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The evolving diagnosis and classification of CNS hypersomnolence disorders

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Abstract

Purpose of Review We describe the evolution and limitations of current diagnostic criteria and classification systems of CNS hypersomnolence disorders and propose some changes.

Recent Findings An unsupervised cluster analysis of 1100 Europeans with hypersomnolence identified the narcolepsy type 1 phenotype but not other categories listed in ICSD-3.

Summary There are long-standing unsolved issues regarding the diagnosis and classification of central disorders of hypersomnolence. These include delineating and identifying phenotypes and unique conditions ("sui generis"), sleep deprivation's impact on phenotypes and how to separate sleep deprivation as a trigger from other causes, as well as the association of excessive sleepiness with other disorders. We discuss these issues and present a novel, straightforward classification system with consistent terminology to get out of the impasse and do justice to people with hypersomnolence.

Keywords Hypersomnolence · Narcolepsy · Hypersomnia · Classification · Diagnosis

Introduction

The introduction of polysomnography in the 1970s has driven the development of sleep medicine as a new discipline. Based upon this new diagnostic method, not only new scientific knowledge was gained, but also sleep-related disorders were identified and differentiated.

This created a need to establish a classification scheme for sleep disorders and define uniform diagnostic criteria. In 1979, the "Diagnostic Classification of Sleep and Arousal Disorders" was established, and in 1990, the first version of the "International Classification of Sleep Disorders" was issued [1, 2].

What Prevents Us from Having an Ideal Classification?

Currently, sleep clinicians worldwide apply the diagnostic criteria of the third edition of the International Classification of Sleep Disorders (ICSD-3) for making their diagnoses. It is the only international classification dedicated to sleep disorders and made by sleep experts. ICSD-3 is used worldwide and termed "international," but formally it is the American Academy of Sleep Medicine (AASM) classification [3].

Other regularly updated classifications cover all (mental and) medical disorders, such as the ICD-11 and DSM-5-TR [4, 5]. They more or less define similar diagnostic categories. However, there are some differences in the criteria and strictness of their description or need to be present to make a specific diagnosis.

Despite its global use, there is a long-lasting debate, particularly regarding the chapter on central disorders of hypersomnolence. It is an ongoing discussion due to the unknown pathophysiology of these disorders and the lack of progress in the quest for it. One exception has been

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narcolepsy type 1 (NT1). Recent work using unsupervised cluster analysis in the large European EU-NN prospective database, containing full data of almost 1100 people with central disorders of hypersomnolence, supports the concept that current categories are arbitrary. The analysis showed clusters that identified the phenotype of NT1 but not other categories listed in ICSD-3 [6•]. This probably explains that we have only been able to identify a biomarker for NT1. Identifying markers and understanding the pathophysiology of a disorder is only possible if homogeneous groups are identified and studied. The current non-NT1 categories are based on clinical concepts, polysomnography results, and/or associated testing (Multiple Sleep Latency Test). The MSLT results have more recently been inconsistent, questioning the validity of separating diagnostic categories based only on MSLT results [7•, 8].

Different classifications, including the ICSD3, struggle mainly with three unsolved discussions:

- To distinguish chronic sleep deprivation induced by lifestyle or social or environmental circumstances from disorders causing hypersomnolence as a cause for excessive daytime sleepiness. A related question is: What is the influence of added sleep deprivation in conditions causing EDS? This has hardly been assessed, although it might also influence the chance of identifying biomarkers. This is also true for MSLT results. According to recommendations, MSLT is valid when 6 h of nocturnal sleep are documented the night before the test, although it may be impacted by more than the sleep duration the night before. These may also be relevant questions for sleep-related breathing disorders that have been hardly addressed.
- The characterization of different phenotypes. For instance, the phenotype better described by an increased need (10 h) for sleep over a day needs to be differentiated from a phenotype characterized by the inability to stay awake during the day.
- Is it good sense to define categories suggesting that EDS complaints are associated with or even caused by other disorders? How to know if EDS complaints are part of other (mental) disorders? To date, categories such as hypersomnia or narcolepsy "associated" with or "caused" by a medical condition and also "associated" or "caused" by psychiatric disorders exist in the ICSD. But, is it relevant to have these categories, as they mainly cause misperception and hardly ever benefit patients? In insomnia, they do not exist. The ICSD-3 nor DSM-5 defines categories like "Insomnia due to depression" or "Insomnia associated with depression" or "Insomnia associated with psychosis" although these orders often co-exist. There has been recent improvement regarding this issue. DSM-5-TR has abandoned these categories for "hypersomnolence" categories but not for narcolepsy, and, interestingly, ICD 11 abandoned them for narcolepsy but not for "hypersomnia" disorders.

The debate regarding the ICSD-3 chapter on central disorders of hypersomnolence is, however, not limited to the diagnostic categories and their criteria. There appear to be essential practice differences worldwide regarding which of the diagnostic criteria are applied when there are multiple options (i.e., for narcolepsy, the MSLT for hypocretin-1/orexin A measurement in the CSF). There are also concerns regarding the method and rigor used to rule out other causes, particularly sleep deprivation, before a diagnosis is contemplated. In Europe, actigraphy is essential to assess or rule out sleep deprivation as a cause of EDS. In cases of doubt, sleep extension is advised and verified before scheduling ancillary investigations. Ancillary investigations are only performed when complaints remain after sleep extension. In the USA and other parts of the world, using actigraphy to identify chronic sleep deprivation is much less common. Usually, history-taking and diary information are considered to be sufficient. This may explain the discrepancy between the USA and Europe regarding the prevalence of NT2. In Europe, this is a tiny percentage of patients with narcolepsy, but in the USA, NT2 is a frequent diagnosis, probably 2 to 3 times as frequent as NT1 [9–11]. Since chronic sleep deprivation and shift work can cause this phenotype, it seems probable that the difference is mainly explained by the scrutiny of the exclusion of sleep deprivation as a cause. This is supported by European studies [12, 13•].

Lastly, the ICSD-3 and other diagnostic classifications do not adequately consider that diagnostic tests cannot be performed everywhere in the world due to a lack of resources.

The ultimate goal for classification is to be based on the underlying neurobiological causes and have clear implications for treatment or, ideally, prevention and healing [14•]. This ideal situation is far from reality for disorders characterized by daytime sleepiness (EDS and excessive need for sleep (ENS)). Only for narcolepsy with cataplexy/NT1 do we know the pathophysiology. The pathophysiology here is reflected in a sensitive and specific biomarker that also is the causative problem: the hypocretin-1 concentration in the CSF. This is incorporated in the recent editions of all the discussed classifications. For the rest of the disorders, the current classifications are flawed by inconsistencies and are based on complaints or presumed pathophysiology. For diagnosis, current classifications either require objectification or not require or not objective findings on ancillary investigations that may be specific or not. These classifications are

Table 1 Diagnostic criteria for excessive daytime sleepiness (EDS) and excessive need for sleep (ENS), adapted from Lammers et al.

EDS		ENS	
Clinical presentation	*Criteria*	*Clinical presentation*	*Criteria*
1. Inability to stay awake in monotonous situations with unintended napping and possibly sleep attacks	Daily or near daily presence of symptom 1 *or* daily presence of symptom 2 *and* one other symptom (3–5)	1. An increased need for sleep in daily life. Must comprise at least 10 h per 24 h and/or at least 9 h of nocturnal sleep	Daily or near daily presence of all 3 symptoms
2. Presence of a feeling of daytime sleepiness throughout most of the day as opposed to symptoms of fatigue		2. Presence of at least one of the symptoms listed for EDS *and/or* the presence of sleep inertia/sleep drunkenness	
3. Acquired need for scheduled napping during the day		3. Sleep extension will not (fully) compensate the symptoms of no. 2	
4. Difficulty with sustained attention and vigilance			
5. Automatic behaviors that be attributed to EDS			

Table 2 Diagnostic criteria for narcolepsy, idiopathic hypersomnia, and idiopathic excessive sleepiness (adapted from Lammers et al., 2020)

Level	Narcolepsy	Idiopathic hypersomnia	Idiopathic excessive sleepiness
Level 1 – definite	A. EDS and/or typical cataplexy *and* orexin deficiency (CSF) B. EDS and typical cataplexy *and* MSLT with msl < 8 min *and* > 1 SOREMP*	A. ENS (acquired) B. Objective evidence for increased sleep using PSG and actigraphy**	A. EDS B. MSLT: msl < 8 min##
Level 2 – probable	A.EDS and typical cataplexy *and* MSLT with *either* msl < 8 min *or* > 1 SOREMP B. EDS (without typical cataplexy) but with HH and/ or SP and/or disturbed nocturnal sleep *and* MSLT with either msl < 5 min and > 1 SOREMP *or* msl < 8 min and > 2 SOREMP *and* HLA-DQB1*0602 positive #	A. ENS (acquired) B. Objective support*** for increased sleep using PSG and actigraphy	A. EDS B. MSLT: msl > 8 min and < 12 min## *Subtype R (REM type)*: MSLT/PSG: ≥ 1 SOREMP SART: normal or abnormal *Subtype N (NREM type)*: MSLT/PSG: no SOREMP SART: normal *Subtype A (Attention)*: MSLT/PSG: no SOREMP SART: abnormal

EDS, excessive daytime sleepiness; ENS, excessive need for sleep; CSF, cerebrospinal fluid; MSLT, multiple sleep latency test; SOREMP, sleep onset REM period; PSG, polysomnography; SART, sustained attention to response task

Remarks: *Including nocturnal sleep. #Other causes for EDS need to be excluded. **Two weeks actigraphy and 32 h polysomnography supporting at least 9 h nocturnal sleep or 10 h sleep over the 24 h of the day. ***Similar to ** but with 24 h polysomnography or with results almost meeting the 9/10 h criterium. ##Diagnostic criteria for Narcolepsy or IH not fulfilled, and other causes for EDS need to be excluded

based on historical concepts that are no longer tenable or based only on expert opinion.

We have not made relevant progress during the last decades because we are kept hostage in circular reasoning. The lack of reliable biomarkers prevents us from defining homogeneous diagnostic categories. The relatively arbitrary diagnostic categories stop identifying biomarkers and progress in understanding the pathophysiology of the central disorders of hypersomnolence beyond NT1.

It explains the mixed policy of classification of disorders other than NT1 over the last decades.

Potential Solutions

Potential solutions are frustrated by substantive discussions that lack guidance of reliable data and are influenced by reimbursement issues. There is insecurity and maybe fear for insurance companies that may no longer reimburse

diagnostic procedures or treatments for some patients when changing diagnostic categories. There is also concern that patients may not be able to deal with receiving a different diagnostic label or may feel uncomfortable with a classification that allows levels of uncertainty. As long as newly formulated categories are tentative, this will remain a debate. It seems, however, to be an inevitable step we need to take to bring progress and identify proven homogeneous and relevant diagnostic categories. The introduction of levels of certainty is also an essential part of this process.

Notably, the introduction of degrees of certainty should not be mistaken as uncertainty about the existence of a serious medical problem. The uncertainty should only concern the specific diagnostic category. Patients are taken more seriously with such an approach. They will have much less chance to be confronted with a completely different diagnosis over time, compared to the current situation, if this will be introduced.

Presently, IH is often diagnosed when criteria for narcolepsy are not fulfilled and hence is often interpreted as sleepiness/ENS of unknown origin with a heterogeneous phenotype. This, however, is not a fair description of the disease and does not reflect the severity of limitations existing by IH. This may also be in part by complex terminology. A classification system should use simple, clear, consistent terminology and be more precise in this context. This will help to ensure that the classification can be applied everywhere.

The exact definition of a precise number of hours of sleep per 24 h of the day remains uncertain. However, this problem may, for the time being, also be solved by introducing levels of certainty. We currently only have arguments, supported by the unsupervised cluster analysis among other studies [6•], for those who do not qualify for narcolepsy with cataplexy. It supports delineation of a diagnostic category for excessive need for sleep which seems to include sleep drunkenness as additional symptom.

We strongly believe that being daring is the only way to move forward. We need this to progress in understanding and optimizing the treatment of sleep disorders, which is what people with sleep disorders and society expect. We must not be kept hostage to an unworkable classification, as the current structure and criteria hardly allow improvements based on evolving scientific insight.

Conclusion

We need a novel structure allowing the implementation of new scientific insights and the discovery of new biomarkers. We will never identify biomarkers of diagnostic categories that allow too much variation in phenotypes or allow too many options to diagnose. We also need a link/bridge towards related disorders such as ADHD/ADD, OSA and chronic fatigue.

A recent consensus statement of European experts suggests, along these lines, the following definitions for excessive daytime sleepiness and excessive need for sleep and novel classification for narcolepsy, idiopathic hypersomnia, and idiopathic excessive sleepiness (for details, please see Lammers et al., 2020 [14•]: Tables 1 and 2).

Declarations

Human and Animal Rights and Informed Consent There are no conflicts with human and animal rights. Informed consent is not applicable. This is an opinion paper; therefore, ethical approval does not apply.

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