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NEUROLOGY • REVIEW

Excessive daytime sleepiness in narcolepsy and central nervous system hypersomnias

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Abstract

Purpose Excessive daytime sleepiness (EDS) is the core complaint of central nervous system (CNS) hypersomnias. In this mini-review, we summarized EDS features in CNS hypersomnias to provide a guide for differential diagnosis purposes.

Methods A review of recent literature was performed to provide an update in CNS hypersomnias.

Results At clinical evaluation, narcolepsy patients report a good restorative potential of sleep together with the frequent occurrence of dreaming even during short-lasting naps. These features are mirrored by the neurophysiological evidence of REM sleep at sleep onset (SOREMP) during the Multiple Sleep Latency Test (MSLT), a specific marker. Conversely, patients with idiopathic hypersomnia (IH) complain sleep inertia and prolonged nocturnal sleep. Polysomnographic studies show high sleep propensity on the MSLT or high 24-h total sleep time during continuous monitoring. Patients with insufficient sleep syndrome (ISS) can present with variable clinical EDS features in between narcolepsy and IH. ISS diagnosis is based on the clinical evidence of nocturnal sleep curtailment (weekdays versus vacations) associated with the disappearance of EDS complaint after sleep extension. Polysomnographic data are not required, but when the MSLT is performed, ISS patients can present with SOREMP arising from non-REM stage 2 sleep (vs narcolepsy patients entering into SOREM most frequently from wakefulness). Kleine-Levin Syndrome is characterized by recurrent episodes of enormously prolonged sleep time lasting days associated with abnormal cognition and behavior intermixed by asymptomatic periods, a sleep pattern that can be well documented by actigraphy.

Conclusions Different CNS hypersomnias present with specific features of EDS are useful to guide the clinician to apply and interpret appropriate neurophysiological investigations.

Keywords Dreaming · Sleep inertia · Automatic behavior · Narcolepsy · Idiopathic hypersomnia · Sleep deprivation

Physiological and pathological sleepiness: from the general population to central nervous system hypersomnias

Sleepiness is a sensation intrinsically related to the inner drive to sleep, and is therefore modulated by the physiological processes regulating sleep across the 24-h cycle, namely the homeostatic and circadian drives [1]. Accordingly, sleepiness reaches its maximum during nighttime hours and, albeit of minor intensity, can also occur in mid-afternoon independently from previous eating [2]. Aside subjective feelings, sleepiness is closely connected to the overall process of falling asleep and can present with a variety of behavioral, physiological, neurophysiological, and psychomotor characteristics that render the phenomenon multifaceted from the investigational standpoint

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suggesting the need for multidimensional approaches to fully capture its diversity [3]. In this context, it is important to highlight the presence of gender-related differences in subjective sleepiness perception that is more commonly characterized in young women by a subjective feeling and in older man by self-reported sleep propensity in passive and active conditions [4]. Sleepiness is also strongly influenced by neurobehavioral activities (e.g., motion) and environmental factors (e.g., external stimuli) that can enhance or mask its intensity by acting on the sleep-promoting drive [5].

The overall goal of characterizing sleepiness in the clinical arena is to distinguish physiological sleepiness from hypersomnolence (or excessive daytime sleepiness (EDS)), the latter being defined as "the inability to stay awake and alert during the major waking episodes of the day, resulting in periods of irrepressible need for sleep or unintended lapses into drowsiness or sleep" [6]. EDS severity varies widely and can be clinically classified in terms of severity addressing the conditions and consequences of its appearance ranging from sleep occurrence in monotonous conditions to sleep attacks while performing a task or being in an interactive context. Indeed, when asking in general terms about sleepiness, up to one-fourth of the general population (26%) report its occurrence, but when integrating questions on associated symptoms (16%) and on its frequency (5%), the prevalence decreases pointing to the key importance of the operational definition of sleepiness itself [7]. EDS is indeed a common complaint in the field of sleep medicine reflecting the qualitative and quantitative insufficiency of sleep, as well as the misalignment between personal circadian typology and sleep patterns as determined by social and working schedules. In clinical practice, EDS should be addressed at clinical interview, possibly with the ancillary use of questionnaires to minimize inter-individual differences. Such questionnaires including the Epworth Sleepiness Scale [8] and other promising tools [9], as well as specific objective in-laboratory tests, such as the MSLT are required to classify CNS hypersomnias or to document response to treatment in particular conditions, such as, the Maintenance of Wakefulness Test (MWT) [10].

EDS is the core complaint of CNS hypersomnias, a group of disorders that require the absence and/or adequate treatment of disturbed nocturnal sleep and misaligned circadian rhythms to demonstrate the central origin of EDS. The main CNS hypersomnias are narcolepsy (type 1, type 2), idiopathic hypersomnia, Kleine-Levin syndrome, and insufficient sleep syndrome, as well as hypersomnias associated with medical or psychiatric disorders and with medication or substances. Over time, the diagnostic criteria defining the above disorders have changed reflecting the increase pathophysiological knowledge on narcolepsy together with the controversies in defining the boundaries of narcolepsy [6]. Indeed, narcolepsy is biologically marked by its relation with hypocretin neurotransmission, with narcolepsy type 1 being the exclusive disease associated with hypocretin deficiency and cataplexy making the disorder a unique hypocretin deficiency syndrome [11], whereas the features of the other CNS hypersomnias appear in overlap and suffer from insufficient aetiological knowledge. We will discuss the clinical and neurophysiological features of EDS in CNS hypersomnias (excluding the forms related to comorbid diseases or to medications/substances) to provide a suggested guide to distinguish sleepiness subtypes at clinical assessment and correctly use/interpret the currently available objective laboratory tests.

Narcolepsy

Narcolepsy was first described by Westphal and Gelineau [12, 13], opening an enduring debate between physicians supporting a neurological and a psychiatric disease etiology [14]. In this context, the psychoanalyst Vogel first observed the rapid occurrence of REM sleep at sleep onset under EEG monitoring of a patient with narcolepsy and, while claiming to unravel the proof of the psychiatric disease origin, he was in fact depicting the neurophysiological disease marker that is still used for diagnostic purposes to this date [6, 15]. Subsequent studies defined that narcolepsy is characterized by a high daytime sleep propensity coupled with early occurrence of REM sleep at sleep onset [16], the so-called sleep onset REM periods (SOREMPs) that are still routinely measured during the standardized MSLT procedure to confirm narcolepsy diagnosis [10, 17].

From the clinical standpoint, patients with narcolepsy typically wake up refreshed in the morning and experience overwhelming daytime sleepiness with a possible periodicity of 2 h culminating in daytime sleep episodes with SOREMPs and increased length of nocturnal non-REM–REM sleep cycles [18]. Daytime sleep episodes are generally preceded by an intense subjective sleepiness sensation which is rapidly, albeit transiently, reversed by naps. Unwanted sleep can recur several times per day in both monotonous (Video 1) and active (Video 2) conditions, and sleep duration may vary from minutes to over 1 h depending on the patients' comfort. Daytime sleep is most frequently characterized by dreaming occurring even in episodes of short duration, as a clinical correlate of early REM sleep occurrence (Fig. 1), and patients most often feel refreshed at awakening. The recall of a dream and the refreshment after short daytime sleep episodes are clinical clues to distinguish narcolepsy from idiopathic hypersomnia and other EDS conditions [19]. Conversely, resisting sleepiness during daytime frequently leads to the occurrence of an altered state of consciousness where a twilight vigilance condition facilitates automatic behaviors [20]. Automatic behaviors are a dangerous consequence of sleepiness because patients may continue activities with

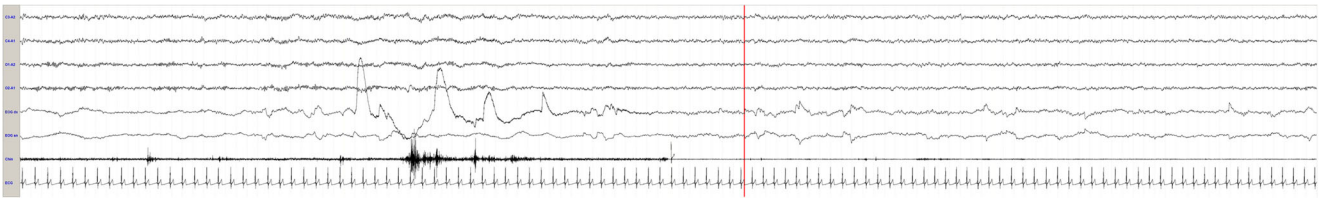

Fig. 1 SOREMP arising from wakefulness during a MWT nap. The polysomnographic tracing shows the direct transition (marked by a red line) from wakefulness to REM sleep in a narcolepsy type 1 patient during MWT execution (see Video 1)

impaired consciousness and subsequent complete amnesia, while presenting the repetitive occurrence of microsleeps at polysomnographic recordings. Such microsleeps may obviously lead to serious consequences. Albeit rarely, patients with narcolepsy may fall into sleep without perception of subjective sleepiness, an extreme symptom labeled as a "sleep attack". Sleep attacks are traditionally considered within the narcolepsy EDS spectrum; however, there is no evidence for their real occurrence in narcolepsy. Most probably, sleepiness sensation precedes sleep episodes but may be scarcely recalled at history taking [21]. Intense sleepiness in narcolepsy can be associated with occurrence of hypnagogic multisensory hallucinations, and sleep episodes can be linked to either hallucinatory content or sleep-related paralyzes [22]. However, EDS in narcolepsy encompasses a large variety of overlapping and disabling symptoms such as fatigue and cognitive difficulties, all significantly contributing to impaired performance at school and work [23], and possibly related also to underlying mood states [24].

Narcolepsy unfortunately arises in childhood or adolescence in the vast majority of cases [25], and in young patients, EDS can present with very different phenotypes. Indeed, children may show one of at least three following phenotypes in clinical practice: (1) the abrupt re-occurrence of a postprandial napping habit coupled with an earlier evening bed time; (2) repeated daytime napping of various durations eventually associated with disrupted nocturnal sleep; and (3) extreme hyperactivity and irritability during the daytime to overcome EDS [26]. Most frequently, wrong diagnoses, including psychiatric conditions and attention deficit hyperactivity disorder (ADHD), may contribute to diagnostic delay [27, 28]. However, the presence of comorbid ADHD symptoms in young narcolepsy patients should be considered together with the atypical EDS presentations in children [29–32]. Such hyperactivity can persist in adulthood [33], a factor that may also interfere with standardized EDS objective assessment when a patient present with clear-cut comorbidity between ADHD and narcolepsy (Video 3).

EDS in narcolepsy can be easily documented an MSLT showing increased sleep propensity and occurrence of SOREMPs [6], a finding that showed a consistent test-retest reliability in cataplectic, hypocretin deficient patients, but not in the borderland cases of narcolepsy [34–36]. In full-blown cases of narcolepsy, continuous polysomnography shows multiple SOREMPs during spontaneous daytime napping [37]. Recent data showed wrist actigraphy to be a good screening tool in patients of all ages suffering from narcolepsy type 1 because of the co-occurrence of daytime motor hypoactivity (i.e., napping) and nocturnal hyperactivity (i.e., sleep disruption and sleep-related motor activity) [38, 39]. Current diagnostic criteria require the presence of pathological MSLT findings coupled with evidence of cataplexy (pathognomonic symptom) or evidence of cerebrospinal hypocretin-1 deficiency to confirm narcolepsy type 1 diagnosis [6]. Indeed, narcolepsy type 1 is considered an auto-immune disease occurring in genetically predisposed subjects after possible environmental triggers such as infection or vaccination [40, 41]. Conversely, narcolepsy type 2 diagnosis requires the presence of pathological MSLT findings in the absence of cataplexy or cerebrospinal hypocretin-1 deficiency [6].

Idiopathic hypersomnia

Idiopathic hypersomnia (IH) is a disorder first characterized by the work of Professor Roth in Prague [42, 43], as a condition of overwhelming EDS with prominent non-REM features, thus also called non-REM narcolepsy [6, 44]. The prominent trait of EDS in IH is "sleep drunkenness", currently labeled as sleep inertia. Sleep inertia is experienced as an extreme awakening difficulty consisting of "confusion, disorientation, poor motor coordination, and repeated return to sleep" at waking up from nocturnal and daytime sleep, coupled with an abnormally prolonged sleep duration [42]. After Roth's description of IH, subsequent work highlighted the continuum in the disease spectrum of CNS hypersomnias [45], and the IH phenotype was further differentiated according to differences in the presentation of REM sleep-related symptoms (paralyzes, hallucinations) and objective (SOREMPs occurrence) findings [46]. IH patients more frequently complain of prolonged nocturnal sleep duration, difficulties with morning awakening, and frequent occurrence of automatic behaviors compared with narcolepsy patients. However, sleep paralyses and hallucinations may be overlapping symptoms that together with variable propensity for REM sleep propensity place IH on a disease spectrum encompassing pure non-REM and REM sleep-related complaints [46]. Studies addressing IH pathophysiology failed in documenting a common genetic or biological basis and met with controversial results on the role of the genetic background [47] or of neurotransmitter systems such as

histamine [48, 49] or GABA [50, 51]. Lacking a biological disease marker and being most often a diagnosis of exclusion of other sleep disorders causing EDS, IH remains a diagnostic dilemma and has been differently defined in subsequent international diagnostic manuals [52]. Indeed, prolonged nocturnal sleep duration makes the diagnosis challenging while applying the classical nocturnal polysomnography plus MSLT approach due to the interference between the MSLT procedure itself (requiring awakening at a specified morning time between 7 and 8 am) and the need to document habitual sleep duration. Two forms of IH have been defined based on nocturnal sleep duration (IH with or without long sleep time defined as a documented sleep period of less than or greater than 10 h) both requiring confirmation of high sleep propensity on the MSLT [53]. Subsequent work applied different sleep laboratory protocols (free-running, free-running with invited napping, bed resting) using continuous polysomnographic recording to overcome the abovementioned limits intrinsic to standard procedures [37, 54, 55]. To date, diagnosis of IH can be based on either the evidence of high sleep propensity at the MSLT without repeated SOREMPs or on the finding of at least 11 h of sleep across the 24 h documented by polysomnography or wrist actigraphy [6]. However, patients with IH most often describe their EDS as such difficulty awakening that they frequently need somebody (or some tricks such as several alarms) to be awakened. Persistent EDS is not alleviated by napping and patients with IH are unable to take short daytime naps [54, 56]. These clinical features are mirrored by the evidence of high slow wave sleep representation across the nighttime and, most notably, in early morning hours [54, 56]. The daytime sleep onset profile on the MSLT differs in IH compared with narcolepsy, with IH patients showing a more prolonged fluctuation between wakefulness and non REM sleep stage 1 before entering into a sustained sleep condition defined as three consecutive epochs of sleep stage 1 or a single epoch of any other sleep stage [57]. EDS therefore differs clinically in IH and narcolepsy not only for the absence of dreaming in daytime sleep, but also for the low refreshing potential of sleep, and for the difficulties in performing short naps during daytime without entering into slow wave sleep, the latter invariably followed by sleep inertia at awakening. However, the burden of IH symptoms is not restricted to morning awakening difficulties and daytime EDS, but includes frequent occurrence of automatic behaviors, frequent anxiety and depression, and vegetative complaints such as temperature dysregulation and feelings of faintness that may be the clinical counterpart of drowsiness as well as reflect the effort to resist sleepiness [58].

Over the long term, patients with EDS and a polysomnographic phenotype of IH may worsen over time to narcolepsy type 1 [59], or may show a benign disease course with a good response to stimulant treatment in two-thirds of cases, or demonstrate spontaneous improvement in 11% of cases [56]. Clinical, neurophysiological, and pathophysiological research is therefore needed to define IH and its relations with the narcolepsy disease spectrum.

Kleine-Levin syndrome

Kleine-Levin syndrome (KLS) is a hypersomnia of central origin characterized by the sudden recurrence of attacks of excessive sleepiness and sleep duration persisting days and variably associated with cognitive dysfunction, altered perception, eating disorder (anorexia or hyperphagia), or disinhibited behavior (such as hypersexuality) with normal sleep patterns and daytime functioning in between the acute phases [6]. The syndrome was described at the beginning of the last century [60, 61]. The disorder is an extremely rare condition with an estimated prevalence of 1.8 cases per million with onset most frequently during adolescence [62, 63]. The disease course is generally benign with a progressive reduction in frequency and intensity of the sleepiness episodes with spontaneous resolution after a median period of 14 years, and generally before age 30 years, at least in patients with onset during adolescence [6, 62].

EDS in KLS has unique characteristics compared with the other CNS hypersomnias. Indeed, patients enter into the acute phases showing an enormous, sudden, increase of sleep time across the 24 h (mean of 18 h, range 15 to 21) and are difficult to awaken. Sleep drunkenness, intense dreaming, and hallucinations are also commonly reported during the attacks [62]. In addition to daytime eating and sexual disorders, patients may experience severe cognitive dysfunction with amnesia and spatio-temporal disorientation, as well as altered perception of themselves and of the environment with feelings of being in a dreamy state and of derealization. Psychiatric symptoms are intense during the attacks and include intense apathy, altered mood, anxiety, and irritability [62]. Approximately 30% of KLS patients can present with prolonged (i.e., > 30 days) attacks. During the acute phases, these patients have shorter sleep duration across the 24 h (mean of 16 vs 18 h) mirrored by longer asymptomatic periods (23 vs 14 weeks). Overall, they suffer from a greater disease burden in terms of spontaneous disease remission and overall impact on academic and work performances compared with the other KLS patients [63].

Even though by definition patients should have normal sleep patterns and daytime functioning outside of the attacks, recent data have disclosed a different picture. Indeed, a psychiatric comorbidity (mostly mood and anxiety disorders) can develop in up to 21% of cases even during the asymptomatic periods possibly related to KLS features such as a longer disease course and prominent psychiatric symptoms during the attacks [64].

Additionally, subtle cognitive deficits affecting processing speed and retrieval strategies for verbal memory may persist in the asymptomatic period and worsen at mid-term (1.7 years) follow-up [65].

To summarize, KLS has peculiar features of EDS and daytime dysfunctions that make the differential diagnosis within the CNS hypersomnias straightforward from a clinical standpoint. Routine polysomnographic assessment (nocturnal polysomnography and MSLT) can show variable results depending on the timing of execution and patients' compliance, whereas prolonged continuous polysomnography and long-term actigraphy can objectively monitor features of EDS during and outside of the symptomatic periods (Fig. 2).

Insufficient sleep syndrome

Chronic sleep deprivation naturally leads to EDS, a condition included within CNS hypersomnias given its importance in their differential diagnosis. The diagnosis can be performed on the basis of clinical criteria, most notably addressing the habitual curtailment of nocturnal sleep associated with EDS (lasting more than 3 months), the resolution of EDS after extension of nocturnal total sleep time, and the tendency to spontaneously extend nocturnal sleep during the weekends or vacations [6]. When considering the diagnosis of insufficient sleep syndrome (ISS), it is important to consider the age-related differences in sleep needs [66], together with the individual chronotype and the potential occurrence of long sleepers (i.e., subjects naturally requiring a long nocturnal sleep time and more easily affected by relative sleep curtailment for social needs). However, if nocturnal polysomnography plus MSLT is performed, sleep-deprived patients generally show high nocturnal sleep efficiency coupled with a pathological daytime sleep propensity with or without multiple SOREMPs [6, 53].

Patients with chronic sleep deprivation more frequently report a different sleep habit during weekdays and weekends, with comparable amount of nocturnal sleep hours during the weekends and approximately 2 h of sleep curtailment during weekdays compared with narcolepsy patients [67]. On the MSLT, ISS patients may show a minimal sleep propensity in the morning and evening, comparable with healthy subjects, whereas narcolepsy patients do not show circadian variations in their high sleep propensity [67]. Several recent studies have addressed the neurophysiological features potentially useful to distinguish ISS from other CNS hypersomnias, focusing on the differential diagnosis between ISS and narcolepsy in non-cataplectic patients who show multiple SOREMPs on the MSLT. Sleep stage sequence analysis shows that ISS patients most frequently enter into SOREMP passing through non-REM sleep stage 2, a sleep onset profile that is also shared by approximately 50% of narcolepsy type 2 patients, whereas a SOREMP generally arises directly from wakefulness or from a non-REM sleep stage 1 in narcolepsy type 1 patients who also show a more severe sleep propensity [68–71]. The differential diagnosis between ISS and narcolepsy can be further improved including the latency to REM sleep (longer in ISS) associated with the duration of REM sleep during the nap (longer in narcolepsy) in addition to the number of SOREMPs on the MSLT [71, 72].

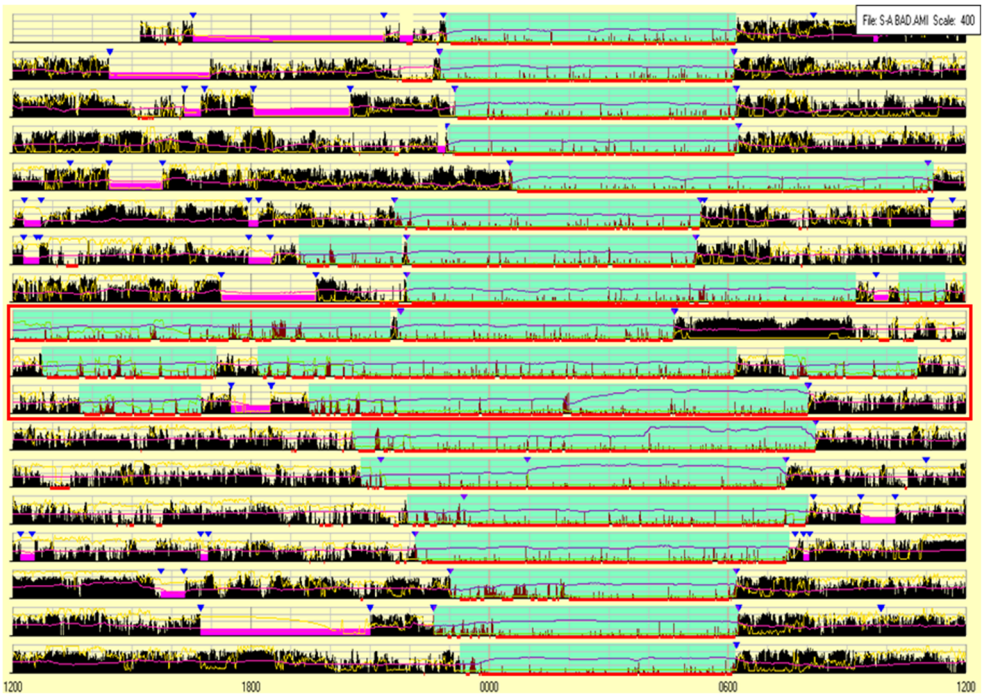

Fig. 2 Actigraphic recording of a Kleine-Levin syndrome patient across the acute attack. Actigraphic monitoring demonstrates the acute phase (highlighted by a red line) of hypersomnolence in a Kleine-Levin syndrome patient who showed the abrupt occurrence of increased 24-h total sleep time up to 19 h for 3 days from a baseline nocturnal sleep duration of 7 h

Table 1 Clinical and neurophysiological EDS features in CNS hypersomnias

Clinical EDS assessment	Narcolepsy type 1	Narcolepsy type 2	Idiopathic hypersomnia	Insufficient sleep syndrome	Kleine-Levin syndrome
Subjective feeling at morning awakening	Refreshed	Refreshed	Sleep inertia	Variably impaired, may differ according to waking up schedules across weekdays and weekends	Difficult to awaken in the attacks
Subjective daytime sleepiness perception	Increased	Increased	Increased	Increased	Increased into the attacks, variable in asymptomatic periods
Subjective sleep propensity in passive conditions	Increased	Increased	Increased	Increased	Not available into the attacks
Subjective sleep propensity in active conditions	Variably increased, activity can ameliorate EDS	Variably increased, activity can ameliorate EDS	Increased	Variably increased, activity can ameliorate EDS	Not available into the attacks
Short daytime napping transiently resolving EDS	Yes	Yes	No	Yes	Not in the attacks with sleep episodes of long duration and followed by sleep inertia
Possibility to perform short daytime napping	Yes	Yes	No	Yes	Not in the attacks with sleep episodes of long duration and followed by sleep inertia
Daytime napping associated with dreaming recall	Yes	Yes	No	Variably	Yes
Course of subjective EDS complaint	Chronic, with frequent acute onset in childhood/adolescence	Chronic	Chronic	Chronic, possibly related to working schedules	Acute onset (adolescence), mostly benign course with remission around 30 years old
Other sleep complaints					
Sleep-related hallucinations	Yes	Yes	Variably reported	Variably reported	Variably reported in the acute phase
Sleep-related paralyses	Yes	Yes	Variably reported	Variably reported	No
Cataplexy	Yes	No	No	No	No
MSLT features					
Sleep latency to the first epoch of sleep	Reduced	Reduced	Reduced	Reduced	Variably available within the attacks (low compliance)
Sleep onset REM periods occurrence	High at baseline and follow-up	High, variable at follow-up	Low	Variable	Variable
REM sleep latency	Short	Variable, higher than in narcolepsy type 1	If present, higher than narcolepsy type 1	Variable, higher than narcolepsy type 1	Variable
Seep stage sequence analysis (SOREMPs naps)	Mostly direct from W/N1 to REM	Variable occurrence of non REM sleep stage 1 or 2 before SOREMP	Mostly passing through non REM sleep stage 2	Mostly passing through non REM sleep stage 2	Not available
Other unconventional MSLT features				Lower REM sleep percentage vs narcolepsy type 1	Not available

Table 1 (continued)

Clinical EDS assessment	Narcolepsy type 1	Narcolepsy type 2	Idiopathic hypersomnia	Insufficient sleep syndrome	Kleine-Levin syndrome
	Higher REM sleep percentage; rapid and direct occurrence of a sustained sleep condition	Lower REM sleep percentage vs narcolepsy type 1	Presence of a fluctuating non REM sleep stage 1/wakefulness before sustained sleep occurrence		
Continuous polysomnographic findings					
Daytime naps (number)	Clearly increased	Increased	Increased	Not available	Increased in the attacks with prolonged duration
Daytime SOREMPs	Present	Present	Absent	Variably present	Variably present in the attacks
24-h total sleep time	Normal/increased	Normal	Variably increased	Reduced during weekdays	Enormously increased during the attacks
Actigraphic findings					
Daytime total sleep time	Increased	Variably reported	Variably increased	Reduced during weekdays	Enormously increased during the attacks
Nocturnal sleep disruption	Present	Absent	Absent	Absent	Absent
Different circadian profile between weekdays and weekends/holidays	No	Variably reported	No	Longer nocturnal sleep duration in weekends/vacations	No

Conclusions

EDS is the core complaint of CNS hypersomnias and clinical assessment should at first distinguish physiological from pathological sleepiness during daytime. It is first necessary to exclude other sleep disorders that cause EDS through clinical and polysomnographic evaluation. Clinicians should investigate particular features of EDS that differentiate the various CNS hypersomnias.

At clinical evaluation, several features of EDS can steer the clinician to suspect the correct CNS hypersomnia, to be confirmed by neurophysiological and biological (most notably cerebrospinal hypocretin-1 assay) objective findings. Such features include a chronic versus intermittent course of EDS, the refreshing effect of nocturnal and daytime sleep, sleep inertia, reported dreaming during daytime sleep episodes, and sleep habits across weekdays and weekends. Important ancillary symptoms may include sleep-related paralysis and hallucinations, cataplexy (pathognomonic for narcolepsy type 1), and other comorbid cognitive or psychiatric symptoms. Neurophysiological findings on conventional nocturnal polysomnography and MSLT assessment, such as daytime sleep propensity and number of SOREMPs can direct the clinician towards a correct CNS hypersomnia diagnosis. Recent data also highlight the potential of other simple parameters obtained on the MSLT (e.g., sleep stage sequence analysis), during prolonged polysomnographic monitoring with different protocols (i.e., free running, bed resting), or during wrist actigraphic monitoring to further differentiate CNS hypersomnias (see Table 1 for an overview). In this context, quantitative analysis of the polysomnographic signal will be of invaluable help when available in clinical practice [73]. Clinical and neurophysiological assessment strategies are needed to increase our incomplete knowledge of the boundaries defining the different CNS hypersomnias. Such strategies are important to help monitor the course of these diseases as well as efficacy of treatments.

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Compliance with ethical standards

The work is a literature review and complied with the tenets of the Declaration of Helsinki, as well as with the ethical standards of the journal. All subjects involved in the pictures or videos provided written informed consent.

Conflict of interest Giuseppe Plazzi participated in advisory board for UCB Pharma, Jazz pharmaceuticals, Bioprojet, and Idorsia outside the submitted work. The other authors have no potential financial conflict of interest to disclose.

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