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CLINICAL REVIEW

Idiopathic hypersomnia

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SUMMARY

Idiopathic hypersomnia continues to evolve from the concept of "sleep drunkenness" introduced by Bedrich Roth in Prague in 1956 and the description of idiopathic hypersomnia with two forms, polysymptomatic and monosymptomatic, by the same Bedrich Roth in 1976. The diagnostic criteria of idiopathic hypersomnia have varied with the successive revisions of the International classifications of sleep disorders, including the recent 3rd edition. No epidemiological studies have been conducted so far. Disease onset occurs most often during adolescence or young adulthood. A familial background is often present but rigorous studies are still lacking. The key manifestation is hypersomnolence. It is often accompanied by sleep of long duration and debilitating sleep inertia. Polysomnography (PSG) followed by a multiple sleep latency test (MSLT) is mandatory, as well as a 24 h PSG or a 2-wk actigraphy in association with a sleep log to ensure a total 24-h sleep time longer than or equal to 660 minutes, when the mean sleep latency on the MSLT is longer than 8 min. Yet, MSLT is neither sensitive nor specific and the polysomnographic diagnostic criteria require continuous readjustment and biologic markers are still lacking. Idiopathic hypersomnia is most often a chronic condition though spontaneous remission may occur. The condition is disabling, sometimes even more so than narcolepsy type 1 or 2. Based on neurochemical, genetic and immunological analyses as well as on exploration of the homeostatic and circadian processes of sleep, various pathophysiological hypotheses have been proposed. Differential diagnosis involves a number of diseases and it is not yet clear whether idiopathic hypersomnia and narcolepsy type 2 are not the same condition. Until now, the treatment of idiopathic hypersomnia has mirrored that of the sleepiness of narcolepsy type 1 or 2. The first randomized, double-blind, placebo-controlled trials of modafinil have just been published, as well as a double-blind, placebo-controlled trial of clarithromycine, a negative allosteric modulator of the γ-aminobutyric acid-A receptor.

Introduction

In contrast to narcolepsy first described in 1877 [1] and named in 1880 [2], and to Kleine–Levin syndrome first described in 1925 [3] and named in 1942 [4], the identification of idiopathic hypersomnia is much more recent, starting with the first description of sleep drunkenness in 1956 [5] and culminating in the coinage of the term idiopathic hypersomnia and the initial description of the condition in 1976 [6]. Thereafter, diagnostic criteria of idiopathic hypersomnia have been published in the International classification of sleep disorders (ICSD) [7] and revised in two later editions, the International classification of sleep disorders, second edition (ICSD-2) [8] and the International classification of sleep disorders, third edition (ICSD-3) [9]. Yet the clinician is still challenged by the absence of pathognomonic clinical features such as cataplexy in narcolepsy type 1 or the episodic hypersomnia associated with at least one of the following: cognitive dysfunction, altered perception, eating disorder or disinhibited behavior, typical of the Kleine-Levin syndrome, the inaccuracy of the "gold standard" multiple sleep latency test (MSLT) and the absence of a biologic marker. Moreover, an animal model is lacking, the pathophysiology is poorly understood, and the treatment is still borrowed from narcolepsy type 1 or 2. In this chapter we aim at formulating an appraisal of where the field is and where it should be heading.

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Abbreviations

ADHD	attention deficit/hyperactivity disorder
CAP	cycling alternating pattern
CGI	clinical global impression
CPAP	continuous positive airway pressure
CHKB	choline kinase beta
CPT1B	carnitine palmitoyl transferase
CSF	cerebrospinal fluid
DAT	dopamine transporter
DM1	myotonic dystrophy type 1
DSM-IV-TR	Diagnostic and statistical manual of mental disorders, 4th edition, text revision
DSM-5	Diagnostic and statistical manual of mental disorders, 5th edition
EEG	electroencephalogram
EQS	excessive quantity of sleep
ESS	Epworth sleepiness scale
GABA	γ aminobutyric acid
HLA	human leucocyte antigen
ICSD	International classification of sleep disorders
ICSD-2	International classification of sleep disorders, 2nd edition
ICSD-3	International classification of sleep disorders, 3rd edition
IgG	immunoglobulin G
MSL	mean sleep latency
MSLT	multiple sleep latency test
MWT	maintenance of wakefulness test
OSAS	obstructive sleep apnea syndrome
PLM	periodic limb movements
PSG	polysomnography
REM	rapid eye movement
RERAs	respiratory effort related arousals
rs	Ref SNP
SOREMPs	sleep-onset REM periods
SNP	single nucleotide polymorphism
SWA	slow wave activity
T-MHA	tele-methylhistamine
TCRA	T-cell receptor alpha

Glossary of terms

Hypersomnolence	as captured in the Diagnostic and statistical manual of mental disorders, 5th edition (DSM-5) focuses on excessive daytime sleepiness
Hypersomnia	as defined in the International classification of sleep disorders, 3rd edition (ICSD-3) focuses upon duration of sleep, hence the diagnostic terms "idiopathic hypersomnia" or "post-traumatic hypersomnia"

Historical account

The concept of idiopathic hypersomnia takes its roots in the description by Roth of "sleep drunkenness", a major difficulty in awakening [5]. One year later, the same author published a book entitled "*Narcolepsy and hypersomnia, from the aspect of physiology of sleep*" [10], in which he distinguished, solely on clinical grounds, 155 patients with narcolepsy and 93 with hypersomnia, and among those, 50 with functional hypersomnia, 29 with organic hypersomnia and 14 with independent "post-dormital" drunkenness. In 1960, Vogel showed that narcoleptic patients fall directly into REM sleep, paving the way to a more accurate distinction of these different forms of hypersomnolence [11]. In 1966, Dement et al. accordingly wrote that "those patients without cataplexy or sleep paralysis who also fail to show sleep-onset REM periods in laboratory tests probably do not have narcolepsy and should be relegated to another diagnostic category [12], a statement reminiscent of the much earlier clinical one by Levin: "I shall restrict the term narcolepsy or Gelineau's syndrome to those cases that present both sleep attacks and cataplexy … Patients with attacks of sleep are common, whereas patients with attacks of sleep and cataplexy are relatively rare, and it would seem wise, for the present, to regard the latter as a separate group" [13]. In 1967, Berti-Ceroni et al. proposed the term "*essential narcolepsy*" for this category of patients [14] and in 1968, Passouant et al. proposed the term "*NREM narcolepsy*" [15]. Later, Roth et al. published an article entitled "*Hypersomnia with sleep drunkenness*" based on 48 patients from the Department of Neurology in Prague and 11 that he had personally examined at the University of Chicago Sleep Laboratory [16]. These patients usually reported that their night sleep was extremely deep and the majority of them (51 of 58) suffered from diurnal hypersomnia, meaning too much daytime sleep. A total of 36 polygraphic recordings, approximately one hour in duration, were performed in 16 patients, during the day, in Prague. None of these patients showed sleep-onset REM periods (SOREMPs). Eleven patients from the Chicago Sleep Laboratory were monitored for two nights each, again without any SOREMPs [17]. Finally, in a landmark article published in 1976, Roth reported 642 personally-observed cases of narcolepsy and hypersomnia and coined the term "*Idiopathic hypersomnia*" [6]. Two forms were proposed: a polysymptomatic form characterized by excessive diurnal sleep of one to several hours duration, prolonged night sleep of a 12–18 h duration and great difficulty upon awakening in the morning, and a monosymptomatic form characterized by the most prominent and often unique manifestation of excessive diurnal sleep of one to several hours duration, however not as irresistible as in narcolepsy [6]. In 1979, the Diagnostic classification of sleep and arousal disorders referred to "*Idiopathic CNS hypersomnolence*" as a disorder of excessive somnolence "characterized by recurrent daytime sleepiness, but "sleep attacks" do not occur because the sleepiness is not as irresistible as in narcolepsy" [18]. In keeping with Dement's statement (see above) and results of previous polygraphic recordings in Chicago [17] and in Prague [16], the Diagnostic classification of sleep and arousal disorders mentioned that polysomnography (PSG) should fail to uncover SOREMPs. In addition, it included a reference to the MSLT, several years before the publication of the "guidelines for the MSLT: a standard measure of sleepiness" [19], indicating that "sleep latencies are usually very short in the daytime (MSLT) as well as at bedtime [18]. In 1990, the ICSD referred to "*Idiopathic hypersomnia*" as an "*intrinsic sleep disorder*" [7]. It also pointed that PSG should rule out SOREMPs; with regard to the MSLT it stated: "The MSLT usually demonstrates a sleep latency of less than 10 min". Of note, neither of these classifications maintained the division of idiopathic hypersomnia into two forms, as proposed earlier by Roth [6]. In 1997, Bassetti and Aldrich proposed three forms of idiopathic hypersomnia: "*classic*", referring to patients who tended to have sleepiness that was not overwhelming, to take long non-refreshing naps up to a 4 h duration, to have prolonged night-time sleep and to have difficulty in awakening in the morning; "*narcoleptic-like*", referring to