Review Article

Clinical update on central hypersomnias

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Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: The central hypersomnias encompass a range of conditions causing persisting or intermittent excessive daytime sleepiness (EDS). These conditions therefore present not infrequently in general clinical sleep practice, and remain in the differential for patients presenting with sleepiness. Our understanding of the pathophysiology, diagnosis and management of these conditions has progressed significantly over recent years, and in this article we review this group of disorders, focussing in particular on recent changes in classification and diagnosis, pathophysiological advances, and novel treatment options.

Keywords: Narcolepsy; hypersomnia; Kleine-Levin; sleep disorders

Submitted Aug 04, 2017. Accepted for publication Sep 05, 2017.
doi: 10.21037/jtd.2017.10.161
View this article at: http://dx.doi.org/10.21037/jtd.2017.10.161

Introduction and nosological classification

The term excessive daytime sleepiness (EDS) has been defined as 'an inability to stay awake and alert during major waking episodes of the day' (1). As a result of the irrepressible need for sleep or vigilance-unintended lapses, EDS may have severe consequences in patients' lives. Although several terms are similarly used in literature, the words sleepiness or hypersomnolence usually designate the abnormal tendency to enter into a sleep state; whilst, by hypersomnia, an increased amount of sleep over a 24-hour period of time is assumed (2). Yet, this distinction is not always precise and, also in the scientific literature, hypersomnia is used interchangeably to refer to EDS. Sleepiness must be adequately differentiated from other prevalent symptoms; fatigue, a difficulty in initiating or sustaining voluntary activities (3), and apathy, characterised by decreased voluntary goal-directed behaviours (4), may be especially problematic to distinguish from hypersomnolence.

EDS is frequently associated with sleep-related breathing disorders, circadian rhythm disorders and other causes of disturbed nocturnal sleep. However, only when these conditions have been excluded, can a diagnosis of a central disorder of hypersomnolence be made. The International Classification of Sleep Disorders 3rd edition (ICSD-3), have included a variety of disorders under the umbrella of 'central disorders of hypersomnolence', where EDS is a cardinal and common feature to all of them (1). The section comprises eight categories containing both primary conditions, caused by intrinsic anomalies of the central nervous system [narcolepsy type 1 and 2 (NT1 and NT2), idiopathic hypersomnia (IH), Kleine-Levin syndrome (KLS)], and secondary forms [hypersomnia due to medical/psychiatric disorders, substances, and insufficient sleep syndrome (ISS)].

Compared to the previous edition of the ICSD (5), a few notable changes have been proposed. The formerly named entities of narcolepsy with cataplexy and narcolepsy without cataplexy have been replaced by the diagnoses of NT1 and NT2, respectively, although the presence of cataplexy is not mandatory for the diagnosis of NT1 if CSF hypocretin deficiency is demonstrated (6). This is justified by the proclamation of hypocretin deficiency as the cause of the disorder (7); but also because a proportion of patients, with low hypocretin levels, will develop cataplexy years after the onset of the EDS (and presumably have the same pathophysiological mechanisms). Additionally, due

to insufficient evidence for the subdivision of IH in two groups, with long or normal sleep time, the distinction has been removed in the new criteria. Moreover, a cluster analysis (8) demonstrated that individuals initially diagnosed with either narcolepsy without cataplexy or IH without long sleep actually formed a single cluster of patients. The authors explained that this was probably related to a rather arbitrary cut-off of two sleep onset rapid eye movement (REM) periods (SOREMPs) in the multiple sleep latency test (MSLT), for their differentiation.

Further modifications of the classification have affected neurophysiological criteria: in addition to the reduced sleep latency required in the MSLT in narcolepsy (types 1 and 2), there is also evidence that supports the value of a SOREMP arising in the initial 15 minutes of the preceding polysomnography (PSG) (9). Therefore, it is now possible to substitute one SOREMP from the MSLT with a (short-latency) REM period of the coupled PSG for the diagnosis of narcolepsy or, equally, to rule out the existence of IH. Also, concerning IH, there is now a criterion based on the total sleep time in a 24-hour PSG (or averaged multi-day actigraphy plus sleep logs) that allows the diagnosis regardless of a negative result in the MSLT. Therefore, the demonstration of a mean sleep latency below 8 minutes is no longer a mandatory diagnostic criterion (10).

The evolution of knowledge in the sleep disorders field, and the absence of reliable clinical markers for central hypersomnias specifically, are reflected in the continuous modifications in terminology and divisions of central disorders of hypersomnolence. Despite the efforts for a clarifying classification, clinicians should consider the possible overlap between conditions and normally sleepy persons, as well as be aware of the common presence of sleep-deprived individuals in the medical setting, in order to establish a correct diagnosis. Furthermore, while the diagnosis of hypersomnolence may be supported by a MSLT, sleepiness is not always accurately detected with this investigation. Thus, the subjective perception of EDS might differ from the objective measure in the sleep test.

In this review, we summarise the main clinical aspects of the conditions included in the group of hypersomnias of central origin (or central disorders of hypersomnolence), and focus on certain novel findings of particular relevance to clinical practice.

NT1

NT1 is a chronic, neurological disorder with a heterogeneous clinical presentation that requires the presence of EDS. The prevalence of the disease has been estimated to be around 0.02–0.067% worldwide (11), and involves a significant socioeconomic burden. Most cases are idiopathic and sporadic, whilst secondary and familial forms are rarely seen.

The age of onset has a bimodal distribution with a peak at about 15 years and a smaller one during adulthood, between 30 and 40 years of age. However, there is usually a significant interval between the onset of symptoms and formal diagnosis (12). Indeed, given the wide variety of manifestations, and the possible lack of awareness of the condition among clinicians, the recognition of the disease can be somewhat challenging. The delay will often result in an obstacle to the management of patients, and an increasing psychosocial impact.

Pathophysiology

The cause of NT1 is a loss of hypothalamic hypocretin-producing neurons (13) that, along with the strong association with human leucocyte antigen (HLA) DQB1*0602 haplotype (14), suggests an underlying autoimmune mechanism. Further HLA and non-HLA gene loci have been linked to a predisposition to narcolepsy (14,15). In addition, the association of T-cell receptor loci and susceptibility to narcolepsy has recently been demonstrated, supporting the hypothesis of a T-cell mediated autoimmune attack (16,17).

Infective agents have been proposed as triggers of the disease, with the finding of high serum titres of antistreptolysin O antibodies in NT1 patients, and higher incidence of narcolepsy after the influenza A (H1N1) virus vaccination (18-20). Increasing risk and incidences of NT1 have been revealed in several populations after the vaccination campaign in 2009 (21-24). The association of narcolepsy with H1N1 vaccination has been investigated extensively, and it has been a matter of controversy over the last years. In this regard, a study (25) demonstrated the presence of antibodies to H1N1 nucleoprotein cross-reacting with human hypocretin receptor 2. Similarly, autoantibodies against ganglioside GM3 (a receptor for influenza virus widely present in the central nervous system) in patients with post-vaccination narcolepsy have been described (26). Lately, in an analysis that explored possible autoantigens in patients with vaccine-associated narcolepsy, a few proteins showed homologous sequences to proteins found in H1N1 virus (27). Furthermore, an intriguing interaction between predisposing genes for narcolepsy and,

possibly, a viral component of the H1N1 vaccine has been described (28). Therefore, the proposed mechanism in narcolepsy currently relies on an autoimmune response that targets hypocretin neurons specifically, in individuals with a genetic susceptibility that is enhanced by an environmental factor.

Clinical features

Hypocretin, also known as orexin, is involved in the maintenance of wakefulness and sleep, the latter through its modulating action over other neurotransmitters (29). The consequent instability of the sleep-wake system, due to reduced hypocretin levels, will lead to a dissociated state with REM sleep intrusions into wakefulness, thus resulting in the characteristic features of NT1.

The leading and only mandatory symptom in narcolepsy is EDS, which is typically described as an irresistible or overwhelming need to sleep. Given that EDS is predominantly present during monotonous situations, it may engender an obstacle to sustained attention and to perform everyday activities. In fact, daytime automatic behaviours are often seen as a result of EDS (30). When patients do fall asleep, episodes are usually but not invariably short (from seconds to a few minutes) and refreshing (31).

Cataplexy is a highly specific symptom of NT1. It is characterised by sudden, usually bilateral, brief loss of muscle tone, generally triggered by positive emotions (joy, laughter and surprise are more commonly reported), with preserved consciousness (30). In addition to a reduction in the electromyographic tone and evidence of wakefulness in the electroencephalogram, cataplexy is accompanied by areflexia and a disappearance of the H-reflex. The loss of muscle tone can be partial, involving the face, limbs or speech musculature, with a mean duration usually less than 10 seconds, or complete (with the exception of the diaphragm and the extraocular muscles), with a slightly longer duration. Episodes lasting more than 5 minutes and up to 60 minutes (so-called 'status cataplecticus') are rare, and often appear as a rebound effect after a prompt withdrawal of anti-cataplectic drugs (32). Cataplexy generally develops 3–5 years after the onset of EDS, but rarely can precede the onset of other features of narcolepsy (30). The frequency of attacks is variable and may range from several per day to a few episodes over an entire year.

Less specific features, but present in around 50% of cases, are sleep paralysis and hypnagogic hallucinations. Sleep paralysis consists of an inability to speak or move voluntary muscles, during the process of waking up or falling asleep, occurring in full consciousness (33). Hypnagogic hallucinations are normally visual, but auditory or sensory experiences might arise. Both symptoms happen more frequently at sleep onset and, when occurring together, may have a frightening or bizarre content.

In addition to the symptoms included in the classical tetrad (EDS, cataplexy, hallucinations and sleep paralysis), disturbed nocturnal sleep is highly prevalent in patients with narcolepsy. The quality of nighttime sleep is partly determined by the repeated awakenings, as well as increased stage N1 of NREM sleep, higher amount of transitions to wake, and decreased percentage of slow wave sleep in recorded PSGs (34).

Further sleep disorders might be associated to patients with narcolepsy, including REM sleep behaviour disorder (RBD), highly suggestive of NT1 when it affects young individuals (35); periodic limb movements during sleep (PLMS); and obstructive sleep apnoea (OSA). Depressive symptoms and anxiety may be comorbid entities in patients with narcolepsy.

The paediatric population is a particularly challenging subgroup of patients for the recognition of narcolepsy. During childhood and, especially, at an early time after the onset of symptoms, cataplectic events are displayed in a variety of forms. Yet, there is an evolution over time towards the common phenotype seen in adults. Negative movements, often involving the face (ptosis, tongue protrusion, facial hypotonia), are commonly found. Dyskinetic/dystonic motor phenomena, and other active motor features (eyebrow raising, facial grimacing, perioral movements), are also frequent (36). In children, EDS may be manifested with prolongation of nocturnal sleep and, paradoxically, with restlessness and irritability (37). Additionally, abrupt weight gain and precocious puberty suggest an impact of NT1 on the metabolic and endocrinological systems (38).

Diagnostic criteria

Following the ICSD-3 criteria, NT1 can be diagnosed when criteria (I) and (II) are met (1):

(I) Daily periods of irrepressible need to sleep or daytime lapses into sleep, for at least 3 months;
(II) The presence of one or both of the following:
  (i) cataplexy and MSLT shows a mean sleep latency ≤8 minutes and two or more SOREMPs (one SOREMP can be replaced with a REM

period within 15 minutes of sleep onset in the preceding PSG);

(ii) CSF hypocretin-1 concentration is either ≤110 pg/mL or <1/3 of the mean values obtained in normal subjects with the same assay.

Of note, the MSLT should be performed according to standard techniques, and hypocretin-1 should be measured by immunoreactivity. The MSLT has not been validated in children yet (37).

The differential diagnosis of NT1 includes all other entities presenting with EDS (NT2, IH, KLS, hypersomnia related to medical/psychiatric disorders or substances, and ISS). Drop attacks, seizures, psychogenic episodes and transient ischaemic attacks may be misdiagnosed as cataplexy-like episodes. Moreover, in the context of sleep deprivation, individuals with shift work, or secondary hypersomnias, MSLTs may show equivalent findings to those required for the diagnosis of narcolepsy (39). Therefore, before the study is implemented, sleep restriction should be excluded, preferably with a 2-week actigraphy, and interfering drugs must be ideally stopped. Nevertheless, certain findings in the MSLT, such as SOREMPs arising from N1 stage or wakefulness (instead of N2 or N3 stages), increase the probability of NT1 (40). Similarly, the same sleep-stage sequence (appearance of the first REM period from N1 or awake) during nocturnal PSG is significantly more frequent in individuals with narcolepsy than with insufficient sleep (41). Moreover, the occurrence of SOREMPs from N1 or wakefulness in the MSLT seems to be related to a worse therapeutic response (42). These outcomes allow clinicians to conveniently use routine investigations as valuable tools in the diagnosis of narcolepsy. The specific sleep-stage sequence will contribute to discriminate similar phenotypes of utterly diverse conditions, and will also help to identify patients with undetected or yet to be developed cataplexy.

In contrast, HLA typing has limited use in the diagnosis of NT1; while 85–95% of patients with NT1 carry the HLA DQB1*0602, this haplotype is also found in 20–30% of the general population. Therefore, only its absence would be helpful to support an alternative diagnosis. Nonetheless, given that 98% of patients with low hypocretin-1 are DQB1*0602 positive, the haplotype determination could be valuable to elucidate an accurate diagnosis in patients that may require a lumbar puncture (33).

Management

To date, treatment of narcolepsy remains symptomatic, with a focused management of those features that predominantly have a deleterious effect on patients' lives. Thus, the management strategy should be individually tailored to the improvement of social and professional functioning of these patients.

Although naps during the day may improve the status of patients, daytime sleepiness is mainly treated with stimulants. Modafinil (and its r-enantiomer armodafinil) are wake-promoting drugs, with a safe profile, and an effect on increasing concentrations of dopamine and other monoamines. Modafinil is considered the first-line therapy for sleepiness in narcolepsy, with very few adverse events (headache, nervousness, nausea).

Methylphenidate, which blocks the reuptake of monoamines, and dexamphetamine, which at low doses releases mainly dopamine, are less well tolerated. Common side effects are irritability, reduced appetite and insomnia. Although these drugs are of potential abuse or tolerance, the addiction rate among patients with narcolepsy is low (43). Extended-release formulations of amphetamines may be useful in cases with disabling EDS where a prolonged duration of action is required.

Sodium oxybate, although used as anti-cataplectic therapy, has a positive effect on EDS. Alternative agents include mazindol (blocks dopamine and noradrenaline reuptake) and selegiline (inhibits monoamine oxydase B). More recent developments include the licensing of pitolisant, the first in a novel class of drugs, a selective histamine H3 inverse agonist (44).

Cataplexy normally also requires pharmacological treatment. Sodium oxybate has a stimulating effect on $GABA_B$ receptors, with a scantily comprehended mechanism of action in narcolepsy. Sodium oxybate constitutes the first-line choice for cataplexy, allowing for local financial factors. The beneficial actions of sodium oxybate in narcolepsy are several: it reduces frequency and intensity of cataplectic episodes, improves EDS, and reduces nocturnal awakenings.

Antidepressants are extensively used for the management of cataplexy. Principally used in the clinical setting are clomipramine (tricyclic antidepressant that may have anticholinergic side effects), venlafaxine (serotonin and noradrenalin reuptake inhibitor) and fluoxetine (selective serotonine reuptake inhibitor), the last two with very few adverse events. Other agents include reboxetine and atomoxetine (noradrenaline reuptake inhibitors). More recently, pitolisant has also been shown to be effective for cataplexy (45).

Treatments for cataplexy are also effective in the management of sleep paralysis and hypnagogic hallucinations (46).

The treatment of disturbed nighttime sleep, frequently seen in patients with narcolepsy, should be weighed up against the risk of increasing EDS. Commonly utilised therapies include benzodiazepines (clonazepam), related hypnotics (zolpidem, zopiclone), and pregabalin. Sodium oxybate also improves nighttime sleep in narcolepsy (47); nightly administration of sodium oxybate increases slow wave sleep and decreases both the stage N1 and number of awakenings.

Regarding other comorbidities (e.g., RBD, PLMS, OSA) there are no specific indications for patients with narcolepsy. However, in order to initiate treatment with sodium oxybate, careful management of OSA is required (48).

Following the recommendations of the Food and Drug Administration (FDA), the medications mentioned above are classified as category C (risk cannot be ruled out) for the treatment of narcolepsy during pregnancy; and according to the European Medicines Agency (EMA), these drugs are not recommended during pregnancy and lactation (49).

Despite the lack of approval by the FDA/EMA, adult medications have been extensively used off-label in children with narcolepsy (37). Modafinil, methylphenidate and sodium oxybate are used to treat EDS. For cataplexy, sodium oxybate and venlafaxine can be initiated (50). Sodium oxybate may also be useful for disturbed nighttime sleep management, and may have a positive effect on weight loss (51). The treatment of precocious puberty with analogues of gonadotropin releasing hormone is recommended (37).

More experimental treatments include $GABA_A$ receptor modulators—clarithromycin modestly reduced EDS (52), and flumazenil was especially useful in female narcoleptics with refractory somnolence (53). Hypocretin-based therapies have been investigated, however the evidence is limited and no indications have been established for their use.

NT2

EDS and REM sleep dysregulation is exhibited in NT2; yet, cataplexy is absent and CSF hypocretin-1 levels should not have been proven to be low. However, given that some patients may develop cataplexy years after the onset of the EDS, it remains a debated issue whether NT2 is a distinct entity (54).

Since the majority of the epidemiological studies included patients with both NT1 and NT2 (55,56), there are no valid data related to the prevalence of NT2. Its challenging detection, due to lack of awareness of the condition, nonspecific criteria, and lack of pathognomonic features such as cataplexy, may result in under or over-diagnosis of the disorder (43).

Pathophysiology

Although the precise pathological mechanism of NT2 is uncertain, a loss of hypothalamic hypocretin-producing neurons (albeit less severe than in NT1) has been demonstrated (57). Furthermore, cases of NT2 may reflect early stages of NT1, where partial lesions of hypocretin neurons lead to sleep symptomatology without decreasing hypocretin concentration significantly. In series of patients with narcolepsy without cataplexy (58), subjects with intermediate levels (110–200 pg/mL) of hypocretin-1 had higher rates of HLA DQB1*06:02 positivity; however, with a moderate global frequency (around 60%) of the haplotype in the group.

To date, NT2 remains a heterogeneous entity, where true cases of narcolepsy without significant hypocretin depletion, early stages of NT1 and misdiagnosis of disorders with similar phenotypes, may coexist.

Clinical features

Chronic EDS along with recurrent episodes of hallucinations and sleep paralysis, lack of cataplexy, and absence of possible psychiatric conditions that might better explain the symptoms, would point at a possible diagnosis of NT2. Daytime naps are usually refreshing and often include dreaming (54). Hypnagogic or hypnopompic hallucinations are present in around 30% of NT2 cases, and sleep paralysis occurs at an average of 3 times per month in series including patients with NT2 (59). In addition, sleep fragmentation may also be common in NT2 patients (54).

Diagnostic criteria

The key to correctly diagnose NT2 relies on an accurate exclusion of other sleep or medical disorders that might mimic its symptoms and sleep tests results. Criteria (I)–(V) of the ICSD-3 (1) must be met:

(I) Daily periods of irrepressible need to sleep or daytime lapses into sleep, for at least 3 months;
(II) MSLT shows a mean sleep latency ≤8 minutes and two or more SOREMPs (one SOREMP can be

replaced with a REM period within 15 minutes of sleep onset in the preceding PSG);

(III) Cataplexy is absent;

(IV) Either CSF hypocretin-1 concentration has not been measured or concentration is >110 pg/mL or >1/3 of the mean values obtained in normal subjects with the same assay;

(V) The hypersomnolence and/or MSLT findings are not better explained by other causes (insufficient sleep, OSA, delayed sleep phase, medication, substance withdrawal).

NT2 phenotype with intermediate hypocretin-1 levels may be a precursor to NT1, and symptomatology or laboratory findings may progress over time. Should cataplexy arise, or subsequent repeat CSF examination show <110 pg/mL levels of CSF hypocretin-1, the diagnosis will shift to NT1.

Differential diagnosis of NT2 includes the rest of central disorders of hypersomnolence, as well as sleep-disordered breathing, PLMS with EDS and multifactorial hypersomnia (age, medication, etc.). It cannot be overemphasised that ISS needs to be excluded before a diagnosis of NT2 is made; ISS affects up to 10% of the adult population and can give rise to a "diagnostic" MSLT (31). However, the possibility of a false-positive result in the MSLT (commonly due to sleep deprivation or shift work) may be moderated by other markers that support the diagnosis of NT2. The sequence of REM periods arising from N1 stage or wakefulness might help to discriminate narcolepsy from other hypersomnias (41) and foresee a worse prognosis in terms of treatment response (42).

The utility of HLA haplotype determination is limited in clinical evaluation of NT2. Only around half of patients with NT2 carry HLA DQB1*06:02, therefore, a positive result does not confer certainty for the diagnosis of this condition (54).

Overall, the identification of NT2 is a diagnosis of exclusion. Sleep specialists should be aware of the clinical and neurophysiological overlap that may exist between NT2, IH and hypersomnia related to psychiatric disorders (60).

Management

Therapeutic approaches mentioned in the NT1 section above, for the management of EDS and disturbed nighttime sleep, are also applicable in NT2.

IH

IH is less frequent than narcolepsy, with a suggested prevalence of 0.0035% (61). The estimated onset occurs in adolescence or in the early 20s (62); and a familial predisposition for IH has been observed (63). The previous distinction of IH into separate diagnoses with and without long sleep time has been dropped in the new classification (1), due to insufficient validation.

Pathophysiology

The cause of IH is still speculative. Anomalies in melatonin secretion and the circadian system have been shown in patients with IH (64,65). Most studies have demonstrated normal levels of CSF hypocretin-1 in IH patients (66,67). Initial reports found decreased CSF levels of histamine in patients with IH and other central disorders of hypersomnolence (68). However, these findings have not been subsequently replicated (69). The utility of certain therapeutic agents with a modulating effect on $GABA_A$ receptors in patients with IH (70) possibly points to their involvement in the pathophysiology of this condition.

Clinical features

Subjects with IH suffer from hypersomnolence that is characteristically exhibited as 'sleep drunkenness' or 'sleep inertia'. These terms denote a difficulty in awakening, or in achieving full alertness on waking from night sleep or a nap (33), that may be accompanied by automatic behaviours and confusion. Nocturnal prolonged and undisturbed sleep is usually seen. Typically, patients with IH describe unrefreshing and long-lasting (>1 hour) naps. Hypnagogic hallucinations and sleep paralysis occurrence seems similar to that of NT2, and are more frequently seen than in controls (71).

Further features such as autonomic symptoms (cold extremities, palpitations, fainting episodes) and low mood may be exhibited (71,72). However, the current presence of a psychiatric disorder should exclude, by definition, the diagnosis of IH.

Diagnostic criteria

New diagnostic criteria (1) for IH are as follows [criteria (I)–(V) must be met]:

(I) Daily periods of irrepressible need to sleep or daytime lapses into sleep, for at least 3 months;

(II) Cataplexy is absent;
(III) MSLT shows fewer than two SOREMPs, or no SOREMPs if the REM latency in the preceding PSG is less than or equal to 15 minutes;
(IV) The presence of at least one of the following:
  (i) MSLT shows a mean sleep latency ≤8 minutes;
  (ii) total 24-hour sleep time is ≥660 minutes on 24-hour PSG monitoring (after correction of sleep deprivation), or by wrist actigraphy plus a sleep log (averaged over at least 7 days);
  (iii) ISS is ruled out (if necessary confirmed by at least 1 week of wrist actigraphy);
(V) The hypersomnolence and/or MSLT findings are not better explained by another sleep disorder, medical/psychiatric disorder, or use of drugs/medications.

Of note, high sleep efficiency (>90%) on the preceding PSG is a supportive finding.

As with NT2, the diagnosis of IH is one of exclusion. Hence, ruling out other sleep, medical and psychiatric disorders (see 'NT2, Diagnostic criteria' section), particularly ISS, is crucial. In patients that show a discrepancy between the mean sleep latency and the total sleep time (the first longer than 8 minutes, the latter shorter than 660 minutes, or vice versa), the establishment of a diagnosis of IH should be considered cautiously. A reasonable approach may include repeating the MSLT at a later date if suspicion for IH is high.

Management

Treatment of EDS in patients with IH is similar to that in narcolepsy, with modafinil the stimulant therapy of choice in most cases. Despite medication, however, sleep drunkenness often persists, although occasionally nighttime stimulants may help. In contrast to ISS, sleep extension may worsen EDS in IH patients (43).

The effectiveness of further agents has been investigated in IH. Patients with this condition seem to benefit from $GABA_A$ receptor modulators. Recent studies have demonstrated that certain drugs, such as clarithromycin (52) and flumazenil (53), decrease EDS in patients with IH. Pitolisant has only shown moderate beneficial effects in patients with IH (73). Additionally, the use of melatonin resulted in decreased EDS, improvement of sleep drunkenness, and shortened sleep time in reported cases of IH (74). Low doses of levothyroxine were effective in the treatment of EDS in a prospective study (75).

KLS

KLS is characterised by recurrent and reversible episodes of hypersomnia and cognitive or behavioural features. The estimated prevalence of KLS accounts for 1–5 cases per million population and has a male predominance. KLS usually emerges in adolescence, with a reported family history in 5% of cases (76).

Pathophysiology

The aetiology of KLS has not been established yet. As a result of the fluctuating course and the usual report of an infection preceding the onset of the disease, an inflammatory or autoimmune aetiology have been suggested. However, there are no consistent data to support this hypothesis. Identified triggers of episodes include upper-respiratory infections (77) and fever, but also alcohol, stress, heat, brain traumatic injury (78), vaccines or illicit drugs (79). In addition, high rates of birth difficulties are commonly reported among patients (76,79). Results in HLA genotyping are inconclusive in KLS (76,77,80), inflammation markers are not present (76) and no systemic immune reaction has been observed during episodes (81). Although CSF hypocretin-1 is usually within the normal range, lower levels have been described during episodes and, in a recent study (82), were related to abnormal autonomic function (lower heart rate and diurnal blood pressure).

The involvement of diencephalic and cortical regions in the pathophysiology of KLS, during the episodes and in asymptomatic phases, has been demonstrated by brain imaging studies. However, results are inconsistent. Single photon emission computed tomography (SPECT) studies have demonstrated hypoperfusion in thalamus, hypothalamus and certain cortical areas during episodes (83-85) that may persist in asymptomatic periods (85). Results in positron emission tomography (PET) works are variable. In line with SPECT findings, some studies have found episodic thalamic hypometabolism that improved in the asymptomatic intervals (86,87). In contrast, other cases have shown thalamo-striatal activation (88), and widespread areas of hypermetabolism, with a few cortical regions showing hypometabolism (89) in the symptomatic phase. Also, persistent hypermetabolism in a wide cortical network was found between episodes in some subjects (89). Altered thalamic activation patterns, seen in functional MRI, have been described in patients with KLS as well (90,91).

Clinical features

During episodes of KLS, patients become increasingly tired, and experience intense fatigue and irresistible need to rest (92). Frequently, the episode includes hypersomnia plus at least one of confusion, apathy or derealisation. Patients appear sleepy, slow, incoherent and amnesic. If the individual is not sufficiently stimulated during an episode, they may sleep for more than 15 hours per day (43). In a large cohort of patients with KLS (79), cognitive impairment, altered perception and eating behaviour disturbances, appeared in 95–100% of subjects. Although disinhibited behaviours (hyperphagia, hypersexuality, childish behaviour) and irritability are characteristic features of KLS, they are less consistently seen (76). Autonomic features such as flushing, sweating, hyperventilating, tachycardia and hypotension may appear as well.

Most episodes start abruptly, develop over a few hours, last for 1–3 weeks, and are followed, in theory, by a complete recovery. The frequency of KLS episodes decreases with time until the spontaneous resolution of the condition, usually after a median course of the disease of 13–14 years (76). Importantly, prolonged episodes (>1 month) predict a worse prognosis of KLS, with more feelings of mind/body split and agitation during episodes, and more residual symptoms (e.g., anxiety, depression, post-episode amnesia).

Despite the requirement of a complete remission of symptomatology, and normal cognition between episodes, some patients show long-lasting mild memory impairment and academic difficulties (93). Also, during asymptomatic periods, patients seem to sleep longer and better than controls, and show remaining mood changes (79).

Diagnostic criteria

The diagnosis of KLS requires criteria (I)–(V) of the ICSD-3 (1):

(I) At least two recurrent episodes of excessive sleepiness and sleep duration, each persisting for 2 days to 5 weeks;
(II) Episodes recur usually more than once a year and at least once every 18 months;
(III) The patient has normal alertness, cognitive function, behaviour and mood between episodes;
(IV) The patient must demonstrate at least one of the following during the episodes:
  (i) cognitive dysfunction;
  (ii) altered perception;
  (iii) eating disorder (hyperphagia or anorexia);
  (iv) disinhibited behaviour (such as hypersexuality);
(V) The hypersomnolence and related symptoms are not better explained by another sleep/medical/neurological or psychiatric disorder (especially bipolar disorder), or drugs/medications.

While the diagnosis of KLS is made on clinical grounds, and no ancillary tests are necessary, 24-hour PSG demonstrates prolonged total sleep time (92).

Mimics of KLS include psychiatric conditions (namely bipolar disorder), temporal lobe epilepsy, intermittent hyper-ammonemic encephalopathy (79), migraine with brainstem aura (94), urea cycle defects, acute intermittent porphyria, Lyme disease, mass lesions and bitemporal insults. Therefore, a proper neurological assessment is crucial in these patients (95). A subtype of KLS is the menstrual-related hypersomnia, where recurrent episodes exclusively emerge during or prior to menstruation.

Management

Only a few number of agents have shown some beneficial effects in the prevention of episodes, namely lithium, carbamazepine, valproic acid, lamotrigine, and certain antidepressants (95,96). Amantadine may be helpful to abort an episode (76), and other stimulants to improve the sleepiness (96).

ISS

ISS is an entity characterised by EDS that results from sleep deprivation. Although the prevalence is unknown, clinical experience shows an extremely high frequency (because of current lifestyles), and it affects mostly adolescents or young adults (40).

Patients with ISS complain from EDS, involuntary naps, unclear 'blackouts' and cognitive symptoms. ISS has a fluctuating course where short habitual sleep duration is typically alternated with considerably longer sleep periods during weekends.

ISS constitutes the main differential diagnosis of all the hypersomnia disorders. Neurophysiological findings in a PSG or a MSLT may mimic those of narcolepsy, with reduced sleep latency, and SOREMPs (though unlikely from N1 stage or wakefulness) (41,42). Nonetheless, high sleep efficiency and increased slow wave sleep may be seen as a rebound effect of chronic deprivation. Actigraphy can support the diagnosis, and generally demonstrates irregular

sleep habits and insufficient sleep time (43).

Sleep extension is the most rapid and effective strategy to improve behaviourally induced sleep restriction (97) and results in remission of sleepiness.

Hypersomnolence due to other causes

There are a variety of medical disorders that can be related to EDS. Recognised categories in the current ICSD-3 include (1): hypersomnia in patients with Parkinson's disease; post-traumatic hypersomnia; hypersomnia in hereditary disorders (e.g., Niemann-Pick type C, myotonic dystrophy); due to lesions of the central nervous system (namely in paramedian thalamus); to endocrine disorders (e.g., hypothyroidism), due to metabolic encephalopathy; and hypersomnia in adequately treated OSA. Additionally, sleepiness may be present in other neurological conditions such as restless legs syndrome, dementia with Lewy bodies and multiple sclerosis. Multiple factors are probably involved in their pathophysiology. Nevertheless, reduced activity in wake-promoting neurons and disinhibited sleep-inducing transmission may be associated.

Hypersomnolence is particularly prevalent in psychiatric conditions and may interfere with illness resolution. Up to 75% of patients with major depressive disorder suffer from somnolence, but it is also frequently seen in bipolar, dysthymic and seasonal affective disorders (98). Characteristically, subjects spend a considerable time in bed, albeit not necessarily sleeping (a conduct called clinophobia). However, approximately 25% of patients with psychiatric hypersomnolence will exhibit a mean sleep latency of less than eight minutes on the MSLT (99).

Lastly, several medications and other substances can be the cause of EDS (especially in the elderly population), such as hypnotic or sedating drugs, dopaminergic agents and alcohol intake (100).

Conclusions

Central disorders of hypersomnolence include a wide range of heterogeneous conditions, which are characterised by excessive sleepiness that often leads to a negative impact on the quality of life of patients. As available tools are rather nonspecific, the diagnosis remains to be one of exclusion in most cases. The variability in presentation and the lack of definite markers result in a challenging process of identification for clinicians.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Pérez-Carbonell L, Leschziner G. Clinical update on central hypersomnias. J Thorac Dis 2018;10(Suppl 1):S112-S123. doi: 10.21037/jtd.2017.10.161

