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Factors de confusió en el diagnòstic de narcolepsia

Gemma Sansa Fayos



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Original Article

Obstructive sleep apnea in narcolepsy

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ABSTRACT

Study objectives: Narcolepsy and obstructive sleep apnea syndrome (OSAS) are two conditions associated with excessive daytime sleepiness (EDS). They may coexist in the same patient but the frequency of this association and its clinical significance is unknown. The presence of obstructive sleep apnea (OSA) in a narcoleptic patient may interfere with the diagnosis of narcolepsy. The aim of the study was to determine the prevalence of OSA in narcolepsy.

Design and setting: University hospital sleep clinic series of narcoleptic patients diagnosed with nocturnal polysomnography and multiple sleep latency test. Patients were systematically interviewed evaluating narcoleptic and OSAS features and their response to continuous positive airway pressure (CPAP) treatment when applied.

Patients: One hundred and thirty-three patients with narcolepsy.

Results: Thirty-three patients (24.8%) had an apnea–hypopnea index greater than 10 with a mean index of 28.5 ± 15.7 . Ten of them were initially diagnosed only with OSAS and the diagnosis of narcolepsy was delayed 6.1 ± 7.8 years until being evaluated in our center for residual EDS after CPAP therapy. In the remaining 23 patients, narcolepsy and OSA were diagnosed simultaneously. Cataplexy occurred with similar frequency in both groups. EDS did not improve in 11 of the 14 patients who were treated with CPAP. The presence of OSA was associated with male gender, older age and higher body mass index.

Conclusions: OSA occurs frequently in narcolepsy and may delay the diagnosis of narcolepsy by several years and interfere with its proper management. In patients with OSA, cataplexy should be actively looked for to exclude the presence of narcolepsy. Treatment with CPAP does not usually improve EDS in narcoleptics with OSA.

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1. Introduction

Narcolepsy is a neurological disorder with a prevalence of 0.03–0.16% [1] characterized by excessive daytime sleepiness (EDS), cataplexy, sleep paralysis and hypnagogic hallucinations. In most cases multiple sleep latency test (MSLT) shows two or more sleep onset periods (SOREMPs). Cataplexy is the most characteristic symptom occurring in 65–75% of the patients and EDS is usually the most disabling feature. EDS in narcolepsy, however, may not always be distinguished from the sleepiness caused by other disorders such as obstructive sleep apnea syndrome (OSAS) [2].

OSAS is a much more prevalent disorder occurring in 2–4% of the adult population [3], whereas EDS is one of the major presenting complaints [2]. In OSAS, increased body mass index (BMI) is a frequent finding that leads to upper airway obstruction causing breath cessation during sleep. Narcolepsy is also associated with

increased BMI [3,4] which may predispose one to comorbid obstructive sleep apnea (OSA). Narcolepsy and OSAS may be confounded because (1) both disorders are associated with EDS and increased BMI, and (2) MSLT in patients with OSAS may occasionally show two or three SOREMPs [5,6].

Due to the high prevalence of OSA, a large number of patients presenting to sleep centers with EDS are evaluated with nocturnal sleep studies only to confirm the presence of sleep disordered breathing. Thus, it is possible that narcoleptics with comorbid OSA presenting to sleep centers with EDS may be diagnosed with OSAS alone and that narcolepsy is overlooked. In the current study we aimed to determine the prevalence of OSA in a large series of narcoleptics diagnosed in our sleep center. We also assessed how many narcoleptics were initially diagnosed only with OSAS before presenting to our sleep center and the effect of continuous positive airway pressure (CPAP) on EDS when applied.

2. Methods

We evaluated 133 consecutive narcoleptics, diagnosed according to ICSD-2 criteria [2] presenting to our center with EDS

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between 1991 and 2007. All patients underwent polysomnography and a 5-nap MSLT the following day. A definite history of cataplexy was present in 104 patients. We included patients without cataplexy and an AHI > 10 only when they had four or five SOREMPs in the MSLT [5,6] or low hypocretin-1 (<110 pg/mL) in the CSF.

At the time of this study all patients were contacted and systematically interviewed regarding the following demographic and clinical parameters: age, sex, BMI, Epworth sleepiness scale (ESS) score, presence or absence of cataplexy and response to CPAP treatment when prescribed. The effect of CPAP therapy was evaluated asking the patients if they had experienced any improvement in their EDS or in their nocturnal sleep quality.

Polysomnography was performed recording electroencephalography (C3, C4, O1, O2 referred to the contralateral ear), electro-oculogram, submental electromyography, right and left anterior tibialis surface electromyography, electrocardiogram, nasal and oral air flow, thoracic and abdominal movements and oxyhemoglobin saturation. Sleep stages were scored according to standard criteria [7]. Sleep efficiency was defined as the ratio of total sleep time to total recording time. Apnea was defined as the absence of airflow for at least 10 s. In obstructive apnea, respiratory effort was maintained, whereas in central apnea, breathing movements were absent. Mixed apnea was defined as a combination of central and obstructive apnea. Hypopnea was defined as a decrease in airflow of at least 30% for at least 10 s with either an arousal or an oxygen desaturation of 3%. The AHI was defined as the average number of apneas and hypopneas per hour of sleep, and sleep apnea was defined by an AHI ≥ 10. The MSLT consisted of 5 naps performed according to published standards [8]. In all patients treated with CPAP, CPAP titration was performed with conventional full nocturnal polysomnography.

For statistical analysis independent Student's *t*-test and Fisher test were used when appropriate.

3. Results

We evaluated 133 consecutive patients with a mean age of 38.6 ± 16.4 (range, 11–80) years. Eighty-eight (66%) were male and 45 (34%) female. The mean BMI was 23.9 ± 4.7 . Polysomnography showed an AHI ≥ 10 in 33 (24.8%) patients with a mean of

28.5 ± 15.7 (Fig. 1). In all of them apneas were obstructive except in two patients who had predominantly central apneas (AHI of 14 and 40, respectively). Patients with AHI ≥ 10 were significantly more often men, older and had a higher BMI than those with AHI < 10 (Table 1). Percentage of cataplexy, ESS score at the time of PSG, sleep latency in the MSLT and number of SOREM periods in the MSLT were not different between patients with AHI ≥ 10 and patients with AHI < 10 (Table 1).

3.1. Diagnosis of narcolepsy initially overlooked

Ten of the 33 (30.3%) narcoleptics with AHI ≥ 10 were initially diagnosed in other sleep centers as having only OSAS. The mean delay in the diagnosis of narcolepsy in these 10 patients was 6.1 ± 7.8 years. Cataplexy occurred in 8 of them and was present in all before they were first evaluated for EDS (a mean of 4.1 ± 5.7 years) and were diagnosed as having only OSAS. In these 8 patients narcolepsy was not diagnosed because patients did not spontaneously report cataplexy and because physicians did not ask for its presence. The other two narcoleptics previously diagnosed only with OSAS had no cataplexy but in our center the MSLT showed in both patients a mean sleep latency of less than 5 min and four SOREM periods. The remaining 23 patients with AHI ≥ 10 were simultaneously diagnosed with narcolepsy and OSA in our center. No differences in gender, age, BMI and frequency of cataplexy were found between patients diagnosed initially only with OSAS and those diagnosed simultaneously with OSA and narcolepsy.

3.2. Effect of CPAP treatment on EDS

Nine of the 10 patients diagnosed only with OSAS were treated with CPAP before they were diagnosed with narcolepsy in our center. None of these patients had been treated with sodium oxybate, modafinil, methylphenidate or any other central nervous system stimulant. With CPAP therapy four of these patients reported no improvement in EDS and in sleep quality, two no improvement in EDS but better nocturnal sleep quality, two a mild improvement in EDS, and one did not tolerate CPAP.

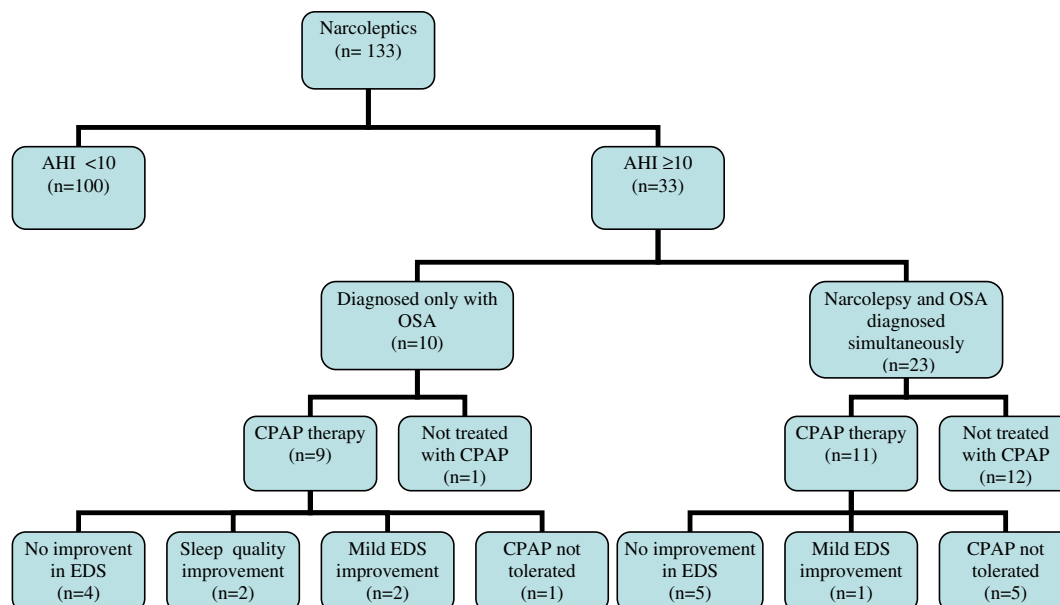


Fig. 1. Flowchart of the patients.

Table 1Demographic and electrophysiological data of narcoleptic patients with AHI \geq 10 and AHI < 10.

	AHI \geq 10 (n = 33)	AHI < 10 (n = 100)	P value
AHI (n) (range)	28.5 \pm 15.7 (11–67)	2.9 \pm 2.6 (0–9)	<0.0001
Male/female (n)	28/5	60/40	0.0063
Age (years)	49.3 \pm 15.4	35.4 \pm 15.5	<0.0001
BMI (kg/m ²)	25.3 \pm 4.0	23.4 \pm 4.8	0.0368
Cataplexy (%)	78.8	78	0.6378
ESS score at the time of diagnosis of narcolepsy	18.8 \pm 4.4	17.4 \pm 4.2	0.152
Sleep efficiency in PSG (%)	80.8 \pm 13.8	84.8 \pm 12.2	0.1941
Sleep latency in MSLT (min)	2.1 \pm 2.1	2.1 \pm 1.7	0.7755
REM sleep latency in MSLT (min)	4.8 \pm 2.6	4.8 \pm 2.8	0.7142
SOREM periods in MSLT (n)	3.1 \pm 1.4	3.3 \pm 1.4	0.2421

AHI, apnea–hypopnea index; BMI, body mass index; PSG, polysomnography; MSLT, multiple sleep latency test; SOREM, sleep onset REM; ESS, Epworth sleepiness scale. Independent Student's *t*-test and Fisher's test were used when appropriate.

Of the 23 patients that were simultaneously diagnosed with narcolepsy and OSA, eleven were initially treated only with CPAP because of a high AHI (mean AHI of 32.2 \pm 13.1). After CPAP therapy, five patients reported no improvement in EDS, one experienced some improvement in EDS and five did not tolerate CPAP.

Overall, 20 out of the 33 patients with an AHI \geq 10 were treated initially only with CPAP. Fifteen reported no change in nocturnal sleep quality or daytime sleepiness, three reported some improvement in EDS (baseline AHI of 56, 53 and 26), and two better nocturnal sleep quality but no change in EDS (baseline AHI of 67 and 13).

4. Discussion

This is the first study evaluating sleep apnea in a large series of patients with narcolepsy and the effect of CPAP therapy in narcoleptics with comorbid OSA.

Previous studies assessing the prevalence of OSA in narcolepsy are scarce and reported results ranging between 2% and 68%. Guilleminault et al. [9] noted two patients with narcolepsy and central sleep apnea. Laffont et al. [10] described the occurrence of sleep apnea in five patients. One had central apneas, one had obstructive apneas and the remaining three had both central and obstructive apneas. Kales et al. [11] studied the prevalence of sleep apnea in a series of 50 narcoleptics with cataplexy and only one had sleep apnea on the polysomnogram (AHI of 67). Chokroverty [12] reported the presence of apneic episodes in 11 of 16 narcoleptic patients, the majority of them with cataplexy. Apneic episodes were predominantly central, but obstructive and mixed events were also observed. A few additional isolated case reports of narcolepsy with OSA have been described [13–15]. Other studies have noted the occurrence of AHI > 5 in 9.8–19% of narcoleptics undergoing polysomnography [16–19].

We found that 24.8% of narcoleptics had an AHI \geq 10. Since we did not evaluate a control group we cannot assess if this prevalence is higher than in the general population. Like in the general population, OSA in narcoleptics was associated with higher BMI, male gender and older age.

In our study, 30% of narcoleptics with AHI \geq 10 were initially diagnosed as having only OSAS in other sleep centers. Eighty percent of them had cataplexy, and this symptom was already present when patients first complained of EDS in other sleep centers. Narcolepsy was not diagnosed then because patients did not spontaneously report that they had cataplexy and because physicians did not ask for its presence. Underrecognition of cataplexy and other narcoleptic symptoms delayed the diagnosis of narcolepsy several years. Young

age and a frank contrast between major sleepiness (e.g., ESS > 15) and mild–moderate OSA (AHI < 30) should help clinicians to suspect narcolepsy. In another study, the diagnosis of narcolepsy was delayed because (1) late-life expression of cataplexy after initial consultation, (2) mild disease, (3) narcolepsy lacking cataplexy with later-life onset of EDS, and, as in our series, (4) misdiagnosis [20]. Lack of diagnosis of narcolepsy delays proper management of the disease with adequate sleep hygiene and with the use of specific medications such as stimulants of the central nervous system, antiepileptics and sodium oxybate, which none of our patients was taking at the time of diagnosis. Moreover, in our study, CPAP was ineffective in most of our narcoleptics with OSA. Although the number of CPAP treated patients is too low to draw a definite conclusion and we did not objectively evaluate EDS after CPAP treatment, our findings might suggest that OSA does not play a major role in the pathophysiology and severity of EDS in narcolepsy.

In conclusion, based on our results we suggest that cataplexy should always be actively looked for (1) in patients referred to sleep centers with EDS and initially suspected to have OSAS, and (2) in patients with OSA and residual EDS despite the correct use of CPAP therapy.

Disclosure statement

This work is not an industry supported study. Dr. Sansa, Iranzo and Santamaria indicate no financial conflicts of interest.

References

- [1] Lavie P, Peled R. Narcolepsy is a rare disease in Israel. *Sleep* 1987;10:608–9.
- [2] American Academy of Sleep Medicine. The international classification of sleep disorders: diagnostic and coding manual. 2nd ed. Westchester, IL: American Academy of Sleep Medicine; 2005.
- [3] Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S. The occurrence of sleep-disordered breathing among middle-aged adults. *N Engl J Med* 1993;328:1230–5.
- [4] Schuld A, Hebebrand J, Geller F, Pollmächer T. Increased body-mass index in patients with narcolepsy. *Lancet* 2000;355:1274–5.
- [5] Chervin RD, Aldrich MS. Sleep onset REM periods during multiple sleep latency test in patients evaluated for sleep apnea. *Am J Respir Care Med* 2000;161:426–31.
- [6] Seneviratne U, Puvanendran K. Excessive daytime sleepiness in obstructive sleep apnea: prevalence, severity, and predictors. *Sleep Med* 2004;5:339–43.
- [7] Rechtschaffen A, Kales A, editors. A manual of standardized terminology, techniques and scoring system for sleep stages of humans subjects. Los Angeles: BIS/BRI, UCLA; 1968.
- [8] Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. *Sleep* 1986;9:519–24.
- [9] Guilleminault C, Eldridge F, Dement WC. Insomnia, narcolepsy and sleep apnea. *Bull Eur Physiopathol Respir* 1972;8:1127–38.
- [10] Laffont F, Autret A, Minz M, Beillevaire T, Cathala HP, Castaigne P. Sleep respiratory arrhythmias in control subjects, narcoleptics and non-cataplectic hypersomniacs. *Electroencephalogr Clin Neurophysiol* 1978;44:697–705.
- [11] Kales A, Cadieux RJ, Soldatos CR, Bixler EO, Schweitzer PK, Prey WT, et al. Clinical and electrophysiologic characteristics. *Arch Neurol* 1982;39:164–8.
- [12] Chokroverty S. Sleep apnea in narcolepsy. *Sleep* 1986;9:250–3.
- [13] Carpio Muñoz V, Carmona Bernal C, García Díaz E, Botebol Benhamou G, Cano Gómez S, Capote Gil F. Association of obstructive apnea syndrome during sleep and narcolepsy. *Arch Bronconeumol* 1998;34:310–1.
- [14] Zamarrón C, García JM, Robles A. Obstructive sleep apnea syndrome and narcolepsy. A report of 2 cases. *Arch Bronconeumol* 1998;34:466.
- [15] Reimao R, Lemmi H. Concomitant narcolepsy and sleep apnea: report of a case. *Arq Neuropsiquiatr* 1986;44:73–7.
- [16] Baker TL, Guilleminault C, Nino-Murcia G, Dement WC. Comparative polysomnographic study of narcolepsy and idiopathic central nervous system hypersomnia. *Sleep* 1986;9:232–42.
- [17] Harsh J, Peszka J, Hartwig G, Mitler M. Night-time and daytime sleepiness in narcolepsy. *J Sleep Res* 2000;9:309–16.
- [18] Mosko SS, Shampain DS, Sassin JF. Nocturnal REM latency and sleep disturbance in narcolepsy. *Sleep* 1984;7:115–25.
- [19] Plazzi G, Serra L, Ferri R. Nocturnal aspects of narcolepsy with cataplexy. *Sleep Med Rev* 2008;12:109–28.
- [20] Rye DB, Dihenia B, Weissman JD, Epstein CM, Bliwise D. Presentation of narcolepsy after 40. *Neurology* 1998;50:459–65.



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BPSY-D-15-00341

EXPLORING THE PRESENCE OF NARCOLEPSY IN PATIENTS WITH SCHIZOPHRENIA

Gemma Sansa; Alba Gavaldà; Carles Gaig; José Monreal; Guadalupe Ercilla; Roser Casamitjana; Gisela Ribera; Álex Iranzo; Joan Santamaria
BMC Psychiatry

Dear Dr Sansa,

Your manuscript "EXPLORING THE PRESENCE OF NARCOLEPSY IN PATIENTS WITH SCHIZOPHRENIA" (BPSY-D-15-00341) has been assessed by our reviewers. Based on these reports, and my own assessment as Editor, I am pleased to inform you that it is potentially acceptable for publication in BMC Psychiatry, once you have carried out some essential revisions suggested by our reviewers.

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A decision will be made once we have received your revised manuscript, which we expect by 06 Jan 2016.

We look forward to receiving your revised manuscript and please do not hesitate to contact us if you have any questions.

Best wishes,

Ruth Benca
BMC Psychiatry

Reviewer reports:

Reviewer #1: This is a well written study on the frequency of narcolepsy-cataplexy in 366 schizophrenia patients. The sample size is sufficient to address the question asked and the fact CSF hypocretin was assessed in some patients is a strength.

In my opinion, there is a significant weaknesses that needs to be addressed and discussed more. Considering the nature of schizophrenia, not all patients may have been willing to respond or able to comprehend the questions on cataplexy or the Epworth. Similarly, patients may not have been able to drive or do some of the things requested by the Epworth, thus the Epworth may have been underestimated. This is especially important in the absence of PSG-MSLT.

The fact questions on symptoms were asked by a psychologist trained in sleep medicine partially protects against this, but is not sufficient; sleep medicine psychologists are not necessarily very well trained in narcolepsy identification or in handling patients with schizophrenia symptoms, How many psychologists conducted these interviews? Were these made aware/educated re the main symptoms of narcolepsy and schizophrenia? How was this handled? For sure a portion of cases must have been difficult to assess and should thus have "missing data". This information is missing and the portion of patients difficult to assess should be reported in the flowchart of Fig.2.

In addition, even with zero cases out of 366, a 95% confidence interval of prevalence could be given. This is also important as it is likely quite large, so that even if the prevalence is 30 times higher than in the general population (for ex. 1%) it could still have been missed.

Finally, it would be good to describe a bit better the population of schizophrenia/SAD patients and the referring psychiatric unit in term of in versus outpatients etc.. The evolution/disposition of dual narcolepsy-schizophrenia patients may be different than regular psychiatric patients, thus it is important to assess how representative of all schizophrenic the population screened is. In this regard, the problem is a bit similar to that of the prevalence of anti NMDA encephalitis in such samples, which is about 1% but vary quite a bit across samples (see Psychol Med. 2014 Sep;44(12):2475-8), although in this case the assay is also an issue.

Details:

DQB1*0602 is now DQB1*06:02; also it is not an "haplotype" but an allele of that locus (line 26).

ref 13 could be replaced by the more recent: Narcolepsy and predictors of positive MSLTs in the Wisconsin Sleep Cohort. Goldbart A, Peppard P, Finn L, Ruoff CM, Barnett J, Young T, Mignot E. Sleep. 2014 Jun 1;37(6):1043-51. doi: 10.5665/sleep.3758.

discussion: polisomnography is polysomnography; schizofrenia should be Schizophrenia

Reviewer #2: This is a well-designed study with important negative findings in regards to the presence of NC in Schizophrenia. However, there is an additional limitation to the study that the authors need to add in the Discussion: there was no apparent assessment of how well-compensated or decompensated the schizophrenic patients were concerning the extent and severity of delusions, hallucinations and behavioral control, which could have had an impact in their interpretations of the study questions and their responses to the sleep questionnaire and ESS. The results of the study may therefore have included some patients with false negative findings for EDS and NC. Just because a schizophrenic patient is an out-patient does not necessarily mean that he is well-compensated.

Page 4, line 33: substitute "possibility" for "option".

Page 5, line 7: insert "outpatient clinic". Also, substitute the word "asked" for "proposed".

Page 5, line 39: insert "schizophrenic" before the "hallucinations" near the end of that line.

Page 6, line 16: insert "for clinical management and ethical reasons," after "in our patients". Next line should begin with "these objective tests for the diagnosis of narcolepsy." Line 22: insert "haplotype" after "HLA."

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BMC Psychiatry

EXPLORING THE PRESENCE OF NARCOLEPSY IN PATIENTS WITH SCHIZOPHRENIA

--Manuscript Draft--

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Instituto de Salud Carlos III (PI11/00900)	Dr Carles Gaig									
Abstract:	<p>Background: There are several case reports of patients with narcolepsy and schizophrenia, but a systematic examination of the association of both disorders has not been done. The aim of this work is to assess the frequency of narcolepsy with cataplexy in a large consecutive series of adult patients with schizophrenia and schizoaffective disorder.</p> <p>Methods: We screened 366 consecutive patients with schizophrenia or schizoaffective disorder with a sleep questionnaire and the Epworth Sleepiness scale (ESS) exploring narcoleptiform symptoms. Those who screened positive were assessed by a sleep specialist, and offered an HLA determination. CSF hypocretin-1 determination was proposed to those who were HLA-DQB1*0602 positive.</p> <p>Results: On the screening questionnaire, 17 patients had an ESS score ≥ 11 without cataplexy, 15 had cataplexy-like symptoms with an ESS score < 11, and four had an ESS score ≥ 11 plus cataplexy-like symptoms. Of those, 24 patients were evaluated by a sleep specialist. Five of these 24 were HLA-DQB1*0602 positive, and three of these five subjects underwent lumbar puncture showing normal hypocretin-1 levels.</p> <p>Conclusions: Our results suggest that narcolepsy with cataplexy is not an unrecognized disease in adult patients with schizophrenia or schizoaffective disorder.</p>									
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1 **EXPLORING THE PRESENCE OF NARCOLEPSY IN PATIENTS WITH**
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ABSTRACT

Background: There are several case reports of patients with narcolepsy and schizophrenia, but a systematic examination of the association of both disorders has not been done. The aim of this work is to assess the frequency of narcolepsy with cataplexy in a large consecutive series of adult patients with schizophrenia and schizoaffective disorder.

Methods: We screened 366 consecutive patients with schizophrenia or schizoaffective disorder with a sleep questionnaire and the Epworth Sleepiness scale (ESS) exploring narcoleptiform symptoms. Those who screened positive were assessed by a sleep specialist, and offered an HLA determination. CSF hypocretin-1 determination was proposed to those who were HLA-DQB1*0602 positive.

Results: On the screening questionnaire, 17 patients had an ESS score ≥ 11 without cataplexy, 15 had cataplexy-like symptoms with an ESS score < 11 , and four had an ESS score ≥ 11 plus cataplexy-like symptoms. Of those, 24 patients were evaluated by a sleep specialist. Five of these 24 were HLA-DQB1*0602 positive, and three of these five subjects underwent lumbar puncture showing normal hypocretin-1 levels.

Conclusions: Our results suggest that narcolepsy with cataplexy is not an unrecognized disease in adult patients with schizophrenia or schizoaffective disorder.

Keywords: Hallucinations; Narcolepsy; Hypocretin; Psychotic Disorders; Schizophrenia.

BACKGROUND

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6 Narcolepsy with cataplexy (narcolepsy type 1) is a chronic neurological disease with an
7 estimated lifetime prevalence of 2.5-5 per 10.000 people [1,2]. Clinically, it is
8 characterized by excessive daytime sleepiness (EDS), cataplexy,
9 hypnagogic/hypnopompic hallucinations and sleep paralysis, as well as other sleep
10 disturbances, such as sleep fragmentation [3]. Symptoms usually begin in adolescence,
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^{1,4} and they are the result of hypocretin deficiency [4].

Hypocretins are neuropeptides that have a central role in the control of alertness [5, 6]. Undetectable or low hypocretin-1 levels in cerebrospinal fluid (CSF) are found in 95% of narcoleptic patients with cataplexy [4, 7]. The mechanism causing this hypocretin deficit is still unknown, but is currently thought to be immune-mediated since up to 85-95% of patients with narcolepsy with cataplexy have the HLA haplotype DQB1*0602 [3, 8].

Hypocretin deficit is closely related to HLA DQ B1*0602 and cases of hypocretin-deficient narcolepsy without this HLA haplotype are exceptional. HLA typing is a useful screen before lumbar puncture since 98% of patients with hypocretin-1 deficiency are DQB1*0602 positive.⁷ There are neurological disorders that can cause secondary narcolepsy [9, 10]. Clear-cut or definite cataplexy is considered a pathognomonic symptom for diagnosing narcolepsy [11] and is defined as more than one episode of generally brief and usually bilaterally symmetrical sudden loss of muscle tone with retained consciousness precipitated by strong emotions typically associated with laughter or elation. Some subjects may report features reminiscent of cataplexy that are not clear-cut, either because they are mild, atypical or only subjective experiences, a situation termed “cataplexy-like” particularly when using questionnaires in population-based studies [12, 13]. Narcolepsy type 1 [9] is diagnosed when hypersomnia is accompanied by 1) cataplexy and abnormal multiple sleep latency test (MSLT) or 2) low values of hypocretin-1 concentration in CSF.

Schizophrenia is one of the most devastating mental illnesses and has an estimated lifetime prevalence of 7, 2 per 1.000 people [14]. The core symptoms of schizophrenia include delusions, hallucinations and thought disorder [15]. Schizophrenic symptoms

1 usually also emerge during adolescence [15, 16]. Dopamine neurotransmission
2 abnormalities in the mesocorticolimbic system with an increase in dopamine synthesis,
3 dopamine release and resting-state synaptic dopamine concentrations play a central role
4 in the generation of schizophrenic symptoms [17, 18]. The etiology of schizophrenia is
5 unknown, although and interplay between genetic and environmental factors has been
6 suggested [15].
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11 There are several previous case reports of narcoleptic patients with psychotic symptoms
12 [19, 20] and of schizophrenic patients with narcoleptic features [21-23]. Two recent
13 studies have evaluated the presence of schizophrenia in a large number of children and
14 adolescents with narcolepsy [24, 25], finding a small group of individuals that
15 developed schizophrenia after being diagnosed with narcolepsy.
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22 Several explanations could account for a possible association between narcolepsy and
23 schizophrenia. Psychosis may develop in narcoleptic patients as a consequence of
24 stimulant therapy, although this side effect seems infrequent even in patients treated
25 with high doses of stimulants over a prolonged period time [23, 26]. Another possibility
26 is that some narcoleptic symptoms, especially hypnagogic and hypnopompic
27 hallucinations, could be misdiagnosed as an active psychotic state of schizophrenia [22,
28 23, 27]. A third option is that narcolepsy and schizophrenia could occur in the same
29 patient because both diseases might share similar physiopathological factors. Finally,
30 the coincidental occurrence of schizophrenia and narcolepsy in the same patient could
31 also occur by chance. The frequency of coexistent schizophrenia and narcolepsy could
32 be expected to be 18-36 cases in a population of ten million based on the independent
33 prevalence of these two diseases. It is possible, however, that patients with
34 schizophrenia who develop narcolepsy could be unrecognized because sleepiness could
35 be attributed to the antipsychotic treatment and cataplexy could be alleviated or masked
36 by the same antidopaminergic treatment [28].
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50 The aim of this work was to assess the frequency of undiagnosed narcolepsy in a large
51 cohort of patients with schizophrenia. Finding some patients with narcolepsy in our
52 patients could support a possible association between narcolepsy and schizophrenia
53 would increase our understanding in both disorders.
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3 **METHODS**
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5 All consecutive patients with schizophrenia or schizoaffective disorder [29] followed at
6 the adult Psychiatry Department of the Hospital Parc Taulí were proposed to participate
7 in the study during their routine visits from February to June of 2013. Patients older
8 than 18 years and able to answer the questions were invited to participate. Patients
9 under 18 years were not included as they are controlled in another Psychiatric
10 Department at our institution. To assess whether narcolepsy was present in
11 schizophrenia, we used a stepwise approach with three phases of evaluation.
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19 In a first phase, consecutive patients were screened with a semi-structured questionnaire
20 where the four main symptoms of narcolepsy were included, namely EDS, cataplexy,
21 hypnagogic / hypnopompic hallucinations and sleep paralysis. This questionnaire was
22 administered by a psychologist (AG) specially trained in sleep disorders. The presence
23 of cataplexy was explored using the following question: “have you ever felt sudden
24 weakness of your muscles when you experience a strong emotion?”. Sleep paralysis
25 was assessed asking: “have you ever felt unable to move for a few moments as if you
26 were paralyzed, just after waking up or when falling asleep despite being awake?”
27 Hypnagogic/hypnopompic hallucinations were explored asking “have you ever noticed
28 or seen things or people that do not actually exist, just after waking up or when falling
29 asleep?”; patients that responded positively were asked to explain what exactly they felt
30 in those moments and try to differentiate these hallucinations from hallucinations that
31 they could appear during wakefulness. Finally the presence of EDS was assessed with
32 the Epworth sleepiness scale (ESS) and an score ≥ 11 was considered indicative of this
33 symptom [30]. Data on age, gender and age at onset of schizophrenia were also
34 collected.
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49 In a second phase of the study, patients with an ESS score ≥ 11 and/or cataplectic-like
50 features were reevaluated by a neurologist from the Multidisciplinary Sleep Unit of the
51 Hospital Parc Taulí (GS) who conducted a systematized clinical interview focusing on
52 the presence and features of EDS, cataplexy, hypnagogic / hypnopompic hallucinations
53 and sleep paralysis. In addition, current medications were evaluated as well as the
54 existence of other sleep disturbances (sleep fragmentation, symptoms suggestive of
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1 obstructive sleep apnea (OSA), insufficient sleep, and circadian rhythm disorder). In
2 those patients in whom EDS and/or cataplexy experiences were considered to be likely
3 present, HLA typing was tested.
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6 As medications such as antidepressants or other psychotropic drugs may significantly
7 affect REM sleep, it is recommended that polysomnography and multiple latency sleep
8 test should be used to diagnose narcolepsy only in patients free of drugs that influence
9 sleep. Drugs must be stopped for at least 14 days (or at least five times the half-life of
10 the drug and longer-active metabolite), confirmed by a urine drug screen [9].
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13 Since psychotropic medications could not be stopped in our patients we could not use
14 these tests for the diagnosis of narcolepsy. However, given that narcolepsy-cataplexy
15 type 1 occurs almost exclusively in patients with HLA DQB1*0602, we tested the
16 presence of this HLA in patients with symptoms suggestive of narcolepsy.
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19 In a third phase, hypocretin-1 level determination in CSF was proposed to those patients
20 who were HLA DQB1*0602 positive. If a patient (and caregiver when necessary)
21 accepted, 5 ml of CSF were obtained and immediately stored at -80°C. The lumbar
22 puncture was performed in the morning, before 11 am. Hypocretin-1 levels in CSF were
23 determined using commercially available direct radio-immunoassay kit (Phoenix
24 Pharmaceuticals, USA) as previously described [4, 31, 32] at the Hospital Clinic of
25 Barcelona. In order to minimize inter-assay variation, reference samples with internal
26 controls with known hypocretin-1 values were included in each assay and the values
27 were adjusted accordingly as recommended [33].
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31 The study was approved by ethics committees of both hospitals (Hospital Parc Taulí and
32 Hospital Clínic), and a written informed consent of patients was obtained.
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35 **RESULTS**

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37 We included 366 consecutive patients with the diagnosis of schizophrenia or
38 schizoaffective disorder (Table 1). There were 226 men and 140 women, with a mean
39 age of 44.3 ± 12 (range, 18-81) years and a mean age at diagnosis of the psychiatric
40 disorder of 25.3 ± 8.1 (range, 7-56) years.
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1 The mean ESS score was 4.1 ± 3.4 (range 0-18). Twenty-two (6%) patients had an ESS
2 ≥ 11 (Figure 1).

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4 Nineteen (5.1%) patients reported cataplexy-like experiences. Thirty-three (9%)
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6 responded that they presented sleep paralysis and 78 (21.3%) hypnagogic/hypnopompic
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8 hallucinations.

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10 Thirty-six (9.8%) patients had an ESS score ≥ 11 and/or responded affirmatively to the
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12 cataplexy question (Figure 2). Seventeen had an ESS score ≥ 11 without cataplexy, 15
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14 presented cataplexy-like symptoms with an ESS score < 10 , and 4 patients had an ESS
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16 score ≥ 11 and/or responded affirmatively to the cataplexy question. All these 36
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18 patients were offered to participate in the second phase, and 27 accepted. Three patients
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20 were excluded after detailed questioning by the sleep specialist (GS) who considered
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22 that neither EDS nor cataplexy-like experiences did occur. Twenty-four patients were
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24 finally included in this second phase, 11 women and 13 men, with a mean age of $39.7 \pm$
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26 10 (range, 21-57) years, and a mean age at onset of the psychiatric disease of 22.8 ± 7.5
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28 (range, 12-44) years. Clinical characteristics of this group of patients are detailed in
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30 Table 2. In 14 patients EDS was temporally related to the beginning of the antipsychotic
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32 treatment. Six out of these 24 patients reported features reminiscent of cataplexy, but
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34 no case of clear-cut cataplexy was found. Five patients presented hallucinations mainly
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36 during sleep-wake transition (two auditory –knock on the wall, a buzz-, one visual –
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38 could not specify which- and two tactile –both being touched-). Sleep paralysis was
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40 present in five out of the 24 patients.

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42 Twelve (50%) patients were snorers and in six of them their bed partners reported
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44 apneas during sleep. Only one patient had been previously diagnosed of obstructive
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46 sleep apnea syndrome with a sleep study, which showed an apnea/hypopnea index of
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48 78, but she did not tolerate CPAP treatment. Nine patients were treated with one
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50 neuroleptic drug, 13 patients with two, and three patients with three. Five patients were
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52 treated with one benzodiazepine, and four with two. Nine patients were treated with one
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54 antidepressant drug, one patient with two, and one patient with three. Eight patients
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56 were treated with one antiepileptic drug, one patient with two and one patient with
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58 three.

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60 Five out of the 24 patients had HLA DQB1*0602, none of them homozygote nor
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62 positive for DQB1*03. Clinical characteristics of these five patients are shown in Table
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64 3. In these 5 patients a lumbar puncture to measure CSF hypocretin-1 was proposed.
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1 Patient 1 and 2 refused. Hypocretin-1 levels were finally determined in three patients
2 showing normal values (> 200pg/ml) in all of them.
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7 **DISCUSSION**

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10 To our knowledge, this is the first study evaluating systematically and prospectively the
11 prevalence of narcolepsy type 1 in a large group of patients with schizophrenia or
12 schizoaffective disorder. Since antidepressants or other psychotropic drugs may
13 significantly affect REM sleep, we did not use polysomnography and multiple latency
14 sleep to diagnose narcolepsy in our patients, given that these drugs could not be stopped
15 for a long enough period of time. We used instead a stepwise approach, with an initial
16 screening of characteristic symptoms of narcolepsy in 366 patients and offering HLA
17 determination in those who referred hypersomnia and/or possible cataplexy. Last step
18 was determining hypocretin in CSF in those who were HLA DQB*0602 positive and
19 had EDS and /or cataplexy-like experiences. We did not find any patient with clear
20 narcolepsy type 1 in our cohort. Although we only measured CSF hypocretin in three
21 patients, they were the majority of subjects reporting hypersomnia and cataplexy-like
22 symptoms who had a positive HLA DQB1*0602. Although there are cases of
23 DQB1*0602 negative patients with narcolepsy type 1, this is highly infrequent since it
24 is estimated that less than one in 500 HLA-negative patients will have low CSF
25 hypocretin-1 levels [34].
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41 It is considered that sleep disturbances, particularly poor sleep quality, are common in
42 schizophrenia [35]. Although hypersomnia is a common side effect of neuroleptics, few
43 studies have focused on this aspect. While some authors [36] found a mean sleep
44 latency >36% longer (sleep propensity was lower) in 30 untreated patients with
45 schizophrenia than in healthy subjects, other authors [37] reported a prevalence of
46 hypersomnia of 24-31% in 1493 treated schizophrenic patients. In our sample the
47 frequency of hypersomnia was remarkably lower and only 5.7% of the patients had an
48 ESS \geq 11, usually temporary related to the beginning of the treatment for the psychiatric
49 disorder or the coexistence of a possible sleep breathing disorder, as in our cohort half
50 of them were snorers, and the mean BMI was 32.8 (moderately obese). The lower
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1 prevalence of hypersomnia in our study could also be due to the long duration of
2 therapy and disease compared to the previous studies [36, 37].
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4 Our findings do not suggest that in a large, single-center sample of adult schizophrenic
5 patients narcolepsy is underdiagnosed. However, it is possible that the association of
6 schizophrenia with narcolepsy could be age dependent, with higher risk of developing
7 schizophrenia in only those patients who had previously initiated narcolepsy in
8 childhood or early adolescence. Huang [25] reported that subjects with narcolepsy
9 linked to schizophrenia were younger than those narcoleptics without schizophrenia
10 (mean age of onset of narcolepsy, 11.25 ± 3.92 years vs 12.59 ± 3.41 years). Canellas²⁴
11 reported that the age of onset of EDS was 12.6 ± 2.3 year, age at narcolepsy diagnosis
12 was 17.9 ± 6.2 years and age at onset of psychotic symptoms was 16.9 ± 3.4 years.
13 Since in our sample, mean age at diagnosis of schizophrenia and schizoaffective disorder
14 was higher, with a mean age of 25 years, we cannot completely exclude that a
15 relationship between narcolepsy and schizophrenia exists only in younger patients.
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27 Our study has limitations such as the lack of a detailed expert sleep history in all the 336
28 patients initially evaluated, the lack of sleep recordings, and the lack of HLA and
29 hypocretin-1 determinations in the whole cohort. However, in the majority of patients
30 reporting EDS and narcoleptiform symptoms in the screening evaluation the sleep
31 expert confirmed these symptoms. On the other hand, sleep recordings are less useful in
32 patients treated with psychotropic drugs and the determination of CSF hypocretin-1 in
33 such a large sample of patients with schizophrenia is almost unfeasible.
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45 **CONCLUSIONS**

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48 Based in our findings, narcolepsy is not an underrecognized disease in adult patients
49 with schizophrenia or schizoaffective disorder. Complaints of hypersomnia are rare in
50 these patients and whereas hypnagogic/hypnopompic hallucinations are the most
51 frequent narcoleptiform symptom.
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COMPETING INTERESTS

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3 Drs Sansa, Gavaldà, Gaig, Monreal, Ercilla, Casamitjana, Ribera, Iranzo and
4 Santamaria disclose that they don't have any involvement with organization(s) with
5 financial interest in the subject matter of the paper, or any actual or potential conflict of
6 interest.
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CONTRIBUTION OF THE AUTHORS

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15
16 GS contributed on the design of the work, the acquisition, analysis and dinterpretation
17 of data for the work.
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21 GE and RC contributed on the analysis of data.
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24 AG contributed on acquisition of data.
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27 CG and JS contributed on the design of the work and interpretation of data.
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29

30 AI, GR and JM contributed revising the paper critically for important intellectual
31 content.
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REFERENCES

1. Silber MH, Krahn LE, Olson EJ, Pankratz VS. The epidemiology of narcolepsy in Olmsted County, Minnesota: a population-based study. *Sleep*. 2002; 25:197-202.
2. Longstreth WT, Jr., Koepsell TD, Ton TG, Hendrickson AF, van Belle G. The epidemiology of narcolepsy. *Sleep*. 2007; 30:13-26.
3. Dauvilliers Y, Arnulf I, Mignot E: Narcolepsy with cataplexy. *Lancet*. 2007; 369:499-511.
4. Mignot E, Lammers GJ, Ripley B, Okun M, Nevsimalova S, Overeem S, Vankova J, Black J, Harsh J, Bassetti C, Schrader H, Nishino. The role of cerebrospinal fluid hypocretin measurement in the diagnosis of narcolepsy and other hypersomnias. *Arch Neurol*. 2002; 59:1553-62.
5. de Lecea L, Kilduff TS, Peyron C, Gao X, Foye PE, Danielson PE, Fukuhara C, Battenberg EL, Gautvik VT, Bartlett FS, Frankel WN, van den Pol AN, Bloom FE, Gautvik KM, Sutcliffe JG. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. *Proc Natl Acad Sci USA*. 1998; 95:322-7.
6. Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, Williams SC, Richardson JA, Kozlowski GP, Wilson S, Arch JR, Buckingham RE, Haynes AC, Carr SA, Annan RS, McNulty DE, Liu WS, Terrett JA, Elshourbagy NA, Bergsma DJ, Yanagisawa M. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. *Cell*. 1998; 92:573-85.
7. Bourgin P, Zeitzer JM, Mignot E. CSF hypocretin-1 assessment in sleep and neurological disorders. *Lancet Neurol*. 2008; 7:649-62.
8. Mignot E, Lin X, Hesla PE, Dement WC, Guilleminault C, Grumet FC. A novel HLA DR17,DQ1 (DQA1-0102/DQB1-0602 positive) haplotype predisposing to narcolepsy in Caucasians. *Sleep*. 1993; 16:764-5.
9. American Academy of Sleep Medicine (ed). International classification of sleep disorders. 3rd ed. American Academy of Sleep Medicine, Darien, IL, 2014.
10. Tsutsui K, Kanbayashi T, Tanaka K, Boku S, Ito W, Tokunaga J, Mori A, Hishikawa Y, Shimizu T, Nishino S. Anti-NMDA-receptor antibody detected in

encephalitis, schizophrenia, and narcolepsy with psychotic features. *BMC Psychiatry*. 2012; 12:37.

11. Bassetti C, Aldrich MS. Narcolepsy. *Neurol Clin*. 1996; 14:545-71.
12. Anic-Labat S, Guilleminault C, Kraemer HC, Meehan J, Arrigoni J, Mignot E. Validation of a cataplexy questionnaire in 983 sleep-disorders patients. *Sleep*. 1999; 22:77-87.
13. Mignot E, Lin L, Finn L, Lopes C, Pluff K, Sundstrom ML, Young T. Correlates of sleep-onset REM periods during the Multiple Sleep Latency Test in community adults. *Brain*. 2006, 129:1609-23.
14. McGrath J, Saha S, Chant D, Welham J. Schizophrenia: a concise overview of incidence, prevalence, and mortality. *Epidemiol Rev*. 2008, 30:67-76.
15. van Os J, Kapur S. Schizophrenia. *Lancet*. 2009; 374:635-45.
16. Jablensky A, Sartorius N, Ernberg G, Anker M, Korten A, Cooper JE, Day R, Bertelsen A. Schizophrenia: manifestations, incidence and course in different cultures. A World Health Organization ten-country study. *Psychol Med Monogr Suppl*. 1992; 20:1-97.
17. Laruelle M. Imaging dopamine transmission in schizophrenia. A review and meta-analysis. *Q J Nucl Med*. 1998; 42:211-21.
18. Guillin O, Abi-Dargham A, Laruelle M. Neurobiology of dopamine in schizophrenia. *Int Rev Neurobiol*. 2007; 78:1-39.
19. Undurraga J, Garrido J, Santamaria J, Parellada E. Treatment of narcolepsy complicated by psychotic symptoms. *Psychosomatics*. 2009; 50:427-8.
20. Walterfang M, Upjohn E, Velakoulis D. Is schizophrenia associated with narcolepsy? *Cogn Behav Neurol*. 2005; 18:113-8.
21. Bhat SK, Galang R. Narcolepsy presenting as schizophrenia. *Am J Psychiatry*. 2002; 159:1245.
22. Douglass AB, Shipley JE, Haines RF, Scholten RC, Dudley E, Tapp A. Schizophrenia, narcolepsy, and HLA-DR15, DQ6. *Biol Psychiatry*. 1993; 34:773-80.
23. Kishi Y, Konishi S, Koizumi S, Kudo Y, Kurosawa H, Kathol RG. Schizophrenia and narcolepsy: a review with a case report. *Psychiatry Clin Neurosci*. 2004; 58:117-24.
24. Canellas F, Lin L, Julià MR, Clemente A, Vives-Bauza C, Ollila HM, Hong SC, Arboleya SM, Einen MA, Faraco J, Fernandez-Vina M, Mignot E. Dual

cases of type 1 narcolepsy with schizophrenia and other psychotic disorders. *J Clin Sleep Med*. 2014; 10:1011-8.

25. Huang YS, Guilleminault C, Chen CH, Lai PC, Hwang FM. Narcolepsy-cataplexy and schizophrenia in adolescents. *Sleep Med*. 2014; 15:15-22.
26. Pawluk LK, Hurwitz TD, Schluter JL, Ullevig C, Mahowald MW. Psychiatric morbidity in narcoleptics on chronic high dose methylphenidate therapy. *J Nerv Ment Dis*. 1995; 183:45-8.
27. Ullman KC. Narcolepsy and schizophrenia. *Am J Psychiatry*. 1977; 134:822.
28. Okura M, Riehl J, Mignot E, Nishino S. Sulpiride, a D2/D3 blocker, reduces cataplexy but not REM sleep in canine narcolepsy. *Neuropsychopharmacology*. 2000; 23:528-38.
29. American Psychiatric Association (ed). *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed., Rev. ed. American Psychiatric Association, Washington, DC, 2000.
30. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991; 14:540-5.
31. Nishino S, Ripley B, Overeem S, Nevsimalova S, Lammers GJ, Vankova J, Okun M, Rogers W, Brooks S, Mignot E. Low cerebrospinal fluid hypocretin (Orexin) and altered energy homeostasis in human narcolepsy. *Ann Neurol*. 2001; 50:381-8.
32. Ripley B, Overeem S, Fujiki N, Nevsimalova S, Uchino M, Yesavage J, Di Monte D, Dohi K, Melberg A, Lammers GJ, Nishida Y, Roelandse FW, Hungs M, Mignot E, Nishino S. CSF hypocretin/orexin levels in narcolepsy and other neurological conditions. *Neurology*. 2001; 57:2253-8.
33. Nishino S, Kanbayashi T. Symptomatic narcolepsy, cataplexy and hypersomnia, and their implications in the hypothalamic hypocretin/orexin system. *Sleep Med Rev*. 2005; 9:269-310.
34. Han F, Lin L, Schormair B, Pizza F, Plazzi G, Ollila HM, Nevsimalova S, Jennum P, Knudsen S, Winkelmann J, Coquillard C, Babrzadeh F, Strom TM, Wang C, Mindrinos M, Fernandez Vina M, Mignot E. HLA DQB1*06:02 negative narcolepsy with hypocretin/orexin deficiency. *Sleep*. 2014; 37:1601-08.
35. Benson KL. Sleep in schizophrenia: impairments, correlates, and treatment. *Psychiatr Clin North Am*. 2006; 29:1033-45.

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36. Kluge M, Himmerich H, Wehmeier PM, Rummel-Kluge C, Dalal M, Hinze-Selch D, Kraus T, Dittmann RW, Pollmächer T, Schuld A. Sleep propensity at daytime as assessed by Multiple Sleep Latency Tests (MSLT) in patients with schizophrenia increases with clozapine and olanzapine. *Schizophr Res.* 2012; 135:123-7.
37. Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RS, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med.* 2005; 353:1209-23.

FIGURES

Figure 1. Epworth Sleepiness Scale values.

Distribution of Epworth Sleepiness Scale scores in the 366 patients screened are shown in the following figure.

Figure 2. Flow-chart describing the study results.

Of the 366 patients screened, 35 presented hypersomnia and/or cataplexy. Of them, 5 were HLA positive and no abnormal hypocretin value was obtained.

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TABLES

Table 1. DSM-IV-TR diagnosis. . 65% of the patients were diagnosed as paranoid type of schizophrenia, being schizoaffective disorder diagnosis the second more frequent one.

<u>Diagnosis</u>	<u>DSM-IV-TR diagnosis code</u>	<u>Number of patients (n=366)</u>
Schizophrenia, Disorganized Type	295.10	13 (3.5%)
Schizophrenia, Paranoid Type	295.30	240 (65.6%)
Schizophrenia, Residual Type	295.60	27 (7.4%)
Schizophrenia, Undifferentiated Type	295.90	17 (4.6%)
Schizoaffective Disorder	295.70	69 (18.9%)

Table 2. Clinical characteristics of the patients. Characteristics of the patients included in the second phase (ESS \geq 11 and/or cataplexy) are summarized in the following table.

	PATIENTS (n=24)
Age (years)	39.7 \pm 10.3 (range 21-57)
Age of onset psychiatric disorder (years)	22.8 \pm 7.5 (range, 12-44)
Male gender (%)	54.2
Body Mass Index (n)	32.8 \pm 5.6 (range, 20-43.7)
Epworth Sleepiness Scale score (n)	11.4 \pm 4.1 (range, 2-18)
Duration of EDS (years)	16.8 \pm 14.2 (range, 1-50)
Possible cataplexy (n/%)	6 (25)
Hypnagogic/hypnopompic Hallucinations (n/%)	5 (20.8)
Sleep paralysis (n/%)	5 (20.8)
Estimated Nocturnal sleep amount (hours)	9.7 \pm 2 (range, 5-13.5) (14 patients slept \geq 10 hours/night)
Nocturnal sleep fragmentation (\geq 2 awakenings/night) (%)	1 (4.1)
Refreshing short naps (%)	0 (0)
Circadian rhythm disorder	1 patient had advanced sleep phase disorder 4 patients had delayed sleep phase disorder
Snorers (n/%)	12 (50)
Witnessed apneas (n/%)	6 (25)
Previous diagnosis of OSAS (n/%)	1 (4.1)
Neuroleptic treatment (%)	100
Benzodiazepine treatment (%)	37.5
Antidepressant treatment (%)	45.8
Antiepileptic treatment (%)	54.2

EDS= Excessive daytime sleepiness; OSAS= Obstructive sleep apnea syndrome

Table 3. Table 3. Clinical characteristics of HLA positive patients. The clinical characteristics of the five HLA positive patients with hypersomnia and/or cataplexy are described in this table.

PATIENT	1*	2*	3*	4*	5**
Age (years) /Gender	36/F	47/M	40/M	21/F	32/F
Age at onset of psychiatric disorder (years)	29	12	15	18	19
Age at onset of hypersomnia (years)	29	12	6	18	19
Epworth Sleepiness Score (n)	12	14	14	16	10
Cataplexy present	NO	NO	NO	YES	YES
Sleep paralysis present	NO	YES	YES	NO	NO
Hypnagogic/hypnopompic hallucinations present	NO	NO	NO	YES	YES
BMI (n)	31.2	43.7	26	37.1	20
Snoring present	NO	YES	YES	NO	NO
Witnessed apneas	NO	YES	YES	NO	NO
Mean sleep at nighttime (hours)	8	8	7.5	13	10.5
Hypocretin-1 value (pg/ml)	NA	NA	276.5	333.7	419.8
Current treatment	ZIPRASIDONE TOPIRAMATE OXCARBAZEPINE VALPROIC ACID	RISPERIDONE OLANZAPINE FLUOXETINE PREGABALIN	RISPERIDONE OLANZAPINE CITALOPRAM	CLOZAPINE PALIPERIDONE VENLAFAXINE LORMETAZEPAM	OLANZAPINE FLUOXETINE

* DSM Diagnosis was 295.30 ** DSM Diagnosis was 295.90

BMI= body mass index; NA= not available

Figure 1. Epworth Sleepiness Scale values.

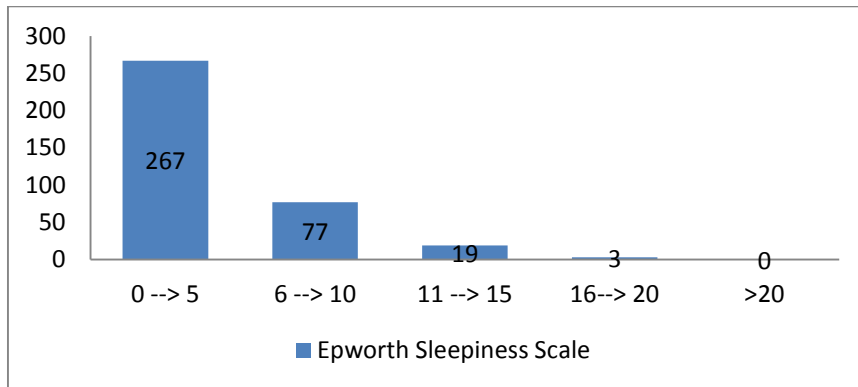
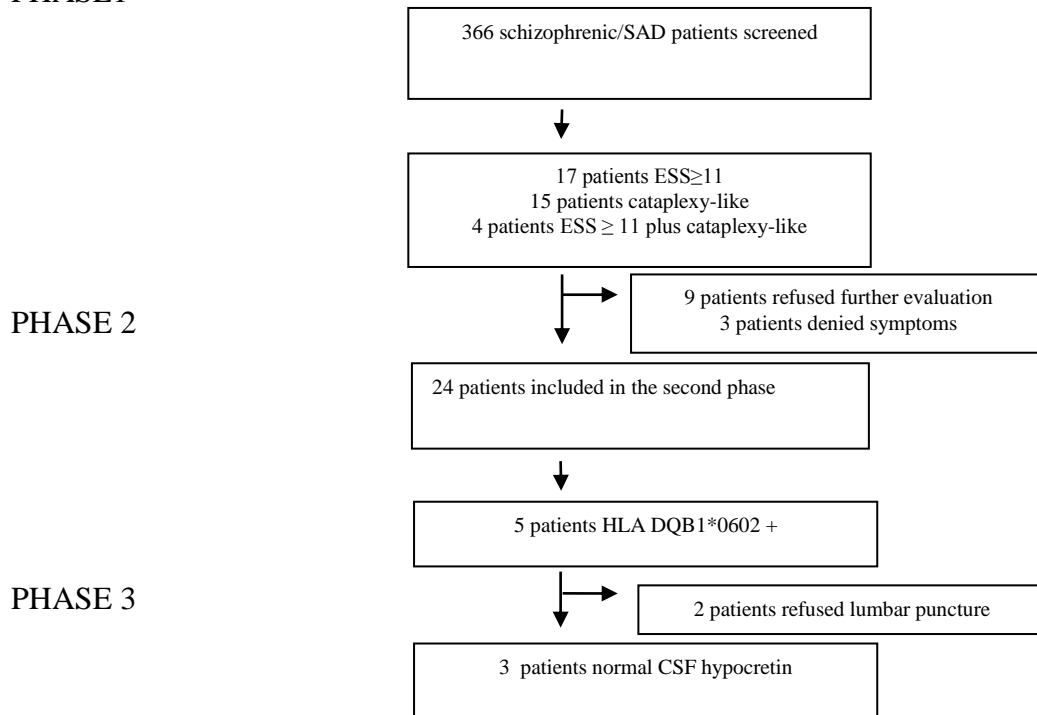


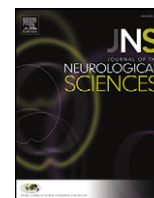
Figure 2. Flow-chart describing the study results.

PHASE 1



SAD= squizoffective disorder

ESS= Epworth Sleepiness Scale



Short communication

Non-random temporal distribution of sleep onset REM periods in the MSLT in narcolepsy



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ABSTRACT

Study objectives: The diagnosis of narcolepsy is supported by the presence of two or more sleep onset REM periods (SOREMPs) in the multiple latency sleep test (MSLT). The distribution of SOREMPs throughout the MSLT has not been systematically studied in narcolepsy. We studied the temporal distribution of SOREMPs in the MSLT of a large series of narcoleptics and calculated the effects of age and the diagnostic value of shorter versions of the test.

Patients: 129 patients consecutively diagnosed with narcolepsy (73.4% with cataplexy) underwent nocturnal polysomnography followed by a five-nap MSLT.

Results: 429 SOREMPs were recorded in 645 MSLT naps (66.5%). The probability of presenting SOREMPs in the fourth nap (3:30 pm) was significantly lower than in the remaining naps: 22.4% SOREMPs in the first nap, 20.5% in the second, 20.5% in the third, 16% in the fourth and 20.5% in the fifth nap ($p < 0.034$). Patients older than 29 years had less SOREMPs than the younger ones ($p:0.045$). Shortening the MSLT to three or four naps decreased the capability of the test to support the diagnosis of narcolepsy in 14.7 and 10% respectively.

Conclusion: The temporal distribution of SOREMPs in the MSLT is not even in narcolepsy, with the fourth nap having the lowest probability of presenting a SOREMP. This should be taken into account when evaluating the results of the MSLT, and particularly when using shorter versions of the test.

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1. Introduction

The multiple latency sleep test (MSLT) consists of a series of four or five nap opportunities at 2-hour intervals that provides an objective measure of sleepiness and detects sleep onset REM periods (SOREMPs) [1]. MSLT results correlate well with spontaneous daytime sleep and spontaneous SOREMPs in daytime continuous polysomnography [2]. It has also demonstrated an excellent intra and interrater reliability in scoring the test [3] and is a gold standard test for the diagnosis of narcolepsy. Pooled data from healthy individuals show that the mean sleep latency in 5 nap MSLT is 11.6 ± 5.2 min [4]. Pathological daytime sleepiness is defined as a mean sleep latency of less than 5 [4,5] or 8 min [6] and is usually caused by sleep breathing disorders, idiopathic hypersomnia, sleep deprivation or narcolepsy [6].

The presence of SOREMPs in the MSLT is suggestive but not pathognomonic of narcolepsy. SOREMPs have also been reported in obstructive sleep apnea or even among healthy adults particularly under sleep deprivation [7]. However the occurrence of more than 3 SOREMPs in the MSLT is highly unusual in conditions other than narcolepsy. The test–retest reliability of the MSLT in patients with central nervous system hypersomnia (excluding narcolepsy with cataplexy) is not good, as 53% of patients changed diagnosis when repeating the test [8].

The sensitivity of the MSLT for the diagnosis of narcolepsy is 70% when combining two or more SOREMPs and a mean sleep latency of less than 5 min, and its positive predictive value is 70% [9]. The highest specificity (99.2%) and positive predictive value (87%) are obtained when three or more SOREMPs are present [9]. Shorter versions of the MSLT (three naps instead of five) have been proposed in order to reduce the cost of the test [10]. In European sleep centers, Pataka assessed the variability in MSLT test performance and found that 21.6% ($n = 19$) of the centers performed routinely only 4 naps, while 35.2% ($n = 31$) performed 4 or 5 naps [11].

The ability to detect SOREMPs by these shorter versions of the MSLT could be influenced by an uneven distribution of these periods throughout the day. There is insufficient and contradictory information regarding the temporal distribution of SOREMPs in the MSLT in patients with

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narcolepsy [12,13]. The capability of shorter MSLT versions to detect 2 or more SOREMPs could also be influenced by age given the decrease in the number of SOREMPs in older narcoleptics [14].

Based on our impression that the distribution of SOREMPs in the MSLT is not even, we retrospectively reviewed a large sample of narcoleptics to study the distribution of SOREMPs in MSLT and analyze the impact on the diagnosis of narcolepsy when shortening the MSLT to 4 or 3 naps. We also analyzed the effect of age on number of SOREMPs.

2. Methods

We evaluated all patients with narcolepsy with and without cataplexy, diagnosed in our center according to the International Classification of Sleep Disorders–2 criteria [6]. All of them underwent a conventional polysomnography (PSG) followed by a 5-nap MSLT the next day. Patients treated with drugs known to affect sleep latency or REM sleep such as antidepressants and benzodiazepines or those working in shifts or having disorganized sleep schedules were excluded. When clinical suspicion of inadequate sleep hygiene patients were asked to extend nocturnal sleep before polysomnography and MSLT were performed.

Demographic and clinical data such as sex, age at the time of the MSLT, age of onset of symptoms, body mass index, daytime sleepiness measured by Epworth Sleepiness Scale at the time of MSLT, and the presence of clear-cut cataplexy were recorded. Laboratory analysis such as HLA and CSF-Hcrt1 levels was reported when available.

PSG and the MSLT protocol were performed according to standard criteria [1,15]. The MSLT consisted of 5 naps at 2-hour intervals, beginning 2 h after the end of the nocturnal sleep recording, with the first nap starting at 9:30 am. Lunch was served at 2 pm, after the third nap.

We compared the frequencies of SOREMPs in the different naps with the McNemar test. We analyzed the effect of age on number of SOREMPs with Wilcoxon test.

The study was approved by the Institutional Review Board of our center, in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Specific national laws have been observed too.

3. Results

We included 129 patients, with a mean age of 37.5 ± 16.2 years (range, 11 to 80), 65% were men and 73.4% had cataplexy. Mean age at onset of symptoms was 22.5 ± 11.6 years and the mean Epworth Sleepiness Scale score was 17.6 ± 4.3 (range, 5–24). Mean BMI was 23.3 ± 4.4 . 90% presented HLA DQB1*0602 and hypocretin determination was available in 24 patients, being in 21 of them ≤ 110 pg/ml (all with cataplexy).

3.1. Distribution of SOREMPs in the different naps

There were 429 (65%) SOREMPs among the 645 recorded naps. Twenty-five (19.4%) patients had 5 SOREMPs, 39 (30.2%) patients had 4, 32 (24.8%) patients had 3, 21 (26.3%) patients had 2, 10 (7.8%) patients had 1, and two (1.5%) patients did not present any SOREMP. All patients with either 0 or 1 SOREMP had clear-cut cataplexy except one patient who had undetectable hypocretin levels in the cerebrospinal fluid.

Of the 429 SOREMPs, 96 (74.8%) appeared in the first nap, 88 (68.2%) in the second, 88 (68.2%) in the third, 69 (53.4%) in the fourth and 88 (68.2%) in the fifth nap. The probability of presenting a SOREMP in the fourth nap was lower ($p < 0.034$) than in any other nap (Table 1) and patients presenting only one SOREMP never had it in the fourth nap.

Table 1
Distribution of SOREMPs in the different naps.

Nap	Number of SOREMPs/ total naps (%)	Mean sleep latency (min)	Mean REM-sleep latency (min)
1st	96/129 (74.4%)	1.99 ± 2.30	4.19 ± 3.10
2nd	88/129 (68.2%)	2.00 ± 2.32	5.00 ± 3.51
3rd	88/129 (68.2%)	2.09 ± 2.45	5.19 ± 3.93
4th	69/129 (53.4%)	1.80 ± 1.70	4.03 ± 2.88
5th	88/129 (68.2%)	2.34 ± 2.64	4.20 ± 3.52

3.2. Effects of age on the number of SOREMPs

When analyzing separately the group of patients with 4 and 5 SOREMPs and the group with 3 or less SOREMPs, patients with 4 and 5 SOREMPs tended to be younger and had a significantly shorter disease duration, shorter sleep latency and shorter REM sleep latency in the MSLT. Patients older than 29 years old presented significantly less SOREMPs than younger narcoleptics ($p 0.045$ Wilcoxon test).

3.3. Effect of using shorter versions of the MSLT

Nineteen patients (14.7%) would have not met the electrophysiological criteria of narcolepsy (≥ 2 SOREMPs and short sleep latency < 8 min) in a 3-nap MSLT and 12 (10%) in a 4-nap MSLT.

4. Discussion

This is the first study evaluating the SOREMP distribution throughout the MSLT in a large series of narcoleptics. We have found that the temporal distribution of SOREMPs is not even in narcolepsy with a lowest REM sleep propensity at the fourth nap (around 3.30 pm).

Our findings support results from previous studies showing a decrease in REM propensity in the afternoon using continuous polygraphic recording [16,17] or MSLT [10]. In our study the occurrence of REM sleep in the fourth nap was the least common, despite the fact that sleep latency tended to be shorter at this nap, dissociating the homeostatic pressure for NREM sleep onset from REM sleep pressure. Although the effects of food in REM sleep are not clear [18,19], lunch time, that in our sleep laboratory is served at 2 pm, could have influenced our results.

Since patients with only one SOREMP never had it in the fourth nap and most patients with a SOREMP in the fourth nap had 3 or more SOREMPs, it may be argued that patients able to overcome the negative circadian pressure to present REM sleep at the time of the fourth nap have a stronger REM propensity. This is not related, however, with a more severe form of the disease since sleep latency in the MSLT, ESS score or frequency of cataplexy is not different than in the group without SOREMP in the fourth nap.

We confirm a decrease in the number of SOREMPs with age, as described by Dauvilliers et al. [14], a fact probably reflecting an improvement of the disease with age.

We think that this uneven distribution of SOREMPs in the MSLT may influence the results of using the 3 or 4-nap versions of the MSLT for the diagnosis of narcolepsy [10,11]. Since presenting three or more SOREMPs in the MSLT has a higher positive predictive value for the diagnosis of narcolepsy than having only two [9] (87% and 70% respectively), we think that using a fixed, three or four-nap MSLT may hinder the diagnostic capability of the test. For the MSLT to have the maximum diagnostic value, it should be performed in the best conditions because its results are influenced not only by motivation [20], sleep deprivation [21], variability of different sleep centers [11] and test–retest variability [8], but also, as we have shown here, by time of the day and age of patient.

Conflict of interest

Drs. Sansa, Salamero, Iranzo and Santamaria indicate no conflicts of interest and nothing to disclose financially. Dr. Falup-Pecurariu was supported through anaEuropean Neurological Society fellowship research project and indicates no conflicts of interest.

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References

- [1] Carskadon MA, Dement WC, Mitler MM, Roth T, Westbrook PR, Keenan S. Guidelines for the Multiple Sleep Latency Test (MSLT): a standard measure of sleepiness. *Sleep* 1986;9:519–24.
- [2] Pizza F, Moghadam KK, Vandi S, Detto S, Poli F, Mignot E, et al. Daytime continuous polysomnography predicts MSLT results in hypersomnias of central origin. *J Sleep Res* 2013;22:32–40.
- [3] Chen L, Ho CK, Lam VK, Fong SY, Li AM, Lam SP, et al. Interrater and intrarater reliability in multiple sleep latency test. *J Clin Neurophysiol* 2008;25:218–21.
- [4] Littner MR, Kushida C, Wise M, Davila DG, Morgenthaler T, Lee-Chiong T, et al. Practice parameters for clinical use of the multiple sleep latency test and the maintenance of wakefulness test. *Sleep* 2005;28:113–21.
- [5] Richardson GS, Carskadon MA, Flagg W, Van den Hoed J, Dement WC, Mitler MM. Excessive daytime sleepiness in man: multiple sleep latency measurement in narcoleptic and control subjects. *Electroencephalogr Clin Neurophysiol* 1978;45:621–7.
- [6] American Academy of Sleep Medicine. The International Classification of Sleep Disorders: Diagnostic and Coding Manual 2nd ed. 2005 [Westchester: IL].
- [7] Marti I, Valko PO, Khatami R, Bassetti CL, Baumann CR. Multiple sleep latency measures in narcolepsy and behaviourally induced insufficient sleep syndrome. *Sleep Med* 2009;10:1146–50.
- [8] 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;15:789–95.
- [9] Aldrich MS, Chervin RD, Malow BA. Value of the multiple sleep latency test (MSLT) for the diagnosis of narcolepsy. *Sleep* 1997;20:620–9.
- [10] Golish JA, Sarodia BD, Blanchard AR, Dinner DS, Foldvary D, Perry MC. Prediction of the final MSLT result from the results of the first three naps. *Sleep Med* 2002;3:249–53.
- [11] Pataka A, Yoon CH, Poddar A, Riha RL. Assessment of multiple sleep latency testing in adults in Europe. *Sleep Med* 2013;14:136–9.
- [12] Nofzinger EA, Thase ME, Reynolds III CF, Himmelhoch JM, Mallinger A, Houck P, et al. Hypersomnia in bipolar depression: a comparison with narcolepsy using the multiple sleep latency test. *Am J Psychiatry* 1991;148:1177–81.
- [13] Mitler MM, Van den Hoed J, Carskadon MA, Richardson G, Park R, Guilleminault C, et al. REM sleep episodes during the Multiple Sleep Latency Test in narcoleptic patients. *Electroencephalogr Clin Neurophysiol* 1979;46:479–81.
- [14] Dauvilliers Y, BSc Gosselin, Paquet J, Touchon J, Billiard M, Montplaisir J. Effect of age on MSLT results in patients with narcolepsy–cataplexy. *Neurology* 2004;62:46–50.
- [15] Rechtschaffen A, Kales A. A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Washington: Public Health Service, US Government Printing Office; 1968.
- [16] Baldy-Moulinier M, Arguner A, Besset A. Ultradian and circadian rhythms in sleep and wakefulness. In: Guilleminault C, Dement WC, Passouant P, editors. *Narcolepsy*. New York: Spectrum; 1976. p. 485–98.
- [17] Billiard M, Salva MQ, De Koninck J, Besset A, Touchon J, Cadilhac J. Daytime sleep characteristics and their relationships with night sleep in the narcoleptic patient. *Sleep* 1986;9:167–74.
- [18] Bruck D, Armstrong S, Coleman G. Sleepiness after glucose in narcolepsy. *J Sleep Res* 1994;3:171–9.
- [19] Sangiah S, Caldwell DF. Reduction of rapid eye movement (REM) sleep by glucose alone or glucose and insulin in rats. *Life Sci* 1988;42:1425–9.
- [20] Bonnet MH, Arand DL. Impact of motivation on Multiple Sleep Latency Test and Maintenance of Wakefulness Test measurements. *J Clin Sleep Med* 2005;15:386–90.
- [21] Gimino VJ. Sleep deprivation can affect the MSLT for days. *J Clin Sleep Med* 2011;15:683.