Article

Journal of Attention Disorders
1–10

DOI: 10.1177/1087054718775826
journals.sagepub.com/home/jad
SAGE

Association of Inattention, Hyperactivity, and Hypersomnolence in Two Clinic-Based Adult Cohorts

Régis Lopez[1,2,3], Jean-Arthur Micoulaud-Franchi[4,5,6], Laura Camodeca[1], Marie Gachet[7], Isabelle Jaussent[2,3], and Yves Dauvilliers[1,2,3]

Abstract

Objective: To assess the relationship between excessive daytime sleepiness (EDS), inattention, and hyperactivity/impulsivity in adults with ADHD and central hypersomnia. **Method:** Drug-free adult patients with ADHD (*n* = 100) or hypersomnia (*n* = 100) were evaluated using a structured clinical interview and self-report questionnaires on ADHD symptoms and EDS. **Results:** In all, 61% of patients with hypersomnia had clinically significant ADHD symptoms with 25% having an ADHD diagnosis (with both childhood and adulthood ADHD symptoms) and 36% ADHD-like symptoms, without history of childhood ADHD. EDS was reported in 47% of patients with ADHD, among whom 22% had a hypersomnolence disorder. **Conclusion:** We confirmed the high frequency of ADHD and ADHD-like symptoms in central hypersomnia, and of EDS and hypersomnolence in ADHD in adults. The nature of the link between EDS, inattention, and hyperactivity appears to be complex that may involve either a cause–effect relationship or intrinsic features of a similar neurodevelopmental dysfunction. *(J. of Att. Dis. XXXX; XX(X) XX-XX)*

Keywords
ADHD, narcolepsy, cataplexy, idiopathic hypersomnia, orexin

Introduction

Children and adults with ADHD frequently experience day- and night-time sleep problems (e.g., excessive daytime sleepiness [EDS], difficulties in falling asleep, night-time awakenings, difficulties in waking up in the morning) and have primary sleep disorders (e.g., restless leg syndrome, parasomnia, circadian rhythm disorders) that may affect their quality of life (Bioulac et al., 2015; Oosterloo, Lammers, Overeem, de Noord, & Kooij, 2006; Surman et al., 2009; Virring, Lambek, Thomsen, Møller, & Jennum, 2016; Walters, Silvestri, Zucconi, Chandrashekariah, & Konofal, 2008; Yoon, Jain, & Shapiro, 2013).

EDS is the core symptom of central hypersomnias that include narcolepsy type 1 (NT1), narcolepsy type 2 (NT2), and idiopathic hypersomnia (IH). NT1 is characterized by EDS and cataplexy, frequently associated with hypnagogic hallucinations and sleep paralysis, and is caused by cerebrospinal fluid (CSF) hypocretin-1/orexin-A deficiency (Dauvilliers, Arnulf, & Mignot, 2007; Kornum et al., 2017). In NT2, cataplexy is absent and CSF hypocretin-1 levels are normal (Andlauer et al., 2012; Baumann et al., 2014). In IH, CSF hypocretin-1 levels are normal (Dauvilliers et al., 2003), and EDS is frequently associated with prolonged nighttime sleep and sleep inertia (Billiard & Sonka, 2016). NT2 and IH symptoms, polysomnographic recordings (PSG) and natural course suggest some overlap, without a clear underlying pathophysiology (Dauvilliers et al., 2016; Lopez et al., 2017). Previous studies suggested a higher prevalence of childhood ADHD in narcoleptic adults and a

[1]Centre National de Référence Narcolepsie Hypersomnies, Unité des Troubles du Sommeil, Service de Neurologie, Hôpital Gui de Chauliac, Montpellier, France
[2]Inserm U1061, Montpellier, France
[3]Université de Montpellier, France
[4]Unité de Sommeil, Hôpital Pellegrin, Bordeaux, France
[5]Université de Bordeaux, France
[6]CNRS, SANPSY, USR 3413, Bordeaux, France
[7]Department of Emergency Psychiatry and Post Acute Care, Hôpital Lapeyronie, Montpellier, France

Corresponding Authors:
Régis Lopez, Département de Neurologie, Hôpital Gui de Chauliac, 80 avenue Augustin Fliche, 34295 Montpellier Cedex 5, Montpellier, France.
Email: r-lopez@chu-montpellier.fr

Yves Dauvilliers, Centre national de référence narcolepsie hypersomnies, Département de Neurologie, CHU Gui-de-Chauliac, 80, avenue Augustin Fliche, 34295 Montpellier Cedex 5, France.
Email: ydauvilliers@yahoo.fr

similar association was recently reported in a large clinical sample of children with NT1 and NT2 (Lecendreux et al., 2015; Modestino & Winchester, 2013; Ohayon, 2013).

The *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.; *DSM-5*; American Psychiatric Association [APA], 2013) also introduced the concept of "hypersomnolence disorder," a syndrome that associates excessive daytime or nighttime sleep, impaired vigilance, or sleep inertia, not due to nighttime sleep disorders, poor sleep hygiene, narcolepsy, and not entirely explained by a medical or mental disorder (APA, 2013; Ohayon, Dauvilliers, & Reynolds, 2012). The diagnostic criteria of the hypersomnolence disorder may overlap with those of IH and NT2 diagnoses in the third edition of the International Classification of Sleep Disorders (ICSD-3; American Academy of Sleep Medicine, 2014).

To our knowledge, little is known about the association between attention, hyperactivity, and EDS symptoms in adult patients with central hypersomnia, especially relative to the different hypersomnia disorders. Similarly, the link between EDS and ADHD symptoms is unclear in adults with ADHD (Bioulac et al., 2015; Ito, Komada, Okajima, & Inoue, 2017; Yoon et al., 2013). It is not known whether ADHD symptoms are the cognitive and behavioral consequences of EDS, or features of an intrinsic disorder related to a dysfunction in the arousal mechanisms. We first hypothesized on a high frequency of ADHD-like symptoms in patients with primary diagnosis of central hypersomnia together with a high frequency of EDS in patients with primary diagnosis of ADHD. We also hypothesized a clinical overlap between hypersomnia patients with a comorbid formal ADHD diagnosis, and ADHD patients with subsequent hypersomnolence disorder diagnosis.

We thus performed a cross-sectional study to assess the frequency, phenotype, age at onset and relationship of daytime sleepiness, attention and hyperactivity symptoms in two clinical adult populations of drug-free patients with a primary diagnosis of ADHD or central hypersomnia. We first assessed (a) ADHD-like symptoms and formal ADHD diagnosis in adult patients with central hypersomnia and (b) sleepiness symptoms and formal hypersomnolence disorder diagnosis in adults with ADHD. We further compared the clinical characteristics of central hypersomnia patients with formal ADHD diagnosis, and ADHD patients with comorbid hypersomnolence disorder.

Method

Patients

From August 2012 to April 2015, 200 consecutive drug-free adults were included in this study. We recruited 100 patients with a primary diagnosis of central hypersomnia (32 NT1, 28 NT2, and 40 IH) and 100 patients with a primary diagnosis of ADHD respectively referred to the national reference center for narcolepsy and the adult ADHD outpatient clinic of the department of neurology of Montpellier, France.

All patients with ADHD were diagnosed according to the *DSM-5* ADHD criteria using a standardized face-to-face clinical interview (APA, 2013). All ADHD patients participated to the study only few days to weeks after being diagnosed and thus before the initiation of any stimulant medication. They were all psychostimulant-naive at the time of the study.

All patients with central hypersomnia underwent one-night PSG followed the next day by the multiple sleep latency test (MSLT) and, if required, a prolonged continuous PSG to diagnose a central disorder of hypersomnolence on the basis of the ICSD-3 criteria (American Academy of Sleep Medicine, 2014). Thirty-two patients with NT1 were diagnosed based on EDS, a history of clear-cut cataplexy and mean MSLT latency ≤8 min with ≥2 sleep onset REM periods (SOREMPs) or CSF hypocretin-1 deficiency (≤110 pg/mL). Twenty-eight patients with NT2 were diagnosed based on EDS, a mean MSLT latency ≤8 min with ≥2 SOREMPs, no cataplexy, normal CSF hypocretin-1 level, if performed. Forty patients with IH were diagnosed based on EDS, normal polysomnography, mean MSLT latency ≤8 min with <2 SOREMPs, or total sleep time ≥11/24 hr on long-term polysomnography (recorded in 27 patients), and normal CSF hypocretin-1 level, if available. CSF hypocretin-1 levels were measured in 43 patients (three IH, 25 NT1, and 15 NT2) to confirm the diagnosis. Two patients (one with NT1 and one with NT2) had severe obstructive sleep apnea syndrome defined as an apnea/hypopnea index above 30/hr. Sixty-four patients with central hypersomnia were treatment-naive at the time of the study, and 36 (nine IH, 18 NT1, and nine NT2) were drug-free (no psychostimulants or anti-cataplectic drugs) for at least 2 weeks prior to the evaluation.

All patients participated in face-to-face standardized clinical interviews to evaluate hypersomnolence and associated symptoms, and ADHD-like symptoms. Participants also completed a battery of standardized questionnaires on ADHD and sleepiness (Figure 1). Participants signed a written informed consent for this study, which was approved by the local research scientific committee.

ADHD Evaluation

All patients underwent a structured interview on ADHD (Diagnostic Interview for ADHD in adults [DIVA-2], available on http://www.divacenter.eu/DIVA.aspx), with experimented clinicians (R.L., L.C., M.G.), to assess the presence of 18 symptoms and the related impairment in childhood (primary school, age 6-12 years, mostly based on informant and school reports) and currently (Kooij & Francken, 2010). The DIVA-2 is a reliable tool for assessing and diagnosing ADHD with an excellent concurrent validity (Ramos-Quiroga et al., 2016). For this study, the DIVA-2 was slightly modified to fulfill the

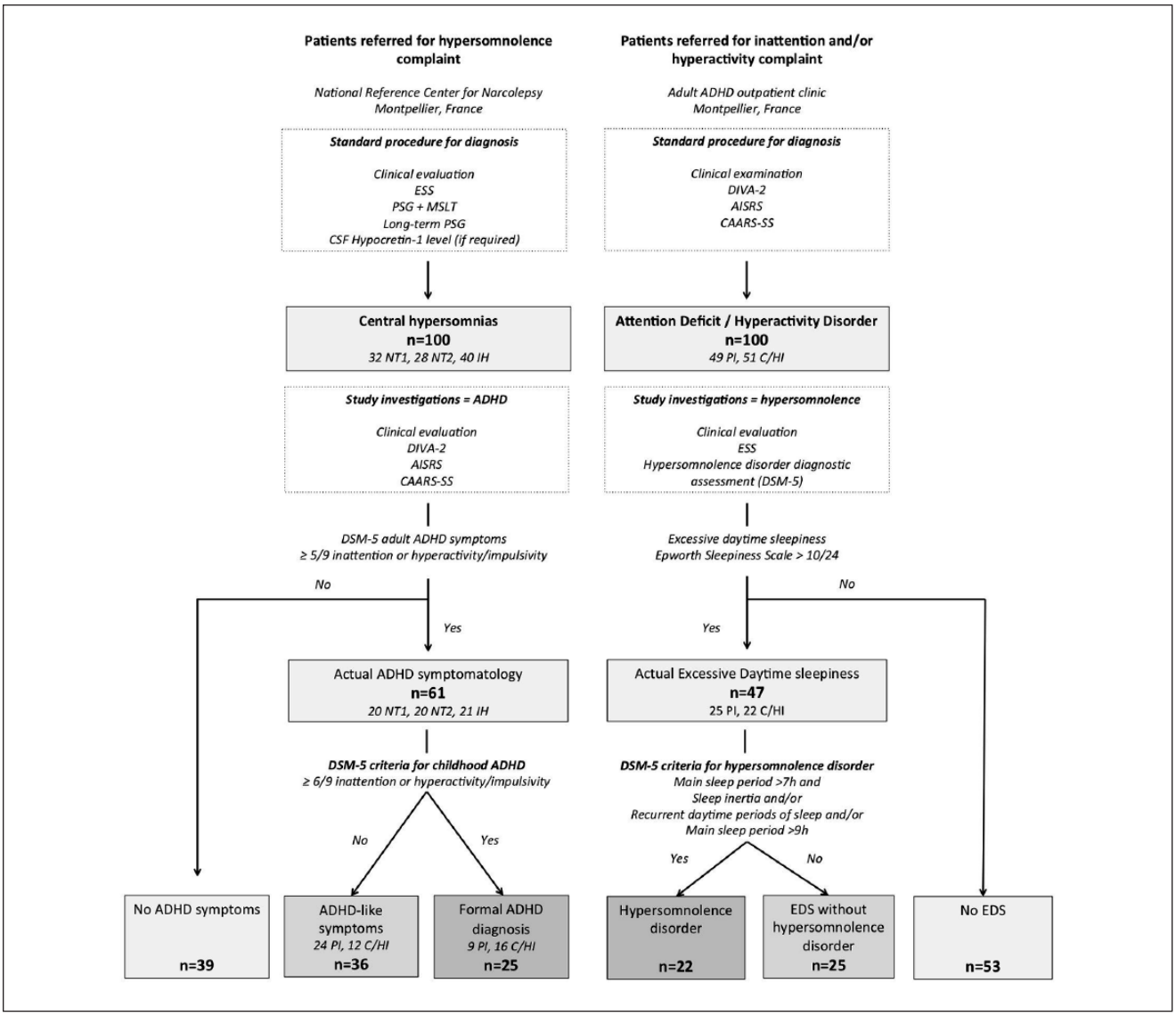

Figure 1. Study flowchart.

Note. ESS = Epworth Sleepiness Scale; PSG = polysomnographic recordings; MSLT = multiple sleep latency test; CSF = cerebrospinal fluid; DIVA = Diagnostic Interview for ADHD in adults; AISRS = ADHD Investigator Rating Scale; CAARS-SS = Conners' Adult ADHD Rating Scale–Self-Report; NT = narcolepsy type; IH = idiopathic hypersomnia; C = combined; HI = hyperactive–impulsive; *DSM-5 = Diagnostic and Statistical Manual of Mental Disorders* (5th ed.); EDS = excessive daytime sleepiness; PI = predominantly inattentive.

recent *DSM-5* criteria for adult ADHD (APA, 2013). The formal *ADHD diagnosis* was made if they had ≥five symptoms of inattention or hyperactivity–impulsivity in adulthood and ≥six before the age of 12 years, with significant impairment in at least two areas of daily life during the last 6 months prior to the interview and in childhood. Based on the *DSM-5* criteria, three ADHD clinical presentations were defined at the time of the interview: (a) predominantly inattentive (ADHD-PI), in the presence of at least five inattention symptoms and fewer than five hyperactive–impulsive symptoms; (b) predominantly hyperactive–impulsive (ADHD-HI), requiring at least five hyperactivity–impulsivity symptoms and fewer than five inattention symptoms; and (c) combined (ADHD-C), when at least five inattention and five hyperactive–impulsive symptoms were reported (APA, 2013).

The severity of the current ADHD symptomatology was assessed with the Conners' Adult ADHD Rating Scale–Self-Report: Short Version (CAARS-S:S) that includes 26 items rated from 0 (*not at all*, never) to 3 (*very much*, very frequently; Conners, Erhardt, & Sparrow, 1999). An overall ADHD index can be computed. The raw indexes were transformed into *t* scores based on age and sex norms. Participants were also asked to report on possible ADHD familial history (first and second degree).

Patients with a primary diagnosis of central hypersomnia with significant ADHD symptoms occurring before the age of 12 years were classified as having formal *ADHD diagnosis* while those with ADHD onset after the age of 12 years were classified as *ADHD-like symptoms* only.

Hypersomnolence Evaluation

All patients completed the *Epworth Sleepiness Scale* (ESS) and a score above 10/24 indicated EDS (Johns, 1991). Age of EDS onset, family history of daytime sleepiness (first and second degree), presence of actual hypnagogic/hypnopompic hallucinations, and sleep paralysis were systematically recorded. A structured interview recorded habitual sleep patterns on weekdays and weekends for the past 2 weeks prior to the interview. The total sleep time per 24 hr was calculated for each patient. The clinical interview also assessed symptoms related to obstructive sleep-disordered breathing (i.e., EDS, loud snoring, episodes of breathing cessation during sleep witnessed by another person, awakening with a dry mouth or sore throat and morning headache); however, no polysomnographic/polygraphic assessment was performed in ADHD patients at time of study to confirm such diagnosis.

Only patients with a primary diagnosis of central hypersomnia had a PSG followed by MSLT. In contrast, patients with ADHD and an ESS score >10 underwent a structured clinical interview to diagnose a hypersomnolence disorder, according to the *DSM-5* (APA, 2013; Ohayon et al., 2012). The diagnosis of hypersomnolence disorder required (a) self-reported EDS for at least 3 months and at least 3 times per week, despite a main sleep period of at least 7 hr and (b) at least one of the following symptoms: (1) periods of irresistible need to sleep or recurrent naps within the same day, (2) a nonrestorative prolonged main sleep episode of more than 9 hr per day; and (3) sleep inertia (i.e., need of multiple alarm clocks to wake up, or need to be pulled out of bed by others, or remaining drowsy for at least 1 hr, this symptom occurring almost every day).

Statistical Analysis

Percentages were used to describe categorical variables and medians and ranges for quantitative variables, which were mostly skewed based on the Shapiro–Wilk test results. Demographic data, sleepiness, and ADHD characteristics were compared between groups using logistic regression models and among three groups using multinomial regression models. When comparisons were statistically significant, two-by-two comparisons were performed using the Bonferroni correction.

For each analysis, demographic variables associated with groups in univariate analysis with $p < .10$ were included in the logistic regression models or multinomial regression models as potential confounding factors. Spearman's rank order correlations were performed to determine associations between continuous variables. The significance level was set at $p < .05$. Analyses were performed using SAS (version 9.4; SAS Inc, Cary, North Carolina).

Results

Clinical Characteristics and ADHD Symptoms in Patients With Central Hypersomnia

Among patients with central hypersomnia ($n = 100$; median age: 27 years; range, 17-66), 41 were males and 36 overweight, body mass index (BMI) > 25 kg/m^2. The median ESS score was 17, 15, and 16 for patients with NT1, NT2, and IH, respectively. The median age at EDS onset was 18.0 years (range, 3.0-64.0), including five subjects with onset before the age of 12 years. Thirty-six subjects reported current hypnagogic hallucinations and 25 sleep paralysis. The median total sleep time was 517.5 min (range, 360-1,140) during weekdays and 645 min (range, 360-1,140) during weekends. Fourteen subjects reported a positive family history of EDS.

Sixty-one patients had ≥5/9 inattention or hyperactivity/impulsivity symptoms at the time of study (Table 1). The CAARS-ADHD index median score was 58 (range, 36-87). In 25 patients, ADHD symptoms started before the age of 12 years, thus fulfilling the *DSM 5* criteria for *ADHD diagnosis* (ADHD-C/HI for 64%: three patients with NT1, eight with NT2, and five with IH; ADHD-PI for 36%). In the other 36 patients, ADHD-like symptoms (i.e., 33% ADHD-C/HI and 67% ADHD-PI-like symptoms) started after the age of 12 years and always after EDS onset (median delay: 3 months [range: 0-360]; Table 1, Figure 1).

Comparison of patients with central hypersomnia with *ADHD diagnosis, ADHD-like symptoms*, or without ADHD symptoms did not show any significant characteristic differences for the demographic data (age, sex, BMI), disease phenotype (age at disease onset, hallucinations, sleep paralysis, and family history of sleepiness) and severity (ESS, MSL, number of SOREMPs, and total sleep duration; Table 1). Conversely, ADHD characteristics were significantly different in the three groups with patients with *ADHD diagnosis* having higher CAARS-ADHD index scores, and more frequently a positive family history of ADHD. In patients with *ADHD-like symptoms*, the CAARS-ADHD index tended to be positively correlated with the ESS score ($r = .33$; $p = .06$) but not in patients with formal ADHD diagnosis.

Comparisons of patients with NT1 ($n = 32$) and patients with non-cataplectic hypersomnia (i.e., NT2 and IH, $n = 68$) showed that patients with NT1 were more frequently classified as *ADHD-like symptoms*, although this comparison was not significant after adjustment for age (Table 2). CAARS-ADHD index and ADHD presentation did not differ significantly between groups.

Table 1. Comparisons of Demographic Data, Sleepiness, and ADHD Characteristics in Patients With a Primary Diagnosis of Central Hypersomnia and Formal ADHD Diagnosis, ADHD-Like Symptoms, or Without ADHD Symptoms.

	No ADHD symptoms (1) *n* = 39		ADHD-like symptoms (2) *n* = 36		ADHD diagnosis (3) *n* = 25			(3) vs. (1)	(2+3) vs. (1)	(2) vs. (3)
Variable	*n*	%	*n*	%	*n*	%	Global *p*	*p*	*p*	*p*
Demographic data										
Sex, male	16	41.03	11	44.00	14	38.89	.92	—	—	—
Age (years)[a]	29.00 [17.00-55.00]		24.00 [17.00-54.00]		28.00 [17.00-66.00]		.26	—	—	—
BMI (kg/m^2)[a]	22.21 [15.92-34.29]		22.20 [17.97-34.63]		24.49 [16.56-36.02]		.33	—	—	—
Sleepiness characteristics										
ESS[a]	16 [9-24]		16 [7-22]		17 [7-23]		.28	—	—	—
Mean sleep latency (min)[a]	6.60 [1.20-10.70]		6.00 [3.20-9.20]		5.70 [0.60-11.00]		.90	—	—	—
SOREMP[a]	2 [0-6]		2 [0-6]		2.5 [0-6]		.48	—	—	—
Age at EDS onset (years)[a]	20.00 [8.00-45.00]		16.00 [5.00-49.00]		18.00 [3.00-64.00]		.34	—	—	—
Sleep paralysis	11	28.95	5	20.83	9	25.71	.78	—	—	—
Hypnagogic hallucinations	11	28.95	8	33.33	17	48.57	.21	—	—	—
Family history of sleepiness	7	17.95	6	24.00	1	2.78	.10	—	—	—
Weekend total sleep time (min)[a]	660.00 [360.00-930.00]		610.00 [450.00-810.00]		630.00 [390.00-1,140.00]		.46	—	—	—
Weekday total sleep time (min)[a]	525.00 [360.00-780.00]		505.00 [420.00-810.00]		532.50 [360.00-1,140.00]		.65	—	—	—
ADHD characteristics										
CAARS-ADHD Index[a]	49.00 [32.00-66.00]		54.00 [36.00-74.00]		62.50 [40.00-87.00]		.0001	.0009	.03	.02
ADHD presentation										
ADHD-PI	—	—	24	66.67	9	36.00	.02			
ADHD-C/HI	—	—	12	33.33	16	64.00				
Family history of ADHD	5	12.82	3	8.33	10	40.00	.008	.06	.99	.02

Note. BMI = body mass index; ESS = Epworth Sleepiness Scale; SOREMP = sleep onset REM periods; EDS = excessive daytime sleepiness; CAARS = Conners' Adult ADHD Rating Scale; PI = predominantly inattentive; C = combined; HI = hyperactive–impulsive.

[a]Continuous variables are expressed as medians (minimum value-maximum value).

Table 2. Comparisons of Demographic Data, Sleepiness, and ADHD Characteristics in Patients With NT1 or NT2/IH.

	NT2/IH $n = 68$		NT1 $n = 32$			
Variable	*n*	%	*n*	%	*p*	*p*[a]
Demographic data						
Sex, male	27	39.71	14	43.75	.70	—
Age (years)[b]	25.00 [17.00-54.00]		32.00 [17.00-66.00]		.002	—
BMI (kg/m^2)[b]	22.21 [15.92-34.63]		25.92 [17.06-36.02]		.12	—
Sleepiness characteristics						
ESS[b]	16.00 [7.00-23.00]		17.00 [9.00-24.00]		.009	.04
Mean Sleep Latency (min)[b]	6.20 [0.60-10.70]		5.25 [1.20-11.00]		.08	.04
SOREMP[b]	0.00 [0.00-5.00]		4.00 [2.00-6.00]		<.0001	<.0001
Age at EDS onset (years)[b]	18.00 [3.00-49.00]		23.00 [12.00-64.00]		.02	—
Sleep paralysis	7	10.77	18	56.25	<.0001	<.0001
Hypnagogic hallucinations	12	18.46	24	75.00	<.0001	<.0001
Family history of sleepiness	11	16.18	3	9.38	.37	.47
Weekend total sleep time (min)[b]	660.00 [360.00-1,140.00]		585.00 [375.00-900.00]		.02	.16
Weekday total sleep time (min)[b]	525.00 [360.00-1,140.00]		510.00 [360.00-780.00]		.62	.99
ADHD characteristics						
CAARS-ADHD Index[b]	54.00 [32.00-87.00]		57.00 [33.00-79.00]		.67	.66
Family history of ADHD	15	22.06	3	9.38	.14	.09
Age at ADHD onset (years)[b]	10.50 [3.00-48.00]		19.00 [5.00-64.00]		.005	.10
ADHD diagnosis	21	30.88	4	12.50	.06	.12
ADHD-like symptoms	20	29.41	16	50.00	.05	.10
ADHD presentation						
ADHD-PI	23	56.10	10	50.00	.65	.78
ADHD-C/HI	18	43.90	10	50.00		

Note. NT1 = narcolepsy type 1; NT2 = narcolepsy type 2; IH = idiopathic hypersomnia; BMI = body mass index; ESS = Epworth Sleepiness Scale; SOREMP = sleep onset REM periods; EDS = excessive daytime sleepiness; CAARS = Conners' Adult ADHD Rating Scale; PI = predominantly inattentive; C = combined; HI = hyperactive–impulsive.
[a]Adjustment for age.
[b]Continuous variables are expressed as medians (minimum value-maximum value).

Clinical Characteristics and EDS in Patients With ADHD

Among patients with primary ADHD ($n = 100$; median age: 32.0 years; range, 17-67), 41 were males and 36 were overweight. The median age of ADHD onset was 6.0 years (range, 4.0-12.0). ADHD-PI was diagnosed in 49 patients, ADHD-HI in one, and ADHD-C in 50. A positive family history of ADHD was found in 57 patients. Twenty-two subjects had hypnagogic hallucinations, 12 sleep paralysis, and none cataplexy. The median ESS score was 10 (range, 0-20), and 47 patients had an ESS score >10 (Figure 1). The median total sleep time was 450 min (range, 270-780) during weekdays and 516 min (range, 240-780) during weekends. Twelve patients reported more than 660 min of total sleeping time during weekends.

Twenty-two patients (six males) with EDS fulfilled the *DSM-5* criteria for *hypersomnolence disorder* with the following characteristics: nonrestorative prolonged main sleep period longer than 9 hr ($n = 18$), sleep inertia ($n = 11$), and recurrent naps ($n = 3$). In contrast, 25 patients with ADHD and EDS had poor sleep hygiene, short nighttime sleep duration (<7 hr, $n = 14$), restless leg syndrome ($n = 6$), and symptoms potentially related to the presence of sleep-disordered breathing ($n = 2$).

Comparison of nonsleepy-, and sleepy-ADHD patients with or without *hypersomnolence disorder* showed that patients with *hypersomnolence disorder* were younger, with higher total sleep time during weekdays and weekends, and tendency for higher frequency of hypnagogic hallucinations and sleep paralysis (Table 3). No correlations were found between the sleepiness parameters (ESS, total sleep time) in all patients with ADHD or categorized as different subgroups according to EDS phenotypes.

Discussion

We examined the relationships between sleepiness, inattention, and hyperactivity symptoms in two large clinical samples of adults with a primary diagnosis of central hypersomnia or ADHD. We found a clinically significant ADHD symptomatology in 61% of patients with central

Table 3. Comparisons of Demographic Data, Sleepiness, and ADHD Characteristics in Patients With Primary ADHD With Isolated EDS, Hypersomnolence Disorder, or Without EDS.

	No EDS $n = 53$		Hypersomnolence disorder $n = 22$		EDS without hypersomnolence disorder $n = 25$		
Variable	*n*	%	*n*	%	*n*	%	*p*
Demographic data							
Sex, male	25	47.17	6	27.27	10	40.00	.29
Age (years)[a]	31.00 [17.00-57.00]		27.50 [18.00-56.00]		36.00 [17.00-67.00]		.03
BMI (kg/m^2)[a]	22.50 [16.41-32.53]		20.87 [19.15-31.51]		21.62 [17.80-29.01]		.66
Sleepiness characteristics							
ESS	6.00 [0.00-10.00]		14.00 [11.00-20.00]		14.00 [11.00-19.00]		NA
Sleep paralysis	7	13.73	5	22.73	0	0.00	NA
Hypnagogic hallucinations	9	17.65	9	40.91	4	16.67	.08
Family history of sleepiness	2	16.67	7	31.82	8	38.10	.46
Age at EDS onset (years)			8.00 [3.00-48.00]		15.00 [3.00-50.00]		.27
Weekend total sleep time (min)[a]	480.00 [240.00-688.00]		650.00 [510.00-780.00]		480.00 [350.00-630.00]		<.0001
Weekday total sleep time (min)[a]	435.00 [270.00-688.00]		620.00 [420.00-780.00]		410.00 [300.00-540.00]		<.0001
ADHD characteristics							
CAARS-ADHD Index[a]	72.00 [59.00-90.00]		76.00 [58.00-90.00]		74.00 [63.00-90.00]		.36
Age at ADHD onset (years)[a]	6.00 [4.00-12.00]		6.00 [4.00-10.00]		6.00 [4.00-12.00]		.51
Family history of ADHD	35	68.63	10	45.45	12	48.00	.09
ADHD presentation							
ADHD-PI	24	45.28	11	50.00	14	56.00	.67
ADHD-C/HI	29	54.72	11	50.00	11	44.00	

Note. EDS = excessive daytime sleepiness; BMI = body mass index; ESS = Epworth Sleepiness Scale; NA = test not applicable; CAARS = Conners' Adult ADHD Rating Scale; PI = predominantly inattentive; C = combined; HI = hyperactive–impulsive.
[a]Continuous variables are expressed as medians (minimum value-maximum value).

hypersomnia and detected EDS in 47% of patients with primary diagnosis of ADHD, which suggest major overlaps between EDS, inattention, and hyperactivity symptoms.

Frequent *ADHD diagnosis* and *ADHD-like symptoms* were identified in patients with primary central hypersomnia. This high ADHD symptoms frequency was already reported in children and adults with hypersomnia (Bayard, Abril, et al., 2011; Bayard, Croisier Langenier, Cochen De Cock, Scholz, & Dauvilliers, 2011; Bayard, Langenier, & Dauvilliers, 2013; Filardi et al., 2017; Lecendreux et al., 2015; Naumann, Bellebaum, & Daum, 2006; Rieger, Mayer, & Gauggel, 2003; Vernet, Leu-Semenescu, Buzare, & Arnulf, 2010; Zamarian et al., 2015), but without taking in account the diagnosis of ADHD according to the *DSM-5* criteria. Significant *ADHD-like symptoms* were found in the present study in one third of patients in whom ADHD symptoms started after EDS onset and after the age of 12 years, which corresponds to the recently extended age of onset (from seven to 12) in the *DSM-5* (APA, 2013). The diagnosis of ADHD could not be formally established in these patients due to the absence of retrospective clinically significant ADHD symptomatology in childhood. A short delay (within a year) between the onset of sleepiness and ADHD symptoms was reported in 63.9% with a borderline positive correlation between ADHD severity and ESS. The main ADHD symptom in these patients was inattention, and two third of them had ADHD-PI. These results suggest that ADHD-like symptoms are the consequences of EDS in this subpopulation. Accordingly, in our recent study on child narcolepsy, ADHD symptom severity was associated with increased levels of EDS (Lecendreux et al., 2015). Similar results were recently observed in adults with NT1, but not in NT2 patients (Filardi et al., 2017).

We also found that 25% of patients with central hypersomnia (mainly patients with NT2 and IH) fulfilled the *DSM-5* criteria for ADHD, with a clear childhood history of ADHD, before the onset of EDS. For these patients, ADHD clinical characteristics were similar to those observed in clinical samples of adults with primary diagnosis of ADHD (Halmoy, Fasmer, Gillberg, & Haavik, 2009; Yoon et al., 2013). Patients with hypersomnia comorbid with a diagnosis of ADHD had more severe ADHD symptomatology, more often ADHD-C/HI presentation and a family history of ADHD compared with patients with ADHD-like symptoms. Moreover, no correlations were found between the severity of ADHD symptoms and EDS parameters in this subpopulation.

We confirmed here the high frequency of EDS (47%) in adults with primary diagnosis of ADHD (Ito et al., 2017). Almost half of them reported poor sleep hygiene, short nighttime sleep duration (<7 hr per night), or a primary sleep disorder, without any association with the ADHD presentation. Along this line, EDS may be the consequence of chronic sleep deprivation or impaired sleep quality in these patients. On the contrary, 22 patients with ADHD (50% of ADHD-PI) fulfilled the *DSM-5* criteria for hypersomnolence disorder, characterized by EDS, long and undisturbed nighttime sleep. Our results, in line with recent findings in adolescents with ADHD reporting high frequency of EDS despite low rates of specific sleep disorders (Langberg et al., 2017), may suggest that inattention, hyperactivity, impulsivity, and EDS may be intrinsic features of a similar dysfunction in the arousal mechanisms in patients with ADHD (Strauß et al., 2018).

Taken together, our results suggest that EDS and ADHD symptoms often coexist in patients with primary diagnosis of ADHD or central hypersomnia. We propose that ADHD symptoms (mainly inattention and with adulthood onset) would be the consequences of EDS in patients with central hypersomnia, and that EDS would be caused by poor nighttime sleep quality in patients with ADHD. However, in another subgroup of patients (25% of patients referred for hypersomnia and 22% of patients referred for ADHD), ADHD and hypersomnolence (day and night) symptoms were severe and with childhood age at onset and may be intrinsic features of a similar neurodevelopmental dysfunction. Accordingly, hypersomnolence and ADHD characteristics (i.e., ESS, family history of sleepiness or ADHD, age at EDS or ADHD onset) were not different between patients with a primary diagnosis of ADHD and comorbid hypersomnolence disorder, and patients with a primary diagnosis of hypersomnia (i.e., NT2 and IH) and comorbid ADHD diagnosis (data not shown). Altogether our results may raise the question of a neurodevelopmental component in IH and NT2, as currently conceptualized for ADHD.

Several limitations should be taken into consideration when interpreting our results. First, this explorative study is cross-sectional and did not include a normal control group. Second, although 100 well-characterized patients with central hypersomnia were included, the sample size was too limited to assess the frequency, phenotype, and relationships of each symptom in the three subcategories (NT1, NT2, and IH). Third, patients with ADHD were recruited in an ADHD outpatient clinic, a setting where patients are likely to be more severely ill, thus limiting the generalization of our findings. Fourth, we did not assess psychiatric comorbidities (i.e., mood and anxiety disturbances), which are highly prevalent in both ADHD and central hypersomnia and could represent significant determinants of the association between EDS and ADHD symptoms (Bayard, Croisier, et al., 2011; Dauvilliers, Lopez, Ohayon, & Bayard, 2013; Kessler et al., 2006; Zamarian et al., 2015). Finally, both ADHD and sleepiness measures were based on patient report. We did not perform neuropsychological assessment to characterize attentional performances and executive functions in patients with central hypersomnia. The hypersomnolence disorder is a clinical-based diagnosis (APA, 2013; Ohayon et al., 2012), and we did not confirm that ADHD patients with EDS fulfilled the central hypersomnia criteria with objective measures such as polysomnography and MSLT as defined in ICSD-3 (American Academy of Sleep Medicine, 2014). Further studies are required to objectively measure hypersomnolence in patients with ADHD to better define the potential association with NT2 or IH.

In conclusion, the nature of the links between EDS, inattention, and hyperactivity appears to be complex that may involve either a cause–effect relationship or intrinsic features of a similar neurodevelopmental dysfunction. The hypersomnolence disorder may thus co-occur with ADHD that warrants a specific clinical attention and treatment.

Authors' Note

R.L. and Y.D. conceived and designed the study. R.L., L.C., M.G., and Y.D. were involved in data collection. R.L., J.-A.M., I.J., and Y.D. were involved in data analysis and interpretation. I.J. supervised the statistical analysis. R.L., J.-A.M., and Y.D. wrote the first draft of the report. All authors reviewed and commented on the draft, and approved the final submission.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: R.L. has received funds for speaking with UCB Pharma and Shire. Y.D. has received funds for speaking and board engagements with UCB Pharma, Jazz, GSK, Flamel, and Bioprojet.

References

American Academy of Sleep Medicine. (2014). *International Classification of Sleep Disorders-Third Edition (ICSD-3)*. Darien, IL: *American Academy of Sleep Medicine*.

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Andlauer, O., Moore, H., IV., Hong, S.-C., Dauvilliers, Y., Kanbayashi, T., Nishino, S., . . . Mignot, E. (2012). Predictors of hypocretin (orexin) deficiency in narcolepsy without cataplexy. *Sleep*, *35*, 1247-1255.

Baumann, C. R., Mignot, E., Lammers, G. J., Overeem, S., Arnulf, I., Rye, D., . . . Scammell, T. E. (2014). Challenges in diagnosing narcolepsy without cataplexy: A consensus statement. *Sleep*, *37*, 1035-1042.

Bayard, S., Abril, B., Yu, H., Cholz, S., Carlander, B., & Dauvilliers, Y. (2011). Decision making in narcolepsy with cataplexy. *Sleep*, *34*, 99-104.

Bayard, S., Croisier Langenier, M., Cochen De Cock, V., Scholz, S., & Dauvilliers, Y. (2011). Executive control of attention in narcolepsy. *PLoS ONE*, *7*(4), Article e33525.

Bayard, S., Langenier, M. C., & Dauvilliers, Y. (2013). Effect of psychostimulants on impulsivity and risk taking in narcolepsy with cataplexy. *Sleep*, *36*, 1335-1340.

Billiard, M., & Sonka, K. (2016). Idiopathic hypersomnia. *Sleep Medicine Reviews*, *29*, 23-33.

Bioulac, S., Chaufton, C., Taillard, J., Claret, A., Sagaspe, P., Fabrigoule, C., . . . Philip, P. (2015). Excessive daytime sleepiness in adult patients with ADHD as measured by the Maintenance of Wakefulness Test, an electrophysiologic measure. *The Journal of Clinical Psychiatry*, *76*, 943-948. doi:10.4088/JCP.14m09087

Conners, C. K., Erhardt, D., & Sparrow, E. (1999). *Conners' Adult ADHD Rating Scales (CAARS)*. North Tonawanda, NY: Multi-Health Systems.

Dauvilliers, Y., Arnulf, I., & Mignot, E. (2007). Narcolepsy with cataplexy. *The Lancet*, *369*, 499-511.

Dauvilliers, Y., Baumann, C. R., Carlander, B., Bischof, M., Blatter, T., Lecendreux, M., . . . Bassetti, C. (2003). CSF hypocretin-1 levels in narcolepsy, Kleine-Levin syndrome, and other hypersomnias and neurological conditions. *Journal of Neurology, Neurosurgery, and Psychiatry*, *74*, 1667-1673.

Dauvilliers, Y., Evangelista, E., Lopez, R., Barateau, L., Jaussent, I., Cens, T., . . . Pierre, C. (2016). Absence of GABA-A receptor potentiation in central hypersomnolence disorders. *Annals of Neurology*, *80*, 259-268.

Dauvilliers, Y., Lopez, R., Ohayon, M., & Bayard, S. (2013). Hypersomnia and depressive symptoms: Methodological and clinical aspects. *BMC Medicine*, *11*, Article 78.

Filardi, M., Pizza, F., Tonetti, L., Antelmi, E., Natale, V., & Plazzi, G. (2017). Attention impairments and ADHD symptoms in adult narcoleptic patients with and without hypocretin deficiency. *PLoS ONE*, *12*(8), Article e0182085.

Halmoy, A., Fasmer, O. B., Gillberg, C., & Haavik, J. (2009). Occupational outcome in adult ADHD: Impact of symptom profile, comorbid psychiatric problems, and treatment: A cross-sectional study of 414 clinically diagnosed adult ADHD patients. *Journal of Attention Disorders*, *13*, 175-187.

Ito, W., Komada, Y., Okajima, I., & Inoue, Y. (2017). Excessive daytime sleepiness in adults with possible attention deficit/hyperactivity disorder (ADHD): A web-based cross-sectional study. *Sleep Medicine*, *32*, 4-9.

Johns, M. (1991). A new method for measuring daytime sleepiness: The Epworth Sleepiness Scale. *Sleep*, *14*, 540-545.

Kessler, R. C., Adler, L., Barkley, R., Biederman, J., Conners, C. K., Demler, O., . . . Zaslavsky, A. M. (2006). The prevalence and correlates of adult ADHD in the United States: Results from the National Comorbidity Survey Replication. American Journal of Psychiatry, *163*, 716-723.

Kooij, J. J. S., & Francken, M. H. (2010). Diagnostic interview for ADHD in adults 2.0 (DIVA 2.0). In Springer Science & Business Media (Ed.), *Adult ADHD: Diagnostic assessment and treatment* (pp. 243-247). Amsterdam, The Netherlands: Pearson Assessment and Information BV.

Kornum, B. R., Knudsen, S., Ollila, H. M., Pizza, F., Jennum, P., Dauvilliers, Y., & Overeem, S. (2017). Narcolepsy. *Nature Reviews Disease Primers*, *3*, Article 16100.

Langberg, J. M., Molitor, S. J., Oddo, L. E., Eadeh, H. M., Dvorsky, M. R., & Becker, S. P. (2017). Prevalence, patterns, and predictors of sleep problems and daytime sleepiness in young adolescents with ADHD. *Journal of Attention Disorders*. Advance online publication. doi:10.1177/1087054717690810

Lecendreux, M., Lavault, S., Lopez, R., Inocente, C. O., Konofal, E., Cortese, S., . . . Dauvilliers, Y. (2015). Attention-deficit/hyperactivity disorder (ADHD) symptoms in pediatric narcolepsy: A cross-sectional study. *Sleep*, *38*, 1285-1295.

Lopez, R., Doukkali, A., Barateau, L., Evangelista, E., Chenini, S., Jaussent, I., & Dauvilliers, Y. (2017). Test-retest reliability of the multiple sleep latency test in central disorders of hypersomnolence. *Sleep*, *40*(12), Article zsx164.

Modestino, E. J., & Winchester, J. (2013). A retrospective survey of childhood ADHD symptomatology among adult narcoleptics. *Journal of Attention Disorders*, *17*, 574-582.

Naumann, A., Bellebaum, C., & Daum, I. (2006). Cognitive deficits in narcolepsy. *Journal of Sleep Research*, *15*, 329-338.

Ohayon, M. M. (2013). Narcolepsy is complicated by high medical and psychiatric comorbidities: A comparison with the general population. *Sleep Medicine*, *14*, 488-492.

Ohayon, M. M., Dauvilliers, Y., & Reynolds, C. F. (2012). Operational definitions and algorithms for excessive sleepiness in the general population: Implications for DSM-5 nosology. *Archives of General Psychiatry*, *69*, 71-79.

Oosterloo, M., Lammers, G. J., Overeem, S., de Noord, I., & Kooij, J. J. (2006). Possible confusion between primary hypersomnia and adult attention-deficit/hyperactivity disorder. *Psychiatry Research*, *143*, 293-297.

Ramos-Quiroga, J. A., Nasillo, V., Richarte, V., Corrales, M., Palma, F., Ibáñez, P., . . . Kooij, J. J. (2016). Criteria and concurrent validity of DIVA 2.0: A semi-structured diagnostic interview for adult ADHD. *Journal of Attention Disorders*. Advance online publication. doi:10.1177/1087054716646451

Rieger, M., Mayer, G., & Gauggel, S. (2003). Attention deficits in patients with narcolepsy. *Sleep*, *26*, 36-43.

Strauß, M., Ulke, C., Paucke, M., Huang, J., Mauche, N., Sander, C., . . . Hegerl, U. (2018). Brain arousal regulation in adults with attention-deficit/hyperactivity disorder (ADHD). *Psychiatry Research*, *261*, 102-108.

Surman, C. B., Adamson, J. J., Petty, C., Biederman, J., Kenealy, D. C., Levine, M., . . . Faraone, S. V. (2009). Association between attention-deficit/hyperactivity disorder and sleep impairment in adulthood: Evidence from a large controlled study. *The Journal of Clinical Psychiatry*, *70*, 1523-1529.

Vernet, C., Leu-Semenescu, S., Buzare, M. A., & Arnulf, I. (2010). Subjective symptoms in idiopathic hypersomnia: Beyond excessive sleepiness. *Journal of Sleep Research*, *19*, 525-534.

Virring, A., Lambek, R., Thomsen, P. H., Møller, L. R., & Jennum, P. J. (2016). Disturbed sleep in attention-deficit hyperactivity disorder (ADHD) is not a question of psychiatric comorbidity or ADHD presentation. *Journal of Sleep Research*, *25*, 333-340.

Walters, A. S., Silvestri, R., Zucconi, M., Chandrashekariah, R., & Konofal, E. (2008). Review of the possible relationship and hypothetical links between attention deficit hyperactivity disorder (ADHD) and the simple sleep related movement

disorders, parasomnias, hypersomnias, and circadian rhythm disorders. *Journal of Clinical Sleep Medicine*, *4*, 591-600.

Yoon, S., Jain, U., & Shapiro, C. (2013). Sleep and daytime function in adults with attention-deficit/hyperactivity disorder: Subtype differences. *Sleep Medicine*, *14*, 648-655.

Zamarian, L., Högl, B., Delazer, M., Hingerl, K., Gabelia, D., Mitterling, T., . . . Frauscher, B. (2015). Subjective deficits of attention, cognition and depression in patients with narcolepsy. *Sleep Medicine*, *16*, 45-51.

Author Biographies

Régis Lopez, MD, PhD, is a psychiatrist at the adult ADHD outpatient clinic of the Department of Neurology in Montpellier, France. He is also a sleep medicine specialist at the sleep disorders unit in Montpellier, France. He has participated in various researches in the area of ADHD and sleep disorders, including hypersomnias and parasomnias.

Jean-Arthur Micoulaud-Franchi, MD, PhD, is specialized in psychiatry, neurophysiology, and sleep medicine in the sleep clinic at Bordeaux University Hospital. He received his PhD degree from Aix-Marseille University. His research addresses the link between neurophysiology, sleep, and health perception in mental disorders at the USR CNRS 3413 SANSPY.

Laura Camodeca, MD, is a psychiatrist specialized in the diagnosis and treatment of adults with ADHD and gerontopsychiatry at Lausanne's university hospital.

Marie Gachet, MD, is a psychiatrist specialized in the diagnosis and treatment of adults with ADHD and bipolar disorder at Montpellier's university hospital.

Isabelle Jaussent, PhD, is a methodologist and epidemiologist specialized in sleep disorders. Her research addresses the link between insomnia, sleepiness, and various aspects of aging in the general population.

Yves Dauvilliers, MD, PhD, is the head of the National Reference Center for Narcolepsy and Idiopathic Hypersomnia at the Montpellier's university hospital. His research addresses the pathophysiology and innovative therapeutics of central disorders of hypersomnolence, and other sleep disorders. He has published several articles and books on these topics.