hypersomnia group,[25] and adjunctive diagnostic tools will be needed to identify this subgroup of patients. Our results could support the advocacy of MSLT results as a trait marker in patients with narcolepsy type 1.[27]

Table 3—Comparisons of sleep parameters between baseline and follow-up MSLT (n = 48).

MSLT Parameters (mean ± SD)	Baseline	Follow-up	Sig.
Mean sleep latency (min)	1.52 ± 0.93	1.54 ± 1.12	.875
Frequency of SOREMP	3.56 ± 0.71	3.40 ± 0.71	.281

MSLT = Multiple Sleep Latency Test, SD = standard deviation, Sig. = significance, SOREMP = sleep onset rapid eye movement period.

There are several limitations in the study that should be taken into consideration. First, the study was based on a small number of patients, thus making it difficult to generalize our results. Second, because the participants were all from the same clinic, site selection bias may have confounded our results. Third, our study design only measured parameters two times, during the baseline visit and follow-up visit, thus limiting the demonstration of the detailed course of parameter changes. Fourth, because all patients were on different combinations of medications, and because the statistical data did not control for this confounding factor, it is difficult to generalize our results to represent the treatment effects of one specific medication or regimen. An additional consideration would be sodium oxybate, a frequently prescribed drug to control excessive daytime sleepiness and cataplexy. It is not approved for prescription in Korea, and this could have influenced high BMI in our participants during the follow-up. Fifth, measurements on the severity of subjective sleepiness with regard to response to treatment were not attained. Last, sex and age effects on MSLT could have confounded the results. Despite the aforementioned limitations, we believe that our results contribute to important questions in the field of narcolepsy where more data on managing patients with and diagnosis of narcolepsy type 1 are needed.

ABBREVIATIONS

BMI, body mass index
BMR, basal metabolic rate

MSLT, Multiple Sleep Latency Test
SOREMP, sleep onset REM period

REFERENCES

1. Cohen FL. Narcolepsy: a review of a common, life-long sleep disorder. *J Adv Nurs.* 1988;13(5):546–556.
2. Krahn LE, Gonzalez-Arriaza HL. Narcolepsy with cataplexy. *Am J Psychiatry.* 2004;161(12): 2181–2184.
3. Ohayon MM, Black J, Lai C, Eller M, Guinta D, Bhattacharyya A. Increased mortality in narcolepsy. *Sleep.* 2014;37(3):439–444.
4. Jennum P, Ibsen R, Knudsen S, Kjellberg J. Comorbidity and mortality of narcolepsy: a controlled retro-and prospective national study. *Sleep.* 2013;36(6):835–840.
5. Ohayon MM. Narcolepsy is complicated by high medical and psychiatric comorbidities: a comparison with the general population. *Sleep Med.* 2013;14(6):488–492.
6. Trotti LM, Staab BA, Rye DB. Test-retest reliability of the Multiple Sleep Latency Test in narcolepsy without cataplexy and idiopathic hypersomnia. *J Clin Sleep Med.* 2013;9(8):789–795.
7. Trotti LM. Another strike against sleepability. *J Clin Sleep Med.* 2016;12(4):467–468.
8. Goldbart A, Peppard P, Finn L, et al. Narcolepsy and predictors of positive MSLTs in the Wisconsin Sleep Cohort. *Sleep.* 2014;37(6):1043–1051.
9. Wu H, Zhuang J, Stone WS, et al. Symptoms and occurrences of narcolepsy: a retrospective study of 162 patients during a 10-year period in Eastern China. *Sleep Med.* 2014;15(6):607–613.
10. Donjacour CE, Aziz NA, Overeem S, Kalsbeek A, Pijl H, Lammers GJ. Glucose and fat metabolism in narcolepsy and the effect of sodium oxybate: a hyperinsulinemic-euglycemic clamp study. *Sleep.* 2014;37(4):795–801.
11. Poli F, Pizza F, Mignot E, et al. High prevalence of precocious puberty and obesity in childhood narcolepsy with cataplexy. *Sleep.* 2013;36(2):175–181.
12. Inocente CO, Lavault S, Lecendreux M, et al. Impact of obesity in children with narcolepsy. *CNS Neurosci Ther.* 2013;19(7):521–528.
13. Shin Y, Yoon I, Han E, et al. Prevalence of narcolepsy-cataplexy in Korean adolescents. *Acta Neurol Scand.* 2008;117(4):273–278.
14. American Academy of Sleep Medicine. *International Classification of Sleep Disorders, Diagnostic and Coding Manual.* 2nd ed. Westchester IL: American Academy of Sleep Medicine; 2005.
15. Cremaschi RC, Hirotsu C, Tufik S, Coelho FM. Narcolepsy type 1 and type 2 - a 10-year follow-up: body mass index and comorbidities. *Sleep Med.* 2017;32:285–286.
16. Wang Z, Wu H, Stone WS, et al. Body weight and basal metabolic rate in childhood narcolepsy: a longitudinal study. *Sleep Med.* 2016;25:139–144.
17. Kovalská P, Kemlink D, Topinková E, Nevšímalová S, Horvat EM, Šonka K. Higher body mass index in narcolepsy with cataplexy: lifelong experience. *Sleep Med.* 2017;32:277.
18. Kim MK, Lee WY, Kang JH, et al. 2014 clinical practice guidelines for overweight and obesity in Korea. *Endocrinol Metab (Seoul).* 2014;29(4):405–409.
19. Korean Agency for Technology and Standards. *7th Size Korea Technical Report.* Government Printing Office; 2015.
20. Nixon JP, Mavanji V, Butterick TA, Billington CJ, Kotz CM, Teske JA. Sleep disorders, obesity, and aging: the role of orexin. *Ageing Res Rev.* 2015;20:63–73.
21. Sakurai T. The role of orexin in motivated behaviours. *Nat Rev Neurosci.* 2014;15(11):719–731.
22. Donadio V, Liguori R, Vandi S, et al. Lower wake resting sympathetic and cardiovascular activities in narcolepsy with cataplexy. *Neurology.* 2014;83(12):1080–1086.
23. Korkmaz S, Aksu M, Tuna M, Baskol G, Bayram F, Hallett M. The impact of sleep deprivation on plasma leptin and ghrelin levels in narcoleptic patients. *J Sleep Disor: Treat Care.* 2017;6(1).
24. Kretzschmar U, Werth E, Sturzenegger C, Khatami R, Bassetti CL, Baumann CR. Which diagnostic findings in disorders with excessive daytime sleepiness are really helpful? A retrospective study. *J Sleep Res.* 2016;25(3):307–313.
25. Andlauer O, Moore H, Jouhier L, et al. Nocturnal rapid eye movement sleep latency for identifying patients with narcolepsy/hypocretin deficiency. *JAMA Neurol.* 2013;70(7):891–902.
26. Folkerts M, Rosenthal L, Roehrs T, et al. The reliability of the diagnostic features in patients with narcolepsy. *Biol Psychiatry.* 1996;40(3):208–214.
27. Mayer G, Lammers GJ. The MSLT: more objections than benefits as a diagnostic gold standard? *Sleep.* 2014;37(6):1027–1028.

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DISCLOSURE STATEMENT

The authors report no conflicts of interest.