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Sex effect on time to diagnosis and clinical features of narcolepsy type 1 and 2

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ABSTRACT

Study objectives: Sex influences sleep through physiological differences and impacts the clinical presentation and quality of life in patients with sleep disorders. However, there is a paucity of evidence regarding differences between men and women affected by narcolepsy. This study aimed to explore the sex-based dissimilarities in time to diagnosis and clinical features in narcolepsy.

Methods: This retrospective observational study included adult patients with narcolepsy type 1 (NT1) and type 2 (NT2). Clinical, polysomnographic, and biofluid parameters were compared between men and women.

Results: The study analyzed 42 patients: 27 with NT1 (64.3 %) and 15 with NT2 (35.7 %). Among these, 18 were male (42.9 %; mean age 34.72 ± 12.89 years) and 24 were female (57.1 %; mean age 37.96 ± 13.2 years). No significant sex differences were observed in the age at onset of symptoms. Notably, females had significantly longer diagnostic delay compared to males ($p = 0.04$) and a higher rate of misdiagnosis before receiving the diagnosis of narcolepsy ($p < 0.001$). Male patients exhibited significantly longer stage 2 of Non-REM sleep percentage compared to females patients ($p = 0.024$). There were no significant differences in psychiatric comorbidities ($p = 0.30$).

Conclusions: Women with narcolepsy experience longer time to obtain the correct diagnosis and are more frequently misdiagnosed with other disorders compared to men. The present findings highlight a potential sex-based disparity in diagnostic practices that may negatively impact the well-being of women with narcolepsy, as their symptoms are more commonly misdiagnosed.

1. Introduction

Over the past decades, there has been growing attention in understanding the effect of sex on the disease biology and the clinical aspects of neurological disorders. Numerous studies recently uncovered that sleep disorders can affect women and men differently [1,2]. Specifically, the prevalence of sleep disorders can be different among women and men (i.e. sleep-disordered breathing are prevalent in men, insomnia and restless legs syndrome are prevalent in women), as well as the impact of sleep disorders on quality of life may differ between sexes [3]. Previous studies showed a sex effect on disease burden, clinical manifestations and symptoms complaints of sleep disorders such as insomnia and REM sleep behaviour disorder [3–5]. Moreover, most recent evidence from animal model studies suggests sex differences in narcolepsy symptoms [6–11]. However, sex differences in patients with narcolepsy remain understudied, with only a few reports focusing on these dissimilarities in diagnosis, clinical symptoms, and disease burden [12–16]. In particular, previous findings were mixed and did not fully and comprehensively consider sex differences regarding the interval between symptoms onset and diagnosis, the incidence of misdiagnosis before narcolepsy, and the clinical, polysomnographic and biofluid features. A few reports documented that female patients with narcolepsy have access to diagnostic sleep testing less likely than men [12] and can have a long delay in receiving a narcolepsy diagnosis [13,14]. Moreover, considering the differences between narcolepsy symptoms in children and adults, there was no report about a possible sex effect in patients diagnosed with narcolepsy in the adult age and with symptoms onset in adolescence.

Therefore, this study aimed to describe the timeliness of disease diagnosis and clinical characteristics among male and female adult patients diagnosed with narcolepsy type 1 (NT1) and type 2 (NT2) in order

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to identify potential sex differences in clinical, polysomnographic and biofluid markers.

2. Methods

2.1. Participants and study design

This is a retrospective observational study performed in adult patients diagnosed with narcolepsy who were admitted at the Sleep Medicine Centre of the University Hospital of Rome Tor Vergata. NT1 and NT2 were diagnosed according to the guidelines of the International Classification of Sleep Disorders – 3rd Edition, and in the case of a diagnosis performed before 2014, the revision of the criteria was done by sleep certified experts (FI, CL, FP) [17].

Inclusion criterion for patients with narcolepsy was detailed clinical charts, describing the diagnostic work-up, the clinical symptoms, and the biomarker assessment. The exclusion criteria were a previous diagnosis of narcolepsy before admission to the sleep medicine centre and lack of completion of the sleep study protocol (including clinical, genetic, polysomnographic and biofluid marker analysis).

The study protocol was considered retrospective and observational according to the STROBE statement by the internal review board of the Ethical Committee of the University Hospital of Rome Tor Vergata.

2.2. Measures assessment

All clinical charts were analyzed and demographic and clinical features were reported in an *ad hoc* database. All the clinical, polysomnographic, genetic and biofluid markers were collected from the medical records.

Regarding the frequency of cataplectic attacks, data were register on a scale from 1 to 5, where 1 represents one or less cataplectic attack per year; 2 indicates more than one cataplectic attack per year but less than one per month; 3 represents more than one attack per month but less than one per week; 4 indicates more than one per week but less than one per day; and 5 represents severe cases with at least one cataplectic attack per day [18].

All patients underwent a complete polysomnography (PSG), followed by multiple sleep latency test (MSLT), according to guidelines and common clinical practice [19]. For this study, data regarding sleep analysis were collected according to the standard criteria [20]. The following standard parameters were considered: time in bed (TIB, time spent in bed between lights off and lights on), sleep onset latency (SL, the time-interval between the lights off and the first sleep epoch), total sleep time (TST, the actual sleep time without SL and awakenings), sleep efficiency (SE, the ratio between TST and TIB), REM sleep latency (REML, the time-interval between the sleep onset and the first epoch of REM sleep), stage 1 of non-REM sleep (N1), stage 2 of non-REM sleep (N2), stage 3 of non-REM sleep (N3), REM sleep, and wakefulness after sleep onset (WASO). The percentages of the sleep stages were calculated over TST. Researchers (AC, FI, CL, AP, FP) scored the PSG recordings based on the international standard criteria of the American Academy of Sleep Medicine [20,21].

The MSLT was performed to objectively test daytime sleepiness and consisted of five trials performed at 2-h intervals [22,23]. The MSLT sessions started 2 h after awakening the day after the polysomnographic recording. Daytime sleep propensity was calculated for each participant as the mean sleep latency (MSL) value from the five sessions and the number of sleep-onset REM periods (SOREMPs) during MSLT.

The hypocretin-1/orexin-A CSF levels were detected with a commercially available ELISA kit (Orexin A/Hypocretin-1 EIA Kit; Phoenix Pharmaceuticals, Burlingame, CA), as previously described [24–26].

2.3. Statistical analysis

The statistical analysis was performed using commercial software SPSS version 25 [27]. First, descriptive statistics were computed to characterize the sample in terms of age, sex, narcolepsy type, age of symptoms onset, cataplexy frequency, the interval between symptoms onset to diagnosis, CSF orexin levels, PSG and MSLT data. Then, depending on the type of variable, chi-square test or Fisher's Exact Test was applied for categorical variables, while the Mann-Whitney test was used for continuous variables for differentiating NT1 to NT2 patients and female to male patients in demographic, clinical, PSG, and MSLT data.

Predictors of narcolepsy diagnosis delay (time between symptoms onset to diagnosis) were assessed using Cox proportional hazards regression model, including all narcolepsy patients (both NT1 and NT2). Sex, presence of cataplexy (Yes or No), and age at symptoms onset were included in the analysis as predictors. Hazard ratio (HR) and 95 % confidence intervals (CI) were reported. P-value was set at $p < 0.05$ for statistical significance.

3. Results

A total of 42 patients with narcolepsy were included in this retrospective observation considering inclusion and exclusion criteria; patients with NT1 were 27 (64.3 %) and with NT2 were 15 (34.7 %). Among these patients, 18 were male (42.9 %; 34.72 ± 12.89 years; 10 NT1 and 8 NT2) and 24 females (57.1 %; 37.96 ± 13.20 years; 17 NT1 and 7 NT2). Patients' demographic and clinical data are present in Table 1 and PSG data are shown in Table 2.

No significant differences were found for the age of symptoms onset according to narcolepsy type and sex. NT1 patients reported higher frequency of sleep-related hallucinations than NT2 patients ($p = 0.003$). Furthermore, no significant differences between sexes were found for the age at onset of cataplexy symptoms in NT1 patients ($p = 0.591$), as well as for the cataplexy score ($p = 0.297$).

No significant differences were found between the two types of narcolepsy for diagnosis delay ($p = 0.291$) and misdiagnosis ($p = 1.00$). However, there was a significant higher time to narcolepsy diagnosis in female patients than in male patients with narcolepsy ($p = 0.036$). Female patients had a significantly higher percentage of misdiagnosis (more frequently diagnosis of neurological or psychiatric diseases before obtaining narcolepsy diagnosis) when compared to male patients with narcolepsy ($p = 0.001$). There were no significant differences between the two groups of narcolepsy patients and between males and females regarding concomitant psychiatric disorders ($p = 1.00$ and $p = 0.299$, respectively).

No differences between the two types of narcolepsy were observed in the MSL at MSLT ($p = 0.182$) and in the number of SOREMPs ($p = 0.053$). No significant differences across sexes were documented in the MSL at MSLT ($p = 0.353$) and in the number of SOREMPs ($p = 0.136$).

Considering sleep polysomnographic measures, no significant differences were observed between NT1 and NT2 patients. Additionally, no significant differences were found across the two groups, except for N2, which was higher in male than female patients ($p = 0.024$).

Demographic and clinical data were investigated through Cox regression models to assess the impact of these factors on diagnosis delay (Table 2). Presence of cataplexy, and age at symptoms onset did not influence the diagnosis delay in patients with narcolepsy. Sex was the only predictor of the diagnostic delay (hazard ratio [HR] = 0.436, $p = 0.020$; Table 3).

4. Discussion

Despite significant efforts in the recent past to improve the recognition and diagnosis of narcolepsy, the time interval between symptoms onset and diagnosis in patients with narcolepsy remains longer than one

Table 1
Demographic and clinical characteristics of patients.

	Narcolepsy Type Differences			*Sex Differences*		
	NT1 (n = 27)	NT2 (n = 15)	*p*-value	Male Patients (n = 18)	Female Patients (n = 24)	*p*-value
Demographic and clinical data						
Mean age, years	35.19 ± 12.75	39.07 ± 13.54	0.379	34.72 ± 12.89	37.96 ± 13.20	0.476
Type of Narcolepsy, (%)						
NT1			NA	10 (55.6 %)	17 (70.8%)	0.347
NT2				8 (44.4%)	7 (29.2%)	
Age of onset, years	22.67 ± 10.48	23.07 ± 10.96	0.813	25.28 ± 11.82	20.96 ± 9.26	0.352
Diagnosis delay, years	6.93 ± 6.28	10.07 ± 9.69	0.291	4.89 ± 3.51	10.42 ± 9.11	0.036
Misdiagnosis, (%)	6 (22.2 %)	4 (26.7 %)	1.000	0	10 (41.7 %)	0.001
Depression	3 (11.1 %)	4 (26.7 %)	NA		3 (12.5 %)	
Epilepsy	2 (7.4 %)				6 (25 %)	
Learning Disabilities	1 (3.7 %)				1 (4.17 %)	
Presence of Psychiatric Symptoms, (%)	7 (25.9 %)	4 (26.7 %)	1.000	3 (16.7 %)	8 (33.3 %)	0.299
Cataplexy, (%)			NA	8 (44.4 %)	15 (62.5 %)	0.449
Mean age of cataplexy onset	27.09 ± 10.50			29.25 ± 12.71	25.93 ± 9.40	0.591
Cataplexy Score	3.27 ± 1.28			2.88 ± 1.36	3.50 ± 1.22	0.297
Sleep-related hallucinations, (%)	15 (55.6 %)	1 (7.1 %)	0.003	5 (27.8 %)	11 (47.8 %)	0.218
Sleep Paralysis, (%)	15 (55.6 %)	9 (64.3 %)	0.742	11 (61.1 %)	13 (56.7 %)	1.000
MSLT and CSF Data						
MSL, min	3.87 ± 1.77	5.01 ± 2.54	0.182	4.70 ± 2.28	3.97 ± 2.01	0.353
SOREMPs, number	2.84 ± 1.11	2.13 ± 0.92	0.053	2.78 ± 1.06	2.41 ± 1.22	0.136
HLA-DQB1*06:02, (%)	26 (100 %)	5 (33.3 %)	<0.001			NA
Orexin A, pg/ml	57.66 ± 29.15	179.02 ± 57.59	<0.001			NA

Data are presented as mean ± standard deviation. Abbreviations: NT1 Narcolepsy type 1; NT2 Narcolepsy type 2; MSLT Multiple sleep latency test; MSL, mean sleep latency; SOREMPs sleep onset rapid eye movement period; NA, Non-applied.

Table 2
Polysomnographic data according to narcolepsy type and sex.

	Narcolepsy Type Differences			*Sex Differences*		
	NT1 (n = 27)	NT2 (n = 15)	*p*-value	Male Patients (n = 18)	Female Patients (n = 24)	*p*-value
TIB (min)	477.67 ± 64.36	429.40 ± 109.45	0.070	452.74 ± 91.58	472.28 ± 71.71	0.526
TST (min)	405.46 ± 69.96	358.60 ± 52.289	0.123	378.10 ± 65.83	402.23 ± 69.51	0.421
SE (%)	84.75 ± 9.31	84.47 ± 11.12	0.873	85.30 ± 11.80	84.07 ± 7.97	0.297
SL (min)	6.58 ± 6.56	6.75 ± 6.29	0.606	5.07 ± 4.51	6.96 ± 6.88	0.515
REML (min)	21.45 ± 25.45	27.83 ± 20.14	0.191	21.60 ± 19.03	25.37 ± 27.07	0.945
REM (%)	19.46 ± 7.16	20.75 ± 5.98	0.657	18.54 ± 6.02	20.99 ± 7.17	0.256
N1 (%)	11.78 ± 9.22	09.46 ± 7.97	0.572	8.99 ± 7.91	12.66 ± 9.30	0.230
N2 (%)	47.21 ± 13.44	47.42 ± 20.02	0.344	54.66 ± 16.81	41.07 ± 11.87	0.024
N3 (%)	20.06 ± 9.23	23.71 ± 12.82	0.461	18.31 ± 7.92	23.85 ± 11.98	0.102
WASO (min)	65.91 ± 42.91	60.92 ± 71.86	0.292	61.06 ± 70.12	66.89 ± 35.65	0.117

Data are presented as mean ± standard deviation.
Abbreviations: TIB, time in bed; TST, total sleep time; SE, sleep efficiency; SL, sleep latency; REML, REM sleep latency; N1, Stage 1 of Non-REM Sleep; N2, Stage 2 of Non-REM Sleep; N3, Stage 3 of Non-REM Sleep; WASO, wake after sleep onset.

Table 3
Cox proportional hazard model for time to narcolepsy diagnosis from symptom onset.

Covariate	Hazard Ratio (95 % CI)	p-value
Sex[a]	0.436 (0.22, 0.88)	0.020
Age of symptoms onset	1.026 (0.99, 1.06)	0.140
Presence of Cataplexy[b]	1.537 (0.81, 2.91)	0.187

[a] Males = 0 and Female = 1.
[b] No cataplexy = 0; Presence of cataplexy = 1.

can expect [28–30]. The present study confirms a considerable delay in narcolepsy diagnosis in women compared to men.

A key finding of our study is the longer diagnosis delay and the higher rate of misdiagnosis in the female patients when compared to male patients. Importantly, sex was the only factor that significantly influenced diagnostic timeliness, even after considering the age of symptoms onset, presence of cataplexy, and PSG features. Our results are in line with previous studies that have associated female sex with a greater diagnosis delay compared to men [13,14]. Zhang and colleagues also documented this phenomenon in a European multicentre cohort, emphasizing that female patients frequently receive alternative diagnoses, including psychiatric disorders (e.g., depression, anxiety) and epilepsy, before being correctly diagnosed with narcolepsy [16]. In our cohort, no male patient presented a misdiagnosis before narcolepsy, although an average diagnosis delay longer than 4 years. These findings reinforce the hypothesis that the lack of symptoms recognition may contribute significantly to the diagnosis delay, and to counteract this issue, red flags for narcolepsy diagnosis have been released [31]. Several factors may contribute to the diagnosis delays or misdiagnosis before narcolepsy diagnosis. One key factor is the insufficient knowledge of the disease among physicians, which creates barriers to suspect narcolepsy. Similarly, the limited awareness of symptoms among adult patients can lead to misdiagnosis, especially when more common or well-known conditions, such as depression, are considered as potential causes. Additionally, social and legal factors, such as reluctance to accept the disease, fear of social or work-related limitations, and concerns about losing a driver's license, may further reduce patients' motivation to search for an accurate diagnosis.

The observed difference in average diagnosis delay in our study (8.05

± 7.71 years) compared to the previously reported delay of approximately 15 years [14,30,32,33], may, in part, reflect the increased awareness and educational efforts aimed at improving the recognition and diagnosis of narcolepsy. However, evidence suggests that while some populations have experienced reductions in diagnosis delay over time [28,30,34], this trend is not consistent across all groups. Zhang et al. [16] reported a mean and median diagnosis delay of 9.7 and 5.3 years, respectively, but found no significant overall decline in diagnosis delay at a population level, despite variations between countries. Unlike prior studies suggesting an improvement in diagnostic timelines, Zhang and colleagues [16] highlighted that such conclusions may be influenced by methodological factors. Our findings further support the persistence of substantial diagnostic barriers, particularly among female patients, who continue presenting prolonged diagnosis delays.

Beyond diagnosis delay, sex differences in narcolepsy symptomatology have been explored in previous studies [13,35,36]. Considering the comparisons within the subgroups of patients diagnosed with NT1 and NT2, no significant sex-related differences were observed in terms of age at symptoms onset, cataplexy frequency, or MSLT data. Conversely to our findings, previous studies have documented that females tend to present the onset of symptoms earlier than man, with more frequent cataplectic attacks, and greater sleepiness at the MSLT [13,35,36]. This observation is notably conspicuous in animal studies [6,7,37], where females often exhibit a more severe form of cataplexy and an earlier age at onset. Despite these findings obtained in animal model studies, conclusive evidence regarding sex-related differences in human narcolepsy remains limited. Gool and colleagues utilized an unsupervised clustering approach to characterize central disorders of hypersomnolence, identifying a distinct clinical phenotype in female patients, including mild cataplexy, hypnagogic hallucinations, and sleep paralysis [38]. Similarly, Ferrazzini and colleagues demonstrated that daytime sleepiness and BMI differed between sexes, with women presenting higher subjective sleepiness scores compared to men [39]. These findings emphasize the role of sex and age in shaping hypersomnolence disorders and reinforce the necessity for sex-specific diagnostic and therapeutic strategies. However, comprehensive systematic analyses and controlled clinical trials specifically addressing sex-related variations in narcolepsy remain insufficient and warrant further investigation.

This study has some limitations that need to be acknowledged. Considering the retrospective design of the study, data collection was only performed through the collection of information present on the clinical charts, potentially omitting relevant clinical details. Nonetheless, several different objective parameters were evaluated, namely polysomnographic, genetic and biofluid markers. Another limitation is that the study was conducted at a single sleep medicine centre in central Italy, which limited sample size and hampered the generalization of the current findings. Moreover, the lack of differentiation between paediatric and adult narcolepsy patients is another limitation. Given that narcolepsy diagnosis exhibits two peaks—one in childhood/adolescence and another in adulthood—future studies should separately examine these populations to determine whether clinical features influence diagnosis delay differently across age groups. Additionally, as some experts suggest that NT2 may represent an heterogeneous condition overlapping with idiopathic hypersomnia or NT1 without cataplexy, and that its distinction remains uncertain [40,41], future research should explore the implications of NT2, considering its diagnostic clarity and potential impact on patient management. Finally, the relatively small sample size may have affected the ability to detect sex-related differences in PSG parameters. While this study found that females had a slightly shorter N2 stage than males, past studies reported that women have higher total sleep time [13], better sleep efficiency [13,14], decreased N1 [14], longer N2 and slow wave sleep duration [14], and increased numbers of arousals [42] than men. The limited statistical power may have prevented the identification of more subtle differences, highlighting the need for future studies with larger cohorts to validate these findings. In conclusion, the present study highlights the persistent issue of diagnosis delay in narcolepsy, particularly among female patients who experience a higher rate of misdiagnosis. These findings reinforce the need for targeted educational programs and sex-specific clinical guidelines to enhance symptom recognition in narcolepsy. Future initiatives should prioritize increasing awareness among healthcare providers and the general public to facilitate earlier diagnosis and reduce the burden of misdiagnosis. Enhanced educational training and awareness campaigns could significantly decrease diagnosis delay and improve patient outcomes in narcolepsy.

CRediT authorship contribution statement

Mariana Fernandes: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Carmen Calvello:** Investigation, Data curation. **Fabio Placidi:** Investigation. **Francesca Izzi:** Investigation. **Alessandro Castelli:** Investigation. **Andrea Pagano:** Investigation. **Nicola Biagio Mercuri:** Supervision. **Claudio Liguori:** Writing – review & editing, Supervision, Investigation, Conceptualization.

Data availability

The data that support the results reported in this study are available from the corresponding author upon reasonable request.

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Non-financial disclosure

None to declare.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] Krishnan V, Collop NA. Gender differences in sleep disorders. Curr Opin Pulm Med 2006;12:383–9. https://doi.org/10.1097/01.mcp.0000245705.69440.6a.
[2] Shaib F, Attarian H. In: Legato MJBT-P of G-SM, Third E, editors. Chapter 40 - sex and gender differences in sleep disorders: an overview. San Diego: Academic Press; 2017. p. 585–601. https://doi.org/10.1016/B978-0-12-803506-1.00046-2.
[3] Theorell-Haglöw J, Miller CB, Bartlett DJ, Yee BJ, Openshaw HD, Grunstein RR. Gender differences in obstructive sleep apnoea, insomnia and restless legs syndrome in adults–What do we know? A clinical update. Sleep Med Rev 2018;38:28–38.
[4] Peng YT, Hsu YH, Chou MY, Chu CS, Su CS, Liang CK, et al. Factors associated with insomnia in older adult outpatients vary by gender: a cross-sectional study. BMC Geriatr 2021;21:1–12. https://doi.org/10.1186/s12877-021-02643-7.
[5] Zeng LN, Zong QQ, Yang Y, Zhang L, Xiang YF, Ng CH, et al. Gender difference in the prevalence of insomnia: a meta-analysis of observational studies. Front Psychiatr 2020;11:1–9. https://doi.org/10.3389/fpsyt.2020.577429.
[6] Piilgaard L, Rose L, Hviid CG, Kohlmeier KA, Kornum BR. Sex-related differences within sleep-wake dynamics, cataplexy, and EEG fast-delta power in a narcolepsy mouse model. Sleep 2022;45:1–15. https://doi.org/10.1093/sleep/zsac058.
[7] Arthaud S, Villalba M, Blondet C, Morel A-L, Peyron C. Effects of sex and estrous cycle on sleep and cataplexy in narcoleptic mice. Sleep 2022;45:1–12. https://doi.org/10.1093/sleep/zsac089.
[8] Sun Y, Tisdale R, Park S, Heu J, Ma S-C, Haire M, et al. The development of sleep/wake disruption and cataplexy as hypocretin/orexin neurons degenerate in male vs. female Orexin/tTA; TetO-DTA Mice. Sleep 2022;45:1–17. https://doi.org/10.1093/sleep/zsac039.

[9] Hayduk R, Flodman P, Spence MA, Erman MK, Mitler MM. HLA haplotypes, polysomnography, and pedigrees in a case series of patients with narcolepsy. Sleep 1997;20:850–7.
[10] Fujiki N, Yoshida Y, Zhang S, Sakurai T, Yanagisawa M, Nishino S. Sex difference in body weight gain and leptin signaling in hypocretin/orexin deficient mouse models. Peptides 2006;27:2326–31.
[11] Dauvilliers Y, Neidhart E, Lecendreux M, Billiard M, Tafti M. MAO-A and COMT polymorphisms and gene effects in narcolepsy. Mol Psychiatr 2001;6:367–72.
[12] Auer M, Frauscher B, Hochleitner M, Högl B. Gender-specific differences in access to polysomnography and prevalence of sleep disorders. J Womens Health (Larchmt) 2018;27:525–30. https://doi.org/10.1089/jwh.2017.6482.
[13] Won C, Mahmoudi M, Qin L, Purvis T, Mathur A, Mohsenin V. The impact of gender on timeliness of narcolepsy diagnosis. J Clin Sleep Med JCSM Off Publ Am Acad Sleep Med 2014;10:89–95. https://doi.org/10.5664/jcsm.3370.
[14] Luca G, Haba-Rubio J, Dauvilliers Y, Lammers G-J, Overeem S, Donjacour CE, et al. Clinical, polysomnographic and genome-wide association analyses of narcolepsy with cataplexy: a European Narcolepsy Network study. J Sleep Res 2013;22:482–95. https://doi.org/10.1111/jsr.12044.
[15] Schmidt MH, Bassetti CLA. Gender differences in narcolepsy: what are recent findings telling us? Sleep 2022:1–16. https://doi.org/10.1093/sleep/zsac126.
[16] Zhang Z, Dauvilliers Y, Plazzi G, Mayer G, Lammers GJ, Santamaria J, et al. Idling for decades: a European study on risk factors associated with the delay before a narcolepsy diagnosis. Nat Sci Sleep 2022:1031–47.
[17] American Academy of Sleep Medicine. International classification of sleep disorders. third ed. IL: Darien; 2014.
[18] Dauvilliers Y, Montplaisir J, Molinari N, Carlander B, Ondze B, Besset A, et al. Age at onset of narcolepsy in two large populations of patients in France and Quebec. Neurology 2001;57:2029–33. https://doi.org/10.1212/WNL.57.11.2029.
[19] Ruoff C, Rye D. The ICSD-3 and DSM-5 guidelines for diagnosing narcolepsy: clinical relevance and practicality. Curr Med Res Opin 2016;32:1611–22. https://doi.org/10.1080/03007995.2016.1208643.
[20] Berry RB, Brooks R, Gamaldo CE, Harding SM, Marcus C, Vaughn BV. The AASM manual for the scoring of sleep and associated events. Rules, Terminol Tech Specif Darien, Illinois. Am Acad Sleep Med 2012;176:2012.
[21] Iber C, Ancoli-Israel S, Chesson AL, Quan SF. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications, vol. 1. Westchester, IL: American academy of sleep medicine; 2007.
[22] Carskadon MA, Dement WC. The multiple sleep latency test: what does it measure. Sleep 1982;5:S67–72.
[23] Carskadon MA. Guidelines for the multiple sleep latency test (MSLT): a standard measure of sleepiness. Sleep 1986;9:519–24.
[24] Liguori C, Placidi F, Albanese M, Nuccetelli M, Izzi F, Marciani MG, et al. CSF beta-amyloid levels are altered in narcolepsy: a link with the inflammatory hypothesis? J Sleep Res 2014;23:420–4. https://doi.org/10.1111/jsr.12130.
[25] Liguori C, Placidi F, Izzi F, Nuccetelli M, Bernardini S, Sarpa MG, et al. Beta-amyloid and phosphorylated tau metabolism changes in narcolepsy over time. Sleep Breath 2016;20:277–83. https://doi.org/10.1007/s11325-015-1305-9.
[26] Liguori C, Romigi A, Nuccetelli M, Zannino S, Sancesario G, Martorana A, et al. Orexinergic system dysregulation, sleep impairment, and cognitive decline in Alzheimer disease. JAMA Neurol 2014;71:1498–505. https://doi.org/10.1001/jamaneurol.2014.2510.
[27] IBM. SPSS - statistical package for social sciences. 2020.
[28] Thorpy MJ, Krieger AC. Delayed diagnosis of narcolepsy: characterization and impact. Sleep Med 2014;15:502–7. https://doi.org/10.1016/j.sleep.2014.01.015.
[29] Bhattarai J, Sumerall SW. Diagnostic delay of narcolepsy: contributing factors and implications for clinicians. Sleep Vigil 2018;2:103–9. https://doi.org/10.1007/s41782-018-0046-9.
[30] Morrish E, King MA, Smith IE, Shneerson JM. Factors associated with a delay in the diagnosis of narcolepsy. Sleep Med 2004;5:37–41. https://doi.org/10.1016/j.sleep.2003.06.002.
[31] Vignatelli L, Antelmi E, Ceretelli I, Bellini M, Carta C, Cortelli P, et al. Red Flags for early referral of people with symptoms suggestive of narcolepsy: a report from a national multidisciplinary panel. Neurol Sci 2019;40:447–56.
[32] Dauvilliers Y, Molinari N, Espa F, Carlander B, Lesperance P, Montplaisir J, et al. Delay of diagnosis of narcolepsy in a European and in a North American population. J Sleep Res 1998;7:56.
[33] Moldofsky H, Broughton RJ, Hill JD. A randomized trial of the long-term, continued efficacy and safety of modafinil in narcolepsy. Sleep Med 2000;1:109–16. https://doi.org/10.1016/s1389-9457(99)00014-3.
[34] Furuta H, Thorpy MJ, Temple HM. Comparison in symptoms between aged and younger patients with narcolepsy. Psychiatr Clin Neurosci 2001;55:241–2.
[35] Luca G, Haba-Rubio J, Dauvilliers Y, Lammers G-J, Overeem S, Donjacour CE, et al. Clinical, polysomnographic and genome-wide association analyses of narcolepsy with cataplexy: a European Narcolepsy Network study. J Sleep Res 2013;22:482–95. https://doi.org/10.1111/jsr.12044.
[36] Mayer G, Kesper K, Peter H, Ploch T, Leinweber T, Peter JH. The implications of gender and age at onset of first symptoms in narcoleptic patients in Germany - results from retrospective evaluation of hospital records. Somnologie 2002;6:13–8. https://doi.org/10.1046/j.1439-054x.2002.02005.x.
[37] Sun Y, Tisdale R, Park S, Ma S-C, Heu J, Haire M, et al. The development of sleep/wake disruption and cataplexy as hypocretin/orexin neurons degenerate in male vs. female Orexin/tTA; TetO-DTA Mice. Sleep 2022;45. https://doi.org/10.1093/sleep/zsac039.
[38] Gool JK, Zhang Z, Oei MSSL, Mathias S, Dauvilliers Y, Mayer G, et al. Data-driven phenotyping of central disorders of hypersomnolence with unsupervised clustering. Neurology 2022;98:e2387–400. https://doi.org/10.1212/WNL.0000000000200519.
[39] Ferrazzini L, Schmidt M, Zhang Z, Khatami R, Dauvilliers Y, Barateau L, et al. Daytime sleepiness and BMI exhibit gender and age differences in patients with central disorders of hypersomnolence. J Sleep Res 2024:e14365. https://doi.org/10.1111/jsr.14365. n/a.
[40] Lammers GJ, Bassetti CLA, Dolenc-Groselj L, Jennum PJ, Kallweit U, Khatami R, et al. Diagnosis of central disorders of hypersomnolence: a reappraisal by European experts. Sleep Med Rev 2020;52:101306. https://doi.org/10.1016/j.smrv.2020.101306.
[41] Fronczek R, Arnulf I, Baumann CR, Maski K, Pizza F, Trotti LM. To split or to lump? Classifying the central disorders of hypersomnolence. Sleep 2020;43:zsaa044. https://doi.org/10.1093/sleep/zsaa044.
[42] Zhang Y, Ren R, Yang L, Zhang H, Shi Y, Sanford LD, et al. Polysomnographic nighttime features of narcolepsy: a systematic review and meta-analysis. Sleep Med Rev 2021;58:101488. https://doi.org/10.1016/j.smrv.2021.101488.