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CLINICAL REVIEW

Idiopathic hypersomnia

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KEYWORDS
Idiopathic hypersomnia, excessive daytime sleepiness, sleep drunkenness

Summary In contrast to narcolepsy and the Kleine–Levin syndrome, idiopathic hypersomnia is a recently described sleep disorder. Absence of associated clinical features such as cataplexy or megaphagia and characteristic polysomnographic features such as sleep-onset REM episodes render positive diagnosis more uncertain in idiopathic hypersomnia than in the fwo former conditions. Consequently there has been an unfortunate tendency to label all difficult to classify cases of excessive daytime sleepiness as idiopathic hypersomnia. At present due to the description of new disorders such as upper airway resistance syndrome, narcolepsy without cataplexy, delayed sleep phase syndrome, all of which were formerly confused with idiopathic hypersomnia and the clear identification of a "polysymptomatic" or "classic" form of idiopathic hypersomnia, the limits of the disorder become more precise. Still there are a number of cases of isolated excessive daytime sleepiness with no prolonged night sleep, no difficulty waking up, which lay between narcolepsy and genuine idiopathic hypersomnia. Thus there is a definite need to further develop laboratory investigations to help identify and classify these cases. Moreover pathophysiology and pathogenesis are still in their infancy and efforts have to be pursued in this direction. Treatment has not made consistent progress except for the use of a new wake promoting compound, modafinil, which has not yet been evaluated in controlled studies.

INTRODUCTION

In comparison with other primary hypersomnias, narcolepsy [1, 2] and the Kleine–Levin syndrome [3, 4], idiopathic hypersomnia stands as a recently identified entity [5, 6]. However, clinical heterogeneity and a lack of widely recognized laboratory tests have led to the condition being overdiagnosed. Moreover, due to the absence of a natural animal model, the pathophysiology of idiopathic hypersomnia is much less understood than that of narcolepsy. Finally the usual treatment of the condition does not differ from the one given for sleep attacks and sleepiness to narcoleptic subjects and it may be that a better understanding of the disorder would lead to a more adequate treatment. This paper is an attempt to review the concept of idiopathic hypersomnia from its first emergence to its present status, the diagnostic procedures, the differential diagnosis, the pathophysiology and pathogenesis and the currently prescribed treatments.

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BACKGROUND

Emergence of the concept

In 1966, Dement *et al.* [7] proposed that subjects with excessive sleepiness but neither cataplexy,

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sleep paralysis nor sleep-onset REM periods (SOREMPs) should not be considered as narcoleptic and should be relegated to another diagnostic category. Subsequently, Berti-Ceroni *et al.* [8] referred to "essential narcolepsy", Passouant *et al.* [9] to "NREM narcolepsy" and Rechtschaffen and Dement [10] simply to "hypersomnia". Remarkably enough the latter authors gave a sound description of the condition including daytime sleep not as irresistible as that of narcolepsy but usually lasting much longer; the absence of disturbed nocturnal sleep but a profound extension of it; post-dormital confusion characterized by major difficulty in coming to full wakefulness following nocturnal sleep.

The Bedrich Roth period

From 1969 to 1980 Roth and co-workers completed the concept with two major contributions: the description of a hypersomnia with "sleep drunkenness" [11] and a classification of hypersomnolent conditions including "idiopathic hypersomnia" [5, 6]. Sleep drunkenness consists of difficulty in coming to complete wakefulness accompanied by confusion, disorientation, poor motor co-ordination, slowness and repeated returns to sleep. Patients report that these symptoms occur at almost every awakening; nearly all report abnormally deep and prolonged sleep as well. Approximately one third of all hypersomnias seen suffered from sleep "drunkenness" [11]

Four years later Roth [5, 6] proposed a classification of hypersomnias including narcolepsy, hypersomnia and the subwakefulness syndrome. Hypersomnia was considered either symptomatic due to organic brain damage, general metabolic or endocrine disease, intoxication; or functional including functional hypersomnia with a short cycle, functional hypersomnia with a long cycle (periodic hypersomnia) and hypersomnia with sleep apnea. The functional hypersomnia with a short cycle was subdivided into "idiopathic hypersomnia", with two forms, monosymptomatic and polysymptomatic and neurotic hypersomnia. The monosymptomatic form manifests itself by excessive daytime sleepiness, while the polysymptomatic form is characterized by excessive daytime sleepiness, nocturnal sleep of abnormally long duration and signs of "sleep drunkenness" upon awakening. Cataplexy, sleep paralysis and hypnagogic hallucinations are not part of the clinical features.

In the same period the heredo-familial aspect of hypersomnia with sleep drunkenness or idiopathic hypersomnia was underscored [12, 13], as well as the consistent socio-economic effects including reduced work performance, poor marks at school, increased number of accidents and so forth [14].

At the end of the decade, idiopathic hypersomnia was referred to as "Idiopathic Central Nervous System (CNS) Hypersomnolence" in the Diagnostic Classification of Sleep Disorders [15], a term to be abandonned in the subsequent International Classification of Sleep Disorders [16].

Intermediate period (1980–90)

During this period centered around the Second International Symposium on Narcolepsy held in Stanford in 1985, there was an attempt to compare narcolepsy and idiopathic hypersomnia with respect to blood pressure, Minnesota Multiphasic Personality Inventory (MMPI) and polysomnographic features [17]. Idiopathic hypersomnia was considered in patients who had no history of cataplexy and satisfied three of the following four criteria: (a) definite history of excessive daytime sleepiness, (b) mean multiple sleep latency index <5 min; (c) no history of hypnagogic hallucinations or sleep paralysis; and (d) no SOREMPs during multiple sleep latency test (MSLT) or nocturnal polysomography (NPSG). Surprisingly enough, prolonged nocturnal sleep and difficulty in awakening were not part of the criteria. Idiopathic hypersomnia patients had lower blood pressure than narcoleptic patients and lower scores on several MMPI scales. They slept longer than narcoleptic patients, entered REM sleep later at night, had more NREM sleep stages 3 and 4 and experienced fewer and briefer awakenings from sleep at night.

At the same time efforts were made to elucidate the pathophysiology of idiopathic hypersomnia. Montplaisir *et al.* [18] found that dopamine and indoleacetic acid, a tryptamine metabolite, were decreased in the cerebrospinal fluid (CSF) of both idiopathic hypersomniac and narcoleptic subjects in comparison with control subjects. On the other hand, Faull *et al.* [19] did not find any difference in the mean CSF concentrations of monoamine metabolites (3.4-dihydroxyphenylacetic acid (DOPAC); 3, methoxy-4hydroxyphenylethyleneglycol (MHPG); homovanillic acid (HAV); 5-hydroxyindoleacetic acid (5-HIAA) in narcoleptic, idiopathic hypersomnia and control subjects. However, later

re-analysis of the results of this second study using principal component analysis showed that all four monoamine metabolites were highly intercorrelated in normal volunteers, whereas HVA and DOPAC, the dopamine (DA) metabolites, did not correlate with the other two metabolites in narcoleptic subjects, and MHPG, the norepinephrin (NE) metabolite, did not correlate with the other three metabolites in the idiopathic hypersomnia subjects [20]. According to these results a malfunction of the DA system could exist in narcolepsy and a malfunction of the NE system in idiopathic hypersomnia.

From a genetic point of view the recently discovered association of narcolepsy with specific human leucocyte antigen (HLA) markers [21] led to immunogenetic studies in idiopathic hypersomnia subjects. Harada *et al*. [22] found no significant difference in the distribution of HLA antigens in 41 subjects with "essential hypersomnia" defined by the following criteria: excessive daytime sleepiness occurring almost every day over a period of at least 6 months; absence of cataplexy; not due to other known disorders associated with daytime somnolence, such as sleep–apnoea syndrome; that is a diverse group of disorders including idiopathic hypersomnia, aborted forms of narcolepsy, and other disorders difficult to categorize. On the other hand, Montplaisir and Poirier, in a group of 18 subjects with idiopathic hypersomnia, found an association with HLA-Cw2 in 22.2% of patients but in only 5.7% of controls and an association with DR5 in 38.9% of patients but in only 14.7% of controls [23], and Honda and Honda noted a decrease in HLA Cw3 in 16 Japanese idiopathic hypersomnia patients [24].

Last decade

In 1990, the International Classification of Sleep Disorders (ICSD) [16] defined idiopathic hypersomnia as "a disorder of presumed central nervous system cause that is associated with a normal or prolonged major sleep episode and excessive sleepiness consisting of prolonged (1–2 h) sleep episodes of non-REM sleep". Clearly this definition did not take into account Roth's distinction of a monosymptomatic and a polysymptomatic form. On the other hand the ICSD proposed eight diagnostic criteria, two of which underlie the borders of the concept:

1. Absence of any medical or psychiatric disorder that could account for the symptom.
2. Does not meet the diagnostic criteria of any other sleep disorder causing excessive sleepiness, e.g. narcolepsy, obstructive sleep apnoea (OSA) syndrome, or post-traumatic hypersomnia. Concerning the latter criterion Guilleminault *et al*. [25] revealed that numerous subjects previously referred to as idiopathic hypersomnia patients may have had upper airway resistance syndrome.

In 1996–98 four papers issued from two sleep disorders centers, one North American (The University of Michigan Medical Center) and one European (Montpellier University) revisited the concept and the borders of idiopathic hypersomnia.

In the North American papers [26, 27] emphasis was put on a substantial overlap in the clinical features of narcolepsy and idiopathic hypersomnia. Three groups of patients were distinguished: patients who had a tendency to have sleepiness that was not overwhelming, to take long unrefreshing naps of up to 4 h, to have prolonged night-time sleep and to have difficulty awakening $\pm$ sleep drunkenness ("classic" idiopathic hypersomnia); patients with clinical features similar to narcolepsy without cataplexy or any indication of abnormal REM sleep ("narcoleptic-like" idiopathic hypersomnia); and patients who had clinical features intermediate between the other two groups ("mixed" idiopathic hypersomnia). Data were obtained from retrospective clinical assessment including a standard 66 item sleep questionnaire, polysomnography including night polysomnography (22:00–06:00 h) and a MSLT, and HLA class II antigens in 18 subjects [27]. Out of 28 patients in whom detailed follow-up evaluations could be obtained, eight (28.5%) had "classic" idiopathic hypersomnia, nine (32.1%) "narcoleptic-like" idiopathic hypersomnia and 11 (39.2%) "mixed" idiopathic hypersomnia. Restless sleep with frequent arousals was described by about half of the patients; hypnagogic hallucinations, sleep paralysis and habitual dreaming were reported by about 40% of the subjects but the hallucinations and dreams tended to be less bizarre and less vivid than in narcoleptics. Neurovegetative symptoms such as tension or migraine-type headaches, orthostatic disturbances, and Raynaud-like symptoms were common but rarely required specific medical care. No increase in the frequency of the human

leukocyte antigens (HLA DR2-DQ1) associated with narcolepsy was documented.

In the European papers [28, 29] emphasis was put on Roth's initial distinction of a well-defined "polysymptomatic" form characterized by excessive day sleep, nocturnal sleep of abnormally long duration and signs of sleep drunkenness and a much poorly defined monosymptomatic form manifested itself only by excessive day sleep. Data were obtained from clinical interview; polysomnography including night 1, day 1 (MSLT) and then a 24 h continuous polysomnography (night 2 and day 2) with the subject instructed not to resist sleep and free to move around, to sit on an armchair or at a table and lie in bed at any time; and HLA DR typing. Out of 23 patients fulfilling the criteria of idiopathic hypersomnia, 13 (56.5%) had the polysymptomatic form and 10 (43.4%) the monosymptomatic form. There was a non-significant trend for mean sleep latency on the MSLT to be longer in the polysymptomatic form (10.4 ± 5.1 min) than in the monosymptomatic form (7.8 ± 3.9) and total sleep time during night 2 (*ad libitum*) was longer in the polysymptomatic form (699.3 ± 130.1 min) than in the monosymptomatic form (573.5 ± 110.2 min) ($P = 0.03$). These results suggested that subjects with the polysymptomatic form had a lesser propensity to fall asleep but a greater difficulty to terminate sleep. Twenty subjects were HLA-DR typed and no difference between patients and controls was in evidence.

In conclusion, the North American group and the European group agreed on a rather well clinically delineated form of idiopathic hypersomnia, referred to as "polysymptomatic" or "classic". This form represented less than a third of the cases of idiopathic hypersomnia for the North American group and more than half of the cases for the European group. The North American group was in favour of intermediate forms between narcolepsy and idiopathic hypersomnia referred to as "narcoleptic-like" and "mixed" idiopathic hypersomnia, whereas the European group was in favour of an as yet unclassified group which should be clearly differentiated from both narcolepsy and classic or polysymptomatic idiopathic hypersomnia.

EVOLUTION AND SOCIO-ECONOMIC EFFECTS

Idiopathic hypersomnia has long been considered to be stable over decades [13]. However recent reports [27, 30] indicate a spontaneous improvement or even a disappearance of excessive daytime sleepiness in some subjects which contrasts with the persistence of excessive daytime sleepiness in narcolepsy [31, 32]. In our present population two subjects with apparently typical idiopathic hypersomnia also recovered after several years. Complications are mostly social and professional, including poor work performance, reduced earning capacity, fear of losing a job, poor marks at school, impaired ability to enjoy recreational activities, more frequent near accidents and accidents due to sleeping at the wheel. Other items include deteriorated memory (mainly recent events), problems of ocular defocussing, food craving, impotence and sensitivity to alcohol [14].

PREVALENCE

Given these nosological incertainties and the absence of epidemiological surveys, it is clear that the prevalence of idiopathic hypersomnia is still unknown. However some predictions can be made. First, different sleep disorder populations have been reported allowing a calculation of the ratio of idiopathic hypersomnia to narcolepsy (Table 1). Interestingly the ratio tends to decrease in the successive reports to a present 10%. This is due to the recent identification of sleep disorders such as the upper airway resistance syndrome and others formerly confused with idiopathic hypersomnia.

AGE OF ONSET

In contrast to narcolepsy, a precise onset of idiopathic hypersomnia is often difficult to determine because of the insidious beginning of the condition and the difficulty, in young persons, of defining long sleep and abnormally long sleep and between normal wakefulness and impaired wakefulness. Thus it is more appropriate to refer to childhood, adolescence, the twenties, and so on, than to a specific year of onset. In our experience it is exceptional for idiopathic hypersomnia to develop after the age of 30.

DIAGNOSTIC PROCEDURES

The diagnosis of idiopathic hypersomnia is mainly based on clinical features and the absence of associated symptoms such as cataplexy, snoring, peri-

Table 1 Prevalences of narcolepsy, narcolepsy without cataplexy and idiopathic hypersomnia in different series

Authors	Narcolepsy	Narcolepsy without cataplexy	Idiopathic hypersomnia	Idiopathic hypersomnia / Narcolepsy
Roth [6]	226	129	174	76.9%
Van den Hoed *et al.* [33]	41	5	17	41.4%
Coleman *et al.* [34]	425	—	150	35.2%
Baker *et al.* [17]	257	—	74	28.7%
Aldrich [26]	258	28	42	16.2%
			− 10 (symptomatic hypersomnias)	12.4%
Billiard *et al.* (present population)	339	31	35	10.3%

odic leg movements or depression. However in a subject with an early onset of the condition who is only diagnosed at 40 or 50 years of age, it is neither inconceivable nor unacceptable that snoring or even sleep apnoeas, periodic leg movements or depression have developed later, without questioning the initial diagnosis. In any case polysomnography and possibly other tests are necessary to rule out other sleep disorders, as idiopathic hypersomnia is still one widely over-diagnosed sleep disorder.

The most common polysomnographic procedure to date is nocturnal sleep recording followed by a MSLT. Sleep shows normal quality with few awakenings, no sleep onset REM periods, normal proportions of all NREM and REM sleep stages. Sleep apneas and periodic limb movements in sleep are theoretically absent but may be acceptable in the case of early onset of the disease and late polysomnography. Waking the patient in preparation for the MSLT may be difficult. MSLT demonstrates a mean sleep latency less than 10 minutes [16, 35]. Sleep onset REM periods are absent. The diagnostic value of the MSLT is somewhat questionable, at least in subjects with the polysymptomatic or classic form. In these cases awakening the subject in the morning in view of the later MSLT sessions precludes documenting the prolonged night sleep and the MSLT sessions preclude recording of prolonged, unrefreshing daytime sleep episode(s). It is therefore appropriate to follow polysomnography and the MSLT by a 24 h continuous polysomnography, either at home with an ambulatory system or in the laboratory, on an *ad lib* sleep/wake protocol, with the subject receiving the instruction of not fighting against sleep and the technician of not interrupting sleep for whatever reason (Fig. 1). However, this procedure should be standardized: at what time should the lights be turned off and on at night? Which types of activity should be allowed during the daytime? At what time should the subjects have their meals?

Another promising test is cognitive evoked potentials (P300). Sangal and Sangal [36] compared normal subjects and patients with excessive daytime sleepiness including those with severe sleep apnoea syndrome, idiopathic hypersomnia and narcolepsy. Idiopathic hypersomnia and obstructive sleep apnoea patients had longer visual P300 latency than normal subjects or narcolepsy patients ($P<0.05$) and idiopathic hypersomnia, and OSA patients longer auditory P300 latency than normal subjects. In addition idiopathic hypersomnia patients had smaller auditory P300 amplitude than narcoleptic patients ($P=0.01$). These results should be confirmed. It is surprising that the population included almost three times as many idiopathic hypersomnia patients as narcolepsy patients whereas the prevalence of idiopathic hypersomnia is about 10 times less than that of narcolepsy.

Despite some reports that suggest an increase frequency of HLA Cw2 and DR5 in idiopathic hypersomnia subjects [23], HLA typing is of no help in the positive diagnosis of idiopathic hypersomnia.

Computed tomography (CT) scan or magnetic resonance (MR) imaging of the brain is indicated when a brain lesion is a consideration.

Finally psychological interview and tests are advisable. Symptoms of neurovegetative instablility and psychological abnormalities are considered frequent features of the clinical picture by Roth [13] and a

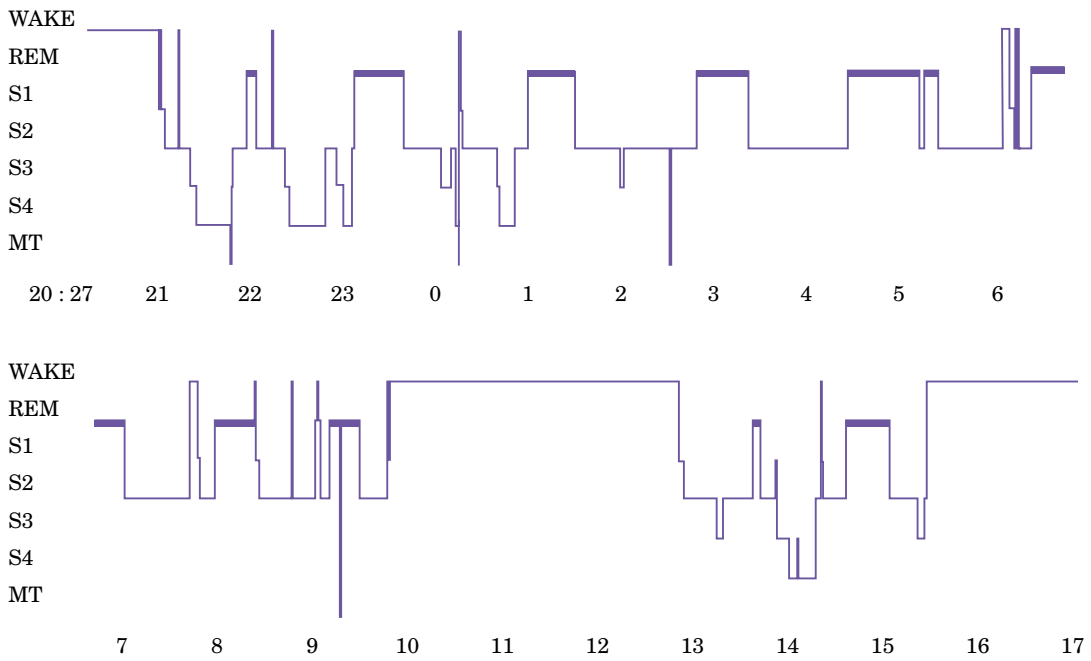

Figure 1 Twenty-four-hour continuous polyomnogram in a 24-year old woman. Night: Total sleep time was 12 h 44 min. Day: the single nap lasted 2 h 36 min.

strong tendency towards introversion and inhibition has been described [37].

Practice Points

Night polysomnography followed by a MSLT is not sufficient to diagnose idiopathic hypersomnia.

It should be complemented by 24-h continuous polysomnography in order to document the spontaneous prolonged duration of the main sleep episode and the presence of daytime nap(s).

Twenty-four hour continuous polysomnography should be standardized.

Cognitive evoked potentials (P300) are of possible interest in the evaluation of subjects with idiopathic hypersomnia.

HLA typing is of no practical benefit to date.

DIFFERENTIAL DIAGNOSIS

Idiopathic hypersomnia is frequently overdiagnosed due to an infortunate tendency to label as such all hypersomnias that do not fit the criteria of either narcolepsy or the sleep apnea syndrome. There is thefore need to consider all the conditions that can be confused with idiopathic hypersomnia.

The first diagnosis to consider is the *upper airway resistance syndrome* [25]. Excessive daytime sleepiness, snoring and fatigue on awakening, are the main clinical features. Low soft palate, long uvula, increased overbite and high, narrow arched palate have also been described. In any event, the presence of multiple brief EEG arousals occurring during polysomnography must draw attention and call for monitoring oesophageal pressure (Pes) to measure transpleural pressure. Quantification of airflow using a face mask with a pneumotachometer is also advisable for calculation of tidal volume, although the mask may affect sleep continuity. The most typical pattern is an EEG arousal occurring after a sequence of breaths, with progressively increasing respiratory efforts indicated by progressively more negative peak end inspiratory pressure in Pes measurements and a simultaneous decrease in tidal volume compared with preceding breaths.

Narcolepsy without cataplexy, also referred to as ambiguous or atypical narcolepsy, essential hypersomnia, primary hypersomnia or hypersomnia with sleep-onset REM periods, is a clinical variant of narcolepsy in which cataplexy is not yet manifested or will never manifest itself. Clinically this disorder differs from idiopathic hypersomnia by more ovewhelming and refreshing

sleep episodes. Positive diagnosis requires the presence of two or more SOREMPs on the MSLT and an association with HLA DQB1*0602-DQA1*0102 alleles.

Hypersomnia associated with mental disorder should be considered in a subject with an abnormal personality or features of psychosis, mood disorders or alcoholism. The complaint of excessive daytime sleepiness is similar to that of patients with idiopathic hypersomnia, except that it may vary from day to day and be associated with poor sleep at night. The MSLT often does not demonstrate a short mean sleep latency [38]. A continuous 24-h polysomnography may show repeated night awakenings and limited sleep during the day-time, despite the patient staying in bed [39].

Post-traumatic hypersomnia may mimic idiopathic hypersomnia closely. Past medical history including an initial coma after head trauma is typical. Hypersomnia usually develops 6–18 months after the head trauma [40]. True post-traumatic hypersomnia is rare.

Communicating hydrocephalus of unknown aetiology does not differ clinically from idiopathic hypersomnia, which underlines the usefulness of brain imaging in subjects with idiopathic hypersomnia.

Hypersomnia following a viral infection such as pneumonia, mononucleosis or Guillain-Barré syndrome usually develops within weeks or months after the infection when the subject realizes that he is not only fatigued but also abnormally sleepy and sleeps for a considerable number of hours daily. The outcome is favourable but total resolution may take months or years [41].

Chronic fatigue syndrome is characterized by persistent or relapsing fatigue that does not resolve with sleep or rest. Polysomnography shows reduced sleep efficiency and may include alpha intrusion into sleep EEG. It is likely that a number of cases labelled as chronic fatigue synrome are unrecognized cases of upper airway resistance syndrome.

Pain or other medical symptoms responsible for fragmented sleep at night may result in excessive sleepiness as may occur in subjects with ankylosing spondylitis or rheumatoid arthritis.

Insufficient sleep syndrome is associated with excessive daytime sleepiness, impaired concentration and lowered energy level. A detailed history of the subject's current sleep schedule is revealing [42].

Delayed sleep phase syndrome is to be considered in some patients whose main complaints are extreme difficulty awaking in the morning and excessive morning sleepiness. These patients are often not sleepy later in the day and go to sleep extremely late at night [43].

Finally, *long sleepers*, also called "healthy hypersomniacs", are individuals who require more sleep at night than the norm. However, when given the time to sleep as long as they want, these subjects are normally refreshed and alert.

PATHOPHYSIOLOGY

In contrast to narcolepsy, no natural model of idiopathic hypersomnia is available. Thus experimental approaches are limited. Destruction of norepinephrin neurons of the rostral third of the locus coeruleus complex or of the norepinephrin bundle at the level of the isthmus in the cat leads to hypersomnia with a proportional increase of NREM sleep and REM sleep suggestive of idiopathic hypersomnia. In this situation telencephalic norepinephrin has been shown to be decreased and 5-HIAA and tryptophan to be increased [44].

Neurochemical studies performed in man in the 1980s [18–20] have been reviewed earlier in this paper. Further analysis of monoamines and monoamine metabolites should be performed in the blood and CSF of subjects with the "polysymptomatic" or "classic" form of idiopathic hypersomnia.

Another perspective is the study of sleep spindles in subjects with idiopathic hypersomnia. As sleep spindles are generated in the thalamus, one could hypothesize that if sleep allows a spontaneous thalamic manifestation in the form of sleep spindles, there might be a relationship between them and hypersomnia. Bove *et al*. [45] counted sleep spindles in well-defined nocturnal stage 2 segments, and tabulated the average sleep spindle density (number of sleep spindles in stage 2/minute stage 2) for the entire night in subjects with narcolepsy, idiopathic hypersomnia and controls. They found that the average sleep spindle density was higher in both cerebral hemispheres in narcoleptic and idiopathic hypersomnia subjects, and was highest in idiopathic hypersomnia subjects. The highest sleep spindle density was recorded at the beginning of night sleep in narcoleptic patients and during the second half of the night in idiopathic hypersomnia subjects. Thus

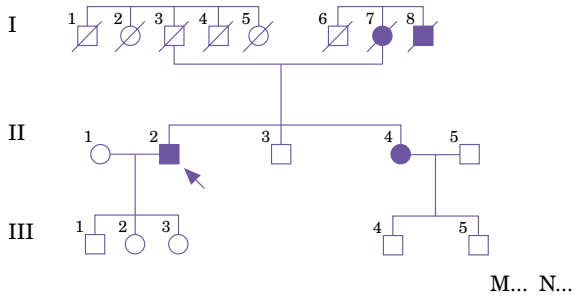

Figure 2 Pedigree of a patient with idiopathic hypersomnia. His sister, mother and maternal uncle were also afflicted with idiopathic hypersomnia.

a high density of sleep spindle activity by the end of the night would suggest an excessive thalamic blockade in accordance with the difficulty in awakening experienced by patients with idiopathic hypersomnia.

PATHOGENESIS

As already mentioned a genetic basis for idiopathic hypersomnia has been suggested by two reports, one by Nevsimalova and Roth [12] and one by Roth [13]. In our present population of 35 idiopathic hypersomnia patients selected according to much more stringent criteria 25 subjects have the polysymptomatic form and 10 the monosymptomatic form. A family history of excessive daytime sleepiness has been found in 10 subjects with the polysymptomatic form (40%), including three with several excessive daytime sleepiness relatives, and in three subjects (30%) with the monosymptomatic form, including one with several excessive daytime sleepiness relatives (Fig. 2). Further studies however need to be performed in order to make sure that relatives affected with excessive daytime sleepiness do not have sleep apnea, upper airway resistance syndrome or other causes of excessive daytime sleepiness. One fact of interest is the presence of one relative with narcolepsy in each of two patients reported by Bassetti and Aldrich [27] and the same finding in two patients of our own population. At this point further genetic studies are needed starting with case control studies. Another orientation has recently been raised by Nevsimalova *et al*. [46]. In 10 subjects fulfilling the criteria of the polysymptomatic form of idiopathic hypersomnia the circadian rhythm of melatonin was phase delayed compared with that in the control subjects (elevated nocturnal melatonin levels shifted towards the morning hours). Moreover the duration of the melatonin signal appeared to be longer in the idiopathic than in the control group. However the difference was not significant. Consequently, difficulty in morning awakening with signs of sleep drunkenness might result from a combination of a phase delay and a prolongation of the melatonin pulse.

TREATMENT

Up to now treatment of idiopathic hypersomnia has relied on the same drugs as for sleepiness and sleep attacks in narcolepsy. Stimulant drugs including dextroamphetamine, methylphenidate, mazindol or pemoline, are the most commonly prescribed medications. According to Bassetti and Aldrich [27] three quarters of patients with idiopathic hypersomnia benefit from stimulants. However morning sleep drunkenness is usually difficult to reduce. Recently, a new compound, modafinil, a drug with wake promoting properties, has produced good results in patients with idiopathic hypersomnia [47]. However, a double-blind controlled study or a comparative study with stimulants has not yet been performed. Up to now melatonin has not been used, but the recent results obtained by Nevsimalova *et al*. [46] raise the possible use of melatonin therapy as a synchronization stimulus.

Unfortunately there is not much to recommend beside pharmacological treatment. Naps are of no use as they are both lengthy and not refreshing. Roth [13] proposed to saturate the patients with sleep by recommending that they sleep for as long as possible during several days and nights in a row. In so doing one of our patients slept for 14 h 50 min during the first 24 h, 12 h 44 min during the second and 9 h 02 min during the third (personal communication). On the other hand Bassetti and Aldrich's patients [27] did not report any improvement of their excessive daytime sleepiness after prolonged sleeping for days.

CONCLUDING REMARKS

There is no doubt that progress has been made in the identification of idiopathic hypersomnia. Genuine idiopathic hypersomnia is characterized by consistent clinical patterns of prolonged nocturnal sleep, great difficulty at waking up and constant or

recurrent excessive daytime sleepiness with day sleep episodes lasting one or several hours in duration. There are other cases of isolated excessive daytime sleepiness not fitting the criteria of either narcolepsy or genuine idiopathic hypersomnia. Further investigations are needed to create new diagnostic categories. Pathophysiology and pathogenesis are still poorly understood but new prospectives are opening. Based on the fact that idiopathic hypersomnia differs from narcolepsy by many aspects, clinical, polysomnographic and biochemical, it is likely that specific treatments will be developed in the coming years.

Research Agenda

1. Research programmes on idiopathic hypersomnia must clearly differentiate the polysymptomatic or classic form from the other form(s).
2. Study of sleep spindles should be replicated.
3. Monoamines and monoamine metabolites assays should be performed in blood and CSF.
4. Advances in the genetics of idiopathic hypersomnia require case control studies and transmission disequilibrium test in triads.
5. Double-blind trials of modafinil versus placebo should be conducted in subjects with idiopathic hypersomnia.

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