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The MSLT: More Objections than Benefits as a Diagnostic Gold Standard?

Commentary on Goldbart et al. Narcolepsy and predictors of positive MSLTs in the Wisconsin Sleep Cohort. SLEEP 2014;37:1043-1051.

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In this issue of *SLEEP*, Goldbart and colleagues take a close look at the validity of the results concerning REM latency (RL) and mean sleep latency (MSL) from repeated nocturnal polysomnographies (NPSG) and multiple sleep latency tests (MSLTs) performed in subjects of the Wisconsin Sleep Cohort Study.[1] Since the year 2000, NPSGs and MSLTs in this large cohort study have been performed every four years. In 2006, Mignot et al. reported on the prevalence and correlates of SOREMPs in 289 males and 267 females. They found multiple SOREMPs in 13.1% of males and 5.6% of females. MSL ≤ 8 min and ≥ 2 SOREMPs were observed in 5.9% males and 1.1% females, all without cataplexy. SOREMPs were not related to age, body mass index, depression or apneic events during sleep, but they were associated with shift work, short sleep, and decreased mean lowest oxygen saturation in males. From these data, the authors concluded the existence of a high prevalence of narcolepsy without cataplexy, and a large number of false positives for the MSLT.[2]

In contrast to the study by Mignot et al.,[2] the report by Goldbart in this issue of *SLEEP* evaluated the stability over time of positive MSLT and SOREMP in NPSG as indicators for narcolepsy in a much larger population sample of 1,518 subjects. The recruitment for the repeat MSLT has a certain bias, as subjects having more than 1 SOREMP were more likely to be included. Cataplexy was scored if it occurred at least once per month when laughing, or telling or hearing a joke. The prevalence of multiple SOREMPs was 7%, while the prevalence of MSL < 8 min on the MSLT was 22%, and the prevalence of the combination of the two was 3.4%.[1] Consistent with the earlier study by Mignot,[2] the percentages found by Goldbart were higher in males than in females. Shift work had a major impact on the results, whereas sleep deprivation only had influence on sleep latencies, not on SOREMPs. Goldbart found that 0.9% of subjects were identified as having cataplexy. Three subjects were concluded to suffer from narcolepsy without cataplexy based on stable complaints and stable MSLT results, and one subject was thought to have narcolepsy with cataplexy.

Goldbart found that the stability of repeated MSLT results after 4 years, as assessed by κ statistics, was extremely low, even after ruling out confounders. This finding is very disappointing, as the MSLT is considered as one of the most important diagnostic tools to assess narcolepsy. What is the value of performing an MSLT in subjects without cataplexy when only 10% to 20% of those who have a positive initial MSLT show it four years later, as in this study? Is it just by chance these individuals had a short duration MSLT on their first assessment? Can we conclude from this population based study that > 2 SOREMPs and MSL < 8 min are not stable markers for narcolepsy without cataplexy? Folkerts et al.[3] and Aldrich et al.[4] found a positive repeat MSLT in 83% to 96% of patients with narcolepsy/cataplexy. Trotti et al.[5] confirmed positive MSLTs in 33% of narcolepsy patients without cataplexy. The present study cannot resolve the question of whether the different types of narcolepsy show different stability of MSLT results over time, as the number of identified narcolepsy patients was too few. The small number of positive MSLT findings at retest is not in favor of recommending a second confirmatory MSLT as suggested by the authors. However, the presented results[1] suggest that a positive MSLT is not a trait marker of narcolepsy without cataplexy, whereas the recent literature suggests this for patients with narcolepsy-cataplexy. It is worthy of note that these considerations exclude patients who did not meet the gold standards for narcolepsy-cataplexy. In a European study of 1,180 patients with narcolepsy-cataplexy, 3.9% of the sample had no SOREMPs during the MSLT, and an additional 5.7% had only 1 SOREMP during a 5 naps MSLT.[6]

Considering the validity of the MSLT results and the major impact of shift work—and to a lesser extent sleep deprivation—the assessment of sleep amount prior to the MSLT as recommended by the American Academy of Sleep Medicine[7] needs a critical appraisal. The routine assessment of prior sleep with sleep logs as done in the present study has some pitfalls. Comparing sleep logs and actigraphic recordings in 54 patients with excessive daytime sleepiness, Bradshaw et al. found a significant overestimation of sleep time in sleep logs by 1.43 ± 1.31 hours.[8] For the interpretation of the results of the present study, this suggests that there could be too many false positive results. This has been addressed by ruling out short sleepers, however, with a possible overestimation of sleep times.[1]

For the sleep medicine community, it is relevant to realize that it took us more than 35 years to obtain insight in what MSLT results may be expected when (repeatedly) applied in the general population, in subjects with and without complaints of sleepiness. The study by Goldbart et al.[1] forces us to interpret MSLT results in patients with much more caution. It took us this long from the first report on the MSLT,[9] despite early indications that additional validation in the general population was

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needed. It seems that we all were too happy to have an objective test to quantify/assess daytime sleepiness.

What can we learn from the Goldbart study? We should consider the current findings as a wakeup call to think out of the box again, and to develop and validate known and new tests to diagnose disorders characterized by excessive daytime sleepiness. Moreover, we might consider focusing more on tests that can separate sleep disorders from life style disorders, instead of trying to stick to unclear categories such as narcolepsy without cataplexy, which may only exist because of the existence of the MSLT and the at-time controversial results it yields. What would be the benefit if we would be able to discriminate narcolepsy without cataplexy from idiopathic hypersomnia by applying the MSLT twice with an interval of at least one month? For the patient and the general population it is much more important to know if excessive daytime sleepiness is caused by a lifestyle problem or a sleep disorder, and how to deal with it or prevent it. A first step in this direction is to apply actigraphy more stringently before performing an MSLT. In addition there is a need to develop and validate new tests to solve the identified problem.

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DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.

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