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Residual sleepiness in obstructive sleep apnoea: phenotype and related symptoms

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ABSTRACT: The characteristics of residual excessive sleepiness (RES), defined by an Epworth score >10 in adequately treated apnoeic patients, are unknown.

40 apnoeic patients, with (n=20) and without (n=20) RES, and 20 healthy controls underwent clinical interviews, cognitive and biological tests, polysomnography, a multiple sleep latency test, and 24-h sleep monitoring.

The marked subjective sleepiness in the RES group (mean ± SD score 16.4 ± 3) contrasted with moderately abnormal objective measures of sleepiness (90% of patients with RES had daytime sleep latencies >8 min). Compared with patients without RES, the patients with RES had more fatigue, lower stage N3 percentages, more periodic leg movements (without arousals), lower mean sleep latencies and longer daytime sleep periods. Most neuropsychological dimensions (morning headaches, memory complaints, spatial memory, inattention, apathy, depression, anxiety and lack of self-confidence) were not different between patients with and without RES, but gradually altered from controls to apnoeic patients without and then with RES.

RES in apnoeic patients differs markedly from sleepiness in central hypersomnia. The association between RES, periodic leg movements, apathy and depressive mood parallels the post-hypoxic lesions in noradrenaline, dopamine and serotonin systems in animals exposed to intermittent hypoxia.

KEYWORDS: Apnoea, continuous positive airway pressure, hypersomnia, obstructive sleep apnoea, residual excessive sleepiness, sleepiness

Excessive daytime sleepiness and cognitive problems are the most frequent symptoms experienced by patients with obstructive sleep apnoea (OSA). Continuous positive airway pressure (CPAP) reduces daytime sleepiness [1, 2] and improves, but does not normalise, the objective measures of sleepiness [2–4]. A minimum of 6% of regular CPAP users experience residual excessive sleepiness (RES) after having their sleep hygiene improved and CPAP adjusted, as well as having had concomitant sleep pathologies (narcolepsy, restless leg syndrome or idiopathic hypersomnia) ruled out [5]. The mechanisms of RES are unknown. Because intermittent hypoxia in animal models damages the arousal systems of the brain [6] and because OSA patients have been exposed to intermittent hypoxia for years before being treated, we raise the question of whether some vulnerable subjects have developed irreversible brain lesions that cause central hypersomnia. There are clinical and neurophysiological markers specific to central hypersomnias (namely narcolepsy and idiopathic hypersomnia). They include a disabling, severe sleepiness despite normal or prolonged (>10 h) night-time sleep, sleep drunkenness (a prolonged and severe confusion upon awakening) without depression or apathy, executive dysfunction and short (<8 min) mean daytime sleep latencies (plus sleep onset in rapid eye movement (REM) periods (SOREMPs) in narcolepsy), which can be better studied using multiple sleep latency tests (MSLTs) and long-term sleep monitoring [7, 8]. We hypothesised that RES would resemble central hypersomnia. In order to test this hypothesis, we extensively studied the clinical, psychiatric and cognitive characteristics and performed polysomnography, MSLT and long-term sleep monitoring in a population of adequately treated OSA patients with RES compared with OSA patients without RES and healthy controls.

For editorial comments see page 7.
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METHODS

Subjects

Over 1 yr, we prospectively selected 25 patients from a series of ~500 patients treated for OSA who were regularly followed at Pitié-Salpêtrière Hospital, Paris, France. They were mostly referred by regional pulmonologists for this problem, after starting and optimising CPAP treatment. They met the following criteria for inclusion: 1) clinical diagnosis of OSA syndrome (including excessive sleepiness) and apnoea/hypopnoea index (AHI) >15 events·h^{-1}; 2) CPAP use on >90% of nights, >6 h·night^{-1} for >6 months, with a residual AHI <5 events·h^{-1} on polysomnography; 3) complaints of daily RES (score on the Epworth sleepiness scale (ESS) >10 out of 24) for >6 months [9]; 4) usual sleep duration normal for age [10] and no extension of sleep during holidays and weekends, with behaviourally induced insufficient sleep syndrome ruled out and a careful check of the CPAP time log; and 5) periodic leg movement-associated arousal index <10 events·h^{-1}. We excluded the patients who had defined causes of RES, including the following: 1) narcolepsy with cataplexy [7]; 2) untreated, severe restless leg syndrome (severity score >20 out of 40) [11, 12]; 3) chronic use of sedative drugs or alcohol; 4) neurological diseases, as determined by a neurological examination and brain magnetic resonance imaging; 5) psychiatric diseases as determined by a psychiatric interview; 6) other medical diseases; and 7) night shift work. Two patients did not speak French fluently enough to undergo the tests and scales, and three patients refused to take part in the study. Eventually, 20 patients with RES completed the study.

20 compliant, nonretired, CPAP-treated OSA patients without RES, matched for age and sex, were recruited from the same department. In addition, 20 healthy, nonretired controls were recruited by advertisement from the general population, matched for sex, with a mean age slightly lower (-5 yrs) than the RES patients, but in an age range that did not affect sleep, sleepiness, cognition and psychological tests [10, 13]. They were selected for ESS ⩽10, without sleep complaints, chronic sleep deprivation, or chronic use of sedative drugs or alcohol. OSA and healthy controls were paid. The participants signed an informed consent. The study was approved by the institutional review board (Comité de Protection des Personnes, Paris, France).

Investigations

Participants were instructed to follow a regular sleep–wake rhythm 1 week before the tests, as checked by sleep and CPAP diaries. They underwent a face-to-face interview and a clinical examination. They completed a standardised questionnaire including the following scales: ESS [9]; Horne–Ostberg morningness–eveningness scale [14]; Fatigue Severity Score [15, 16]; Beck Depression Inventory II [17]; Hospital Anxiety and Depression Rating Scale [18]; Conners' Adult Attention Deficit–Hyperactivity Disorder Rating Scale [19]; and Apathy Scale [20]. The serum ferritin levels (as low levels promote restless legs and periodic leg movements [21]) and class II human leukocyte antigen (HLA) genotype (as the DQB1*0602 genotype is associated with sleepiness and narcolepsy) were determined.

The 48 h-long sleep monitoring procedure included on the first night followed the next day by five standard MSLT naps (08:00, 10:00, 12:00, 14:00 and 16:00 h) that were terminated after 20 min if no sleep occurred and after 15 min of sleep if sleep occurred [22]. The next evening included long-term (24-h) sleep monitoring, in hospital, with a second, uninterrupted night followed by an attempt to sleep for as long as possible the next morning and afternoon, lying in the dark [8]. CPAP was applied during all sleep tests, including the MSLT. Sleep stages, arousals, periodic leg movements and respiratory events (measured with pneumotachography in patients and nasal pressure plus tracheal microphone in controls) were scored visually according to standard criteria [23–26].

Cognitive tests, performed at 10:40 h on the MSLT day, included testing of the executive functions (inhibition and selective attention with the Stroop Colour–Word Interference Test [27]) and visuospatial functions, including visuoconstructional abilities and long-term spatial memory (copy and delayed recall of the Rey–Osterreith Complex Figure [28]). The verbal memory was evaluated with the Free and Cued Selective Reminding Test, a memory task that controls attention and strategy used to maximise learning, and provides a measurement of short-term memory that is not confounded by deficits in other cognitive abilities [29].

Statistical analysis

The normal distribution of the measures was first checked. Continuous measures were compared in the three groups with ANOVA, with two-group *post hoc* comparisons when the probability of type I error was <5%. We did not perform any adjustment for multiple comparisons. Between-group dichotomous variables were compared using the Chi-squared test (Statistica 8.0; Stat Soft Inc, Tulsa, OK, USA).

RESULTS

Characteristics of sleep apnoea syndrome

OSA patients had higher body mass indices (BMIs) than controls, but BMIs were not different between OSA patients with and without RES (table 1). At the time of OSA diagnosis, patients with and without RES had similar sleep patterns, as well as degree of sleepiness and OSA characteristics. Although patients found it difficult to assess the exact onset of sleepiness, none of them suffered from excessive daytime sleepiness for >10 yrs before OSA diagnosis. CPAP was used at the same frequency, and with the same pressure and residual AHI in both groups. The cardiovascular risk factors were similar in the OSA patients with and without RES, and higher than in controls. Upon clinical examination, there were no neurological signs, including parkinsonism (even mild), cerebellar syndrome and upper motor neuron syndrome. The number of patients with treated restless leg syndrome (with a low evening dose of ropinirole, pramipexole or piribedil) was similar between OSA groups. The patients with RES had brain magnetic resonance imaging within the normal ranges, including a few asymptomatic lacunae in two out of 20 patients. The biological measures (HLA DQB1*0602 genotype and ferritin) were similar in the three groups.

Sleep symptoms

Although the nocturnal symptoms were similar in the three groups, half of the patients with RES did not feel refreshed after the night, were tired upon awakening and had morning headaches (table 2). They had no cataplexy, hypnagogic

TABLE 1 Clinical, biological and basal characteristics and efficacy of continuous positive airway pressure (CPAP) in obstructive sleep apnoea (OSA) patients with residual excessive sleepiness (RES) compared with patients without RES and healthy controls

Characteristic	OSA with RES	OSA without RES	Healthy controls	p-value
Patients n	20	20	20	
Age yrs	61.1±9.9	61.8±9.0¶	55.6±10.0	0.09
Females	25.0	35.0	20.0	0.48
BMI kg·m^{-2}	31.3±5.4*	35.4±9.2¶	25.2±3.5	<0.001
Before CPAP				
ESS score 0–24	15.9±5.5	13.2±3.4+	NA	NA
AHI events·h^{-1}	40.7±17.3	48.9±19.0	NA	NA
3% oxygen desaturation index events·h^{-1}	44.9±34.2	53.4±14.0	NA	NA
Time with Sa,O_2 <90% min	50.9±66.7	53.8±46.4	NA	NA
Lowest sleeping Sa,O_2	80.9±8.4	76.8±10.5	NA	NA
Usual sleep duration h:min	6:53±0:55	7:00±1:51	NA	NA
With CPAP				
ESS score 0–24	16.4±3.0*,#	6.2±2.9	5.7±2.7	<0.001
Delta sleepiness score	0.7±2.2#	-7.0±3.4	NA	NA
Time using CPAP months	65±41	76±41	NA	NA
Use days %	94.5±6.4	93.8±10.9	NA	NA
CPAP use per night h:min	6:56±0:56	6:44±1:33	NA	NA
Mean pressure level cmH_2O	10.3±1.8	9.9±2.2	NA	NA
Residual AHI events·h^{-1}	4.3±2.3	3.5±2.3	NA	NA
Comorbidities and cardiovascular risk factors				
Diabetes mellitus	0.0#	25.0¶	0.0	0.006
Blood hypertension	60.0*	50.0	30.0	0.13
Coronary heart disease and stroke	25.0*	15.0	0.0	0.08
At least one cardiovascular risk factor	60.0*	65.0¶	30.0	0.05
Biological results				
HLA DQB1*0602 genotype	15.0	25.0	25.0	0.75
Serum ferritin level pg·L^{-1}	152±93	160±68	250±218	0.13

Data are presented as mean±SD or %, unless otherwise stated. Measurements with CPAP initiation are based on the time using a mask provided by the CPAP machine counter during the 3 months before formal evaluation. BMI: body mass index; ESS: Epworth sleepiness scale; AHI: apnoea/hypopnoea index; Sa,O_2: arterial oxygen saturation; NA: not applicable. *: $p<0.05$ for OSA patients with RES *versus* healthy controls; #: $p<0.05$ for OSA patients with *versus* without RES; ¶: $p<0.05$ for OSA patients without RES *versus* healthy controls. +: n=18.

hallucinations or sleep drunkenness (a symptom specific for idiopathic hypersomnia, characterised by prolonged difficulty waking with automatic behaviour, confusion and repeated returns to sleep).

Sleep measures

The three groups had similar night-time sleep durations, sleep efficiency and latencies to sleep onset and REM sleep (table 3). Only one patient in the RES group, and none in other groups, had a night-time sleep duration >600 min (and a total sleep time per 24 h of 683 min), a definition of hypersomnia with long sleep time. Patients with RES had lower percentages of N3 sleep than patients without RES and controls. Daytime naps were twice as long in patients with RES than in the other groups, but the total sleep time during 24 h was not different among groups. Patients with RES had higher periodic leg movement indices than those without RES, with 40 % of RES patients having an index >15 events·h^{-1}, but the related arousal indices were low and did not differ between groups. The AHIs were low, similar between patient groups and lower than in controls ($p=0.004$).

The MSLT latencies were lower in patients with RES than in those without RES and in controls (table 4 and fig. 1). There were a similar number of subjects with an MSLT latency <8 min in each group, but more RES patients with an MSLT latency <10 min. Patients with RES had more frequent SOREMPs (no SOREMPs, n=12; one SOREMP, n=4; two SOREMPs, n=3; and three SOREMPs, n=1) than those without RES and than the controls. No patients, however, met the criteria for narcolepsy without cataplexy (combining an MSLT latency <8 min and two or more SOREMPs). Two (10%) patients with RES met the criteria used for idiopathic hypersomnia without long sleep time (total sleep time 360–600 min and MSLT latency <8 min).

Psychological assessment

Almost all patients with RES complained of daytime tiredness, with higher fatigue scores (including severe fatigue in 90% of them) than OSA patients without RES and controls (fig. 2). Although they had no clinical depression, the OSA patients had higher depression scores than controls, with no differences

TABLE 2 Sleep and daytime symptoms in 20 obstructive sleep apnoea (OSA) patients with residual excessive sleepiness (RES) compared with 20 patients without RES and 20 healthy controls

Characteristic	OSA with RES	OSA without RES	Healthy controls	p-value
Usual sleep duration h:min	7:02±1:53	7:06±1:09	7:14±1:14	0.92
Multiple awakenings	25.0	45.0	40.0	0.61
Early awakening	45.0	30.0	30.0	0.76
Nocturnal micturitions	35.0	50.0	55.0	0.48
Restless legs symptoms, treated	30.0	15.0	0.0	0.03
Nonrefreshing night	60.0*,#	5.0	5.0	<0.001
Sleep drunkenness	0.0	0.0	0.0	1.0
Morning headache	45.0#	20.0	5.0	0.03
Sleep paralysis	20.0	0.0	5.0	0.22
Hypnagogic hallucinations	0.0	0.0	5.0	0.68
Tired on awakening	55.0*,#	15.0	5.0	0.002
Tired during daytime	95.0*,#	20.0	20.0	<0.001
Nonrefreshing nap	50.0#	35.0	25.0	0.65
Horne–Ostberg score	57.4±7.5	58.3±8.1	57.4±8.9	0.97

Data are presented as mean±SD or %, unless otherwise stated. *: $p<0.05$ for OSA patients with *versus* without RES; #: $p<0.05$ for OSA patients with RES *versus* healthy controls.

TABLE 3 Sleep measurements during night-time and 24-h sleep monitoring in 20 obstructive sleep apnoea (OSA) patients with residual excessive sleepiness (RES) compared with 20 patients without RES and 20 healthy controls

Characteristic	OSA with RES	OSA without RES	Healthy controls	p-value
Night-time sleep				
Total sleep time min	431±70	433±52	452±70	0.51
Sleep efficiency %	78.4±10.5	81.1±7.6	84.5±9.3	0.17
Latency to sleep onset min	23.7±17.7	26.0±16.5	28.4±16.6	0.59
Latency to REM sleep min	91.4±53.1	82.2±33.9	75.6±37.3	0.53
Sleep stages % total				
N1 and N2	60.7±10.5	55.9±11.8	58.1±6.8	0.14
N3	16.8±7.6*,#	24.6±12.2	22.2±7.2	0.01
REM sleep	21.2±8.1	19.4±4.3	19.6±4.0	0.66
Sleep fragmentation				
Arousals events·h^{-1}	23.9±11.3	18.9±8.5	24.1±10.9	0.17
Periodic leg movements events·h^{-1}	22.7±32.2*	7.3±8.6	11.3±27.2	0.16
Periodic leg movement arousals events·h^{-1}	3.8±6.3	1.8±2.4	3.3±5.0	0.46
AHI events·h^{-1}	2.4±2.3#	2.7±3.9¶	7.6±5.8	<0.001
Mean Sa,O_2 awake %	95.7±2.1	96.0±1.4	95.4±1.4	0.57
Mean Sa,O_2 asleep %	95.1±1.4	95.4±1.4	95.1±1.4	0.91
Lowest Sa,O_2 asleep %	89.2±4.8	90.1±5.9	88.0±5.8	0.56
Sleep during 24-h monitoring				
Total sleep time per 24 h min	496±95	460±66	471±77	0.39
Total sleep time >11 h %	5.0	0.0	0.0	0.35
Sleep stages % total				
N1 and N2	62.9±9.2	57.5±12.6	58.9±6.8	0.06
N3	15.7±7.4*,#	23.7±12.1	29.9±9.7	<0.001
REM sleep	20.1±6.1	18.7±4.5	19.2±4.0	0.82
Daytime sleep time min	63±40*,#	26±33	20±25	<0.001

Data are presented as mean±SD, unless otherwise stated. Sleep fragmentation was evaluated during the first night. REM: rapid eye movement; AHI: apnoea/hypopnoea index; Sa,O_2: arterial oxygen saturation. *: $p<0.05$ for OSA patients with RES *versus* without RES; #: $p<0.05$ for OSA patients with RES *versus* healthy controls; ¶: $p<0.05$ for OSA patients without RES *versus* healthy controls.

TABLE 4 Sleep measurements during the multiple sleep latency tests in obstructive sleep apnoea (OSA) patients with residual excessive sleepiness (RES) compared with patients without RES and healthy controls

Characteristic	OSA with RES	OSA without RES	Healthy controls	p-value
Patients n	20	20	20	
Sleep latency min	12.2±0.9*,#	15.8±0.9	15.7±1.0	0.006
Mean sleep latency <8 min	10.0	5.0	10.0	0.84
Mean sleep latency <10 min	40.0*,#	10.0	10.0	0.04
SOREMPs	0.6±0.9*,#	0.1±0.2	0.1±0.4	0.01

Data are presented as mean±SE or %, unless otherwise stated. SOREMP: sleep onset in rapid eye movement period. *: $p<0.05$ for OSA patients with RES *versus* without RES; #: $p<0.05$ for OSA patients with RES *versus* healthy controls.

between patients with and without RES (table 5). The level of anxiety and the symptoms of attention deficit and hyperactivity were similar in patients with and without RES, but patients with RES scored higher than controls for inattention and self-concept score (indicating a lack of self confidence). The apathy scores were similar among the three groups, but more OSA patients (with and without RES) had abnormal scores than controls.

Cognitive assessment

OSA patients reported more memory complaints than the controls, with a trend for a higher percentage in patients with RES ($p=0.07$). Surprisingly, the patients with RES had fewer errors when completing the Stroop test than those without RES (table 6). Though all groups had similar visuospatial abilities, patients (with and without RES) had lower recall scores than controls when copying the figure. All groups had similar performances at the verbal memory test and a similar benefit from the cues.

There was no significant correlation between the ESS in the patients with RES and any sleep, sleepiness, neuropsychological or cognitive measures (online supplementary table).

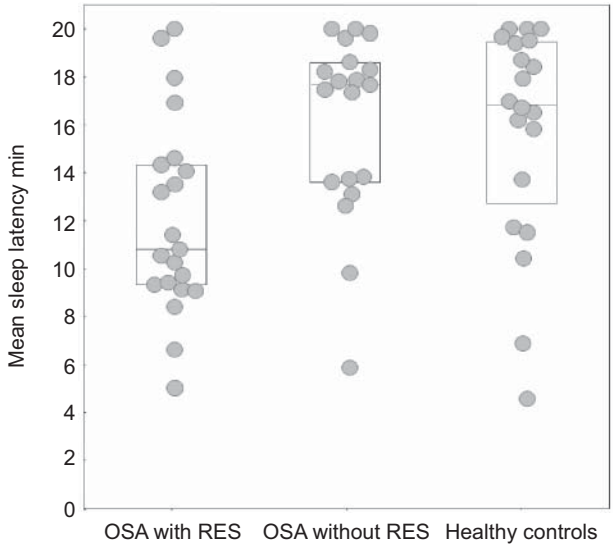

FIGURE 1. Individual mean sleep onset latencies (0–20 min) during the multiple sleep latency test in obstructive sleep apnoea (OSA) patients with and without residual excessive sleepiness (RES), and healthy controls.

Response to stimulant treatment

20 patients with RES used modafinil (400 mg·day^{-1}) for ⩾3 months. 14 patients stopped (side-effects, n=1; no benefit, n=13); hence, six (30%) out of 20 patients were modafinil responders. Seven patients tried methylphenidate as a second choice, with a benefit in two (29%) patients. One patient tried mazindol, without benefit. Two patients tried sodium oxybate, without benefit.

DISCUSSION

Patients with RES tended to be more sleepy before CPAP and had lower stage N3 percentages, more periodic leg movements (without arousals), lower mean sleep latencies and longer daytime sleep durations after CPAP than patients without RES. Only 15% of OSA patients with RES met the international

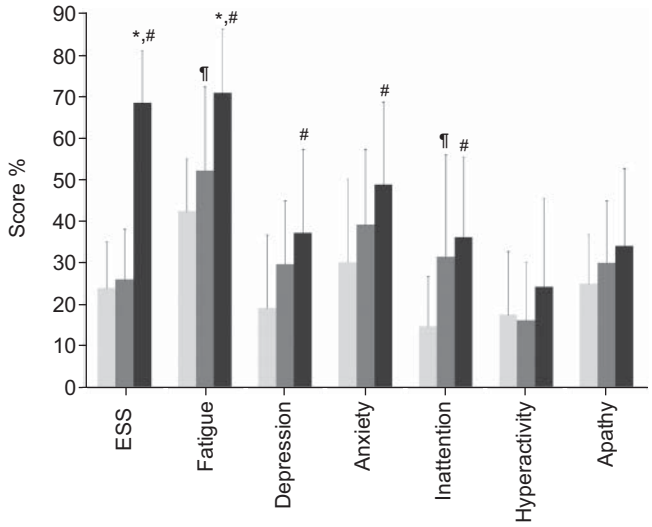

FIGURE 2. Subjective assessment of various neuropsychological dimensions in healthy controls (■) and in obstructive sleep apnoea (OSA) patients without (■) and with (■) residual excessive sleepiness (RES): sleepiness using the Epworth sleepiness scale (ESS), fatigue using the Fatigue Severity Score, depression and anxiety using the Hospital Anxiety and Depression Rating Scale, inattention and hyperactivity using Conners' Adult Scale, and apathy using the Starkstein Scale. The scores are expressed as a percentage of the maximum disability score in each scale. *: $p<0.05$ between OSA patients with RES and without RES; #: $p<0.05$ for OSA patients with RES *versus* healthy controls; ¶: $p<0.05$ for OSA patients without RES *versus* healthy controls.

TABLE 5 Psychological assessment in obstructive sleep apnoea (OSA) patients with residual excessive sleepiness (RES) compared with patients without RES and healthy controls

Characterstic	OSA with RES	OSA without RES	Healthy controls	p-value
Beck Depression Inventory score (0–63)	17.4±11.8*	12.2±6.6¶	3.3±3.3	0.002
Depression score >12	70*	40	20	0.02
Cognitive subscore (0–39)	9.3±8.4*	6.1±4.3¶	1.6±1.8	0.001
Somatic subscore (0–24)	8.1±3.6*	6.1±3.2¶	1.6±1.8	<0.001
HAD depression score (0–21)	7.8±4.2*	6.2±3.2	4.0±3.7	0.01
Depression score >7	40*	20	10	0.09
HAD anxiety score (0–21)	10.2±4.2*	8.2±3.8	6.3±4.2	0.02
Anxiety score >7	65*	55¶	20	0.35
Total CAARS score (0–78)	26.4±9.0*	22.6±12.5	15.3±11.2	0.02
CAARS score >35	10	15	5	0.60
Inattention subscore (0–15)	5.4±2.9*	4.7±3.7¶	2.2±1.8	0.006
Hyperactivity subscore (0–15)	3.6±3.2	2.4±2.1	2.6±2.3	0.30
Impulsivity subscore (0–15)	4.3±2.9	4.3±2.9	3.2±3.6	0.44
Self-concept subscore (0–15)	6.2±3.4*	5.7±3.0¶	3.5±3.2	0.03
Apathy scale (0–42)	14.3±7.8	12.5±6.3	10.4±5.0	0.22
Apathy scale >16	35*	45¶	5	0.03
Fatigue Severity Score (1–7)	5.5±1.2*,#	4.0±1.6¶	3.3±1.0	<0.001
Fatigue Severity Score >4	90*,#	45	20	<0.001

Data are presented as mean±SD or %, unless otherwise stated. HAD: Hospital Anxiety and Depression Rating Scale; CAARS: Conners' Adult Attention Deficit–Hyperactivity Rating Scale. *: p<0.05 for OSA patients with RES *versus* healthy controls; #: p<0.05 for OSA patients with RES *versus* without RES; ¶: p<0.05 for OSA patients without RES *versus* healthy controls.

TABLE 6 Cognitive assessment in obstructive sleep apnoea (OSA) patients with residual excessive sleepiness (RES) compared with patients without RES and healthy controls

Characteristic	OSA with RES	OSA without RES	Healthy controls	p-value
Subjective memory complaint %	95.0*	65.0ƒ	20.0	<0.001
Executive functions#				
Reading time s	59.3±16.5	60.2±10.2	57.7±18.9	0.89
Colour names time s	65.4±18.9	68.8±12.0	63.8±18.0	0.76
Interference time s	106.9±21.3	127.5±41.4	110.1±34.6	0.12
Interference errors	1.8±1.5§	3.4±2.3	2.8±2.0	0.13
Interference index	24.2±7.4	27.9±11.7	27.2±7.1	0.44
Visuospatial abilities and memory¶				
Copy strategy type I or II	60.0	55.0	75.0	0.45
Copy score (0–36)	32.3±2.7	31.6±4.0ƒ	33.4±1.6	0.12
Delayed recall score (0–36)	17.8±7.7*	18.8±7.6ƒ	23.2±5.8	0.06
Withholding %	54.1±22.2*	58.9±22.0	68.6±16.7	0.13
Verbal memory+				
Immediate free–reminding score (0–48)	28.8±6.8	27.4±5.6	31.0±7.3	0.27
Immediate cued selective-reminding score (0–48)	45.5±3.3	45.4±2.7	44.2±6.2	0.63
Delayed free-reminding score (0–16)	11.5±2.5	11.7±2.7	12.6±2.3	0.41
Delayed cued selective-reminding score (0–16)	15.8±0.5	15.8±0.4	15.4±1.4	0.22
Cue benefit %	88.9±12.9	87.3±12.8	83.3±18.0	0.52

Data are presented as % or mean±SD, unless otherwise stated. #: Stroop Colour–Word test; ¶: Rey–Osterrieth Complex Figure Test; +: Free and Cued Selective Reminding Test. *: p<0.05 for OSA patients with RES *versus* healthy controls; §: p<0.05 for OSA patients with RES *versus* without RES; ƒ: p<0.05 for OSA patients without RES *versus* healthy controls.

criteria for central hypersomnia. Most neuropsychological dimensions (fatigue, morning headaches, memory complaints, spatial memory, inattention, apathy, depression, anxiety and lack of self-confidence) were gradually modified from controls to OSA patients without RES and then with RES.

Clinical profile of sleepiness

With high sleepiness scores in patients with RES, we expected to find symptoms, objective measures of sleepiness and executive functions to be abnormal, as in narcolepsy and idiopathic hypersomnia. However, patients had no sleep drunkenness (despite feeling unrefreshed after having slept), no hallucinations, rare sleep paralysis, mostly subnormal MSLT, rare SOREMPs, no sleep excess on long-term monitoring and only a weak benefit from the stimulant modafinil. They could not be considered as ''naturally hypersomnolent'' subjects [30] because the excessive sleepiness was acquired late in life. Compared with other groups, however, the shorter mean sleep onset latency during MSLT (<10 min in 40% of patients) and the longer daytime sleep in patients with RES suggest that they feel something not identified by the usual cut-off used to define hypersomnia. Also, their complaint of severe sleepiness may indicate a neuropsychological syndrome extending beyond the vigilance problem.

A specific neuropsychological syndrome?

Indeed, most psychological dimensions were gradually modified from controls to OSA patients without RES and then with RES. Notably, these scales are not used for diagnosis but to evaluate how patients deviate from norms. The lack of motivation was specific to OSA, not to RES, suggesting that the mesolimbic dopaminergic system [31], which motivates behaviours, is altered. Similarly, no patient with RES had clinical depression, but 70% had mildly abnormal scores. This result could indicate the following: 1) patients with depressed moods score higher on any subjective scale, including the sleepiness and fatigue scales [32]; 2) RES is disabling enough to impact mood; or 3) RES and altered mood are two parallel consequences of post-hypoxic damage in mood and alertness brain structures.

Although almost all patients with RES complained of impaired memory, their performances in verbal and spatial memory tests were similar to those of patients without RES (but lower than controls). Similarly, while they complained of attention deficit, they had normal scores (and even lower interference errors) in the Stroop test, which demands sustained attention. The discrepancies between the complaints of impaired vigilance, memory and attention, and the subnormal tests suggest that the symptoms are too mild to be identified by tests. Alternatively, the sample may be too small to show significant differences or there are no deficits but patients belong to an extreme group of complainers.

Mechanisms of RES

The mechanisms of RES in OSA are numerous [33, 34], including insufficient CPAP adherence and titration, insufficient sleep syndrome, and coexisting sleep, psychiatric and medical disorders. All these causes were ruled out before inclusion. Patients with RES had more periodic leg movements than OSA patients and controls, but these movements were not related to restless leg syndrome (it was absent or treated) or to iron deficiency. Because the movements were not associated with repeated arousals, they were not the cause of RES, as already discussed by other groups [35–37]. The cause of periodic leg movements is as yet unknown; however, because they disappear with low doses of dopaminergic agents [38], they may result from a dysfunction in the dopaminergic system [39].

A post-hypoxic hypersomnia?

We are confident that the classical causes of RES have been ruled out in our patients. Furthermore, our patients had no morphological abnormalities in the brain imaging, as previously shown in OSA patients [40–42]. Hence, we suspect that they suffer from a form of post-hypoxic hypersomnia. In animal models of intermittent hypoxia, sleep time is prolonged (and murine-adapted MSLTs are shorter) even weeks after the intermittent hypoxia exposure is stopped [6], paralleling the longer daytime sleep (on average 1 h) and 3.6 min-shorter MLST of our RES patients. Intermittent hypoxia causes oxidative injury in specific neuronal systems, including the catecholaminergic wake-active neurons [43], serotonergic dorsal raphe nucleus, cortex, cholinergic lateral basal forebrain and CA1 region of the hippocampus [44], but does not affect the other arousal systems (hypocretin and histamine neurons in the lateral hypothalamus). This lack of effect on the hypocretin system could explain why no RES patients meet the polysomnographic criteria for narcolepsy. In addition, patients with RES have higher periodic leg movements and apathy scores (possibly indicating a dopamine dysfunction, although they had no parkinsonism), and lower mood (possibly resulting from a serotonin dysfunction). Brain functional imaging of the monoaminergic systems would be necessary to support the concept of selective damage in RES patients.

The patients with RES did not differ from the other patients at the time of OSA diagnosis, indicating that both patient groups were exposed to the same degree of intermittent hypoxia. Hence, the patients with RES could be more vulnerable to the brain consequences of intermittent hypoxia than those without RES. Indeed, a wide spectrum of RES severities is observed in clinical OSA populations [5, 45], but patients with RES were consistently sleepier than others before CPAP. We imagine that the basis of this vulnerability is genetic. Here, HLA DQB1*0602 genotype was not more frequent in the RES phenotype. A large-scale genome-wide study of OSA patients with and without RES would, however, be more pertinent to identify a potentially genetic vulnerability.

In conclusion, RES in apnoeic patients differs markedly from sleepiness in central hypersomnia and the association between RES, periodic leg movements, apathy and depressive mood parallels the post-hypoxic lesions in noradrenaline, dopamine and serotonin systems in animals exposed to intermittent hypoxia.

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STATEMENT OF INTEREST

None declared.

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