ERS School Course Sleep Medicine

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Non-respiratory causes of excessive daytime sleepiness

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Educational aims

- To present the symptoms, methods of assessment and the different causes of excessive daytime sleepiness when nocturnal respiratory disturbances have been excluded.
- To enable physicians to confirm a diagnosis of sleepiness and recognise the pathology.

Summary

Excessive daytime sleepiness (EDS) is defined as an inability to stay awake and alert during the major waking episodes of the day, resulting in unintended drowsiness or sleep episodes almost daily for at least 3 months. This review will examine the assessment of sleepiness and different causes of EDS.

Physiopathology

Sleepiness is the result of the combined effects of sleep propensity and wake propensity (figure 1). Sleep propensity depends on circadian factors (time of day) and sleep debt (sleep duration and fragmentation). Wake propensity depends on external (environment, exercise, drugs, *etc.*) and internal factors, such as the different types of hypersomnia or other medical

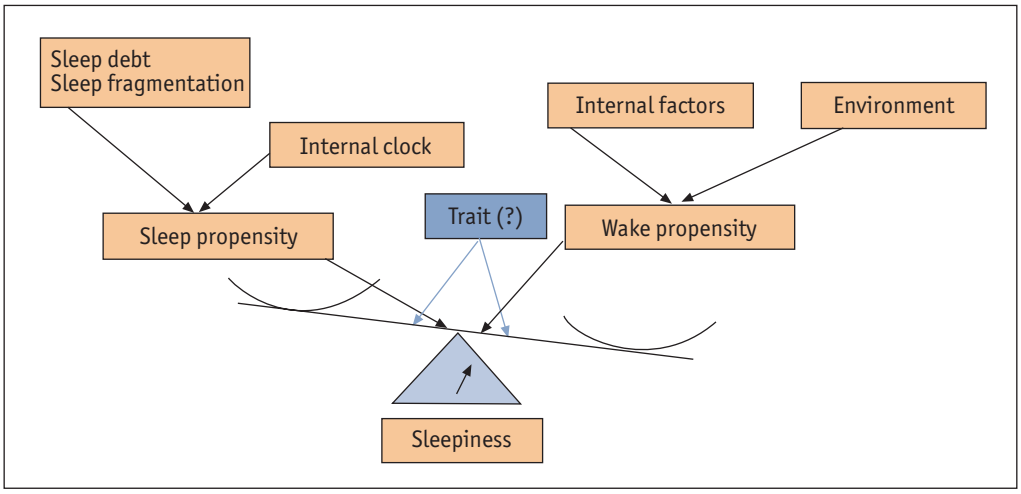

Figure 1
Schematic examining the causes of sleepiness.

disorders usually responsible for EDS. For both sleep and wake propensity, individual factors play a key role concerning the level of sleepiness of each subject.

Clinical presentation

EDS may consist of one or more of the following symptoms: reaction retardation, attention or memory lapses, severe difficulty waking up in the morning, constant drowsiness, the need to fight against sleepiness, difficulty staying awake, dozing or falling asleep (more or less under control) and frequent naps (refreshing or not). Falling asleep is more likely to happen when the subject is in a quiet, warm, dark, less stimulating situation. Falling asleep or dozing can be more or less clearly perceived by the patient and can be more or less under control. Reading, watching television and being a passenger on a bus or a train are examples of situations where this can occur. Falling asleep or dozing while talking, walking or being physically active are signs of severe sleepiness. Dozing whilst driving is exceptionally dangerous and, therefore, it is very important to ask patients about their professional or leisure activities. The consequences of EDS on daily life (profession, studies, family or social life) have been clearly demonstrated, as well as on quality of life.

Clinical interview

A complete clinical interview will determine the following information from patients: the course of sleepiness during daytime, especially at wake time; the occurrence of naps, if they are refreshing or not; the circumstances of falling asleep, *i.e.* adapted or not, dangerous, under control or not; the history of the disease, *i.e.* age of onset, triggering factors, fluctuations, seasonal influence; medical history and treatments; the sleep need, and the habitual sleep duration and sleep schedule, the influence of work schedule; and the sleep timing the patient would choose if allowed to do so.

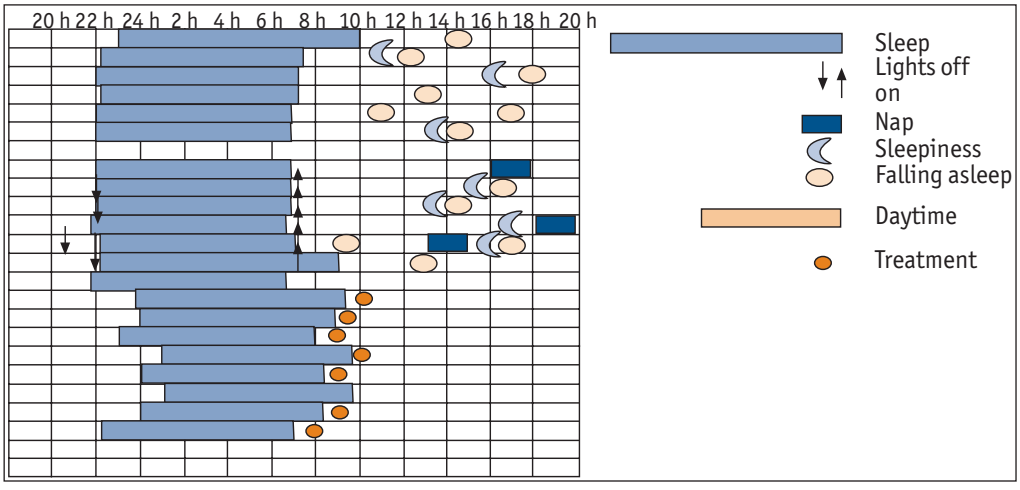

Figure 2
Example of a sleep log.

Clinical assessment of sleepiness

The Epworth Sleepiness Scale is a simple and useful tool to confirm the level of sleepiness and measure improvement following treatment. It assesses the likelihood of patients falling asleep or dozing in eight different situations during previous weeks, using a scale of 0–3, where 0 is "never doze" and 3 is "strong". A total score of 10 is generally taken to indicate EDS.

The sleep log (figure 2) can also be used for clinical assessment. It is completed by the patient for ≥3 weeks and provides a lot of information regarding daytime sleepiness, usual sleep duration and sleep schedule. It is also useful when assessing treatment efficacy.

Pathologies suspected when EDS is present

Narcolepsies

Narcolepsies have a reported prevalence of 2–18 per 10,000 inhabitants. Beside sleepiness, the disease is characterised by the irruption of rapid eye movement (REM) sleep during wakefulness, as well as during sleep. The disease usually appears between 15 and 25 years of age, but may appear at any age. Narcolepsy is caused by the degeneration of a small group of neurones situated in the ventrolateral nucleus of the hypothalamus, containing a recently discovered peptide named hypocretine or orexine, which stabilises wake and sleep states. The levels in the cerebrospinal fluid (CSF) are dramatically decreased, if not absent, in the clinical form "with cataplexy".

The main symptom is severe EDS characterised by lapses into sleep and frequent refreshing naps. Nocturnal sleep is often described as light, unstable and fragmented. Polysomnographic recordings performed during the night usually present severely fragmented and/or disturbed sleep, as well as short REM sleep latency or sleep-onset REM periods (SOREMPs; <20 minutes). Others signs might also be present, such as frightening hallucinations at sleep onset or offset and sleep paralysis, but these can be present in normal subjects.

Cataplexy is present only in narcolepsy and is sufficient to diagnose this form of the disease: "narcolepsy with cataplexy". Cataplexy is characterised by a sudden loss of muscular tone triggered by positive emotions like laugher, pride, elation or surprise. Cataplexy can be complete, resulting in a progressive fall to the floor, or limited, affecting a specific part of the body, *e.g.* face, neck, hands, knee. Cataplexy usually follows EDS in the course of the disease by 1–2 years.

Cataplexy is not necessary to diagnose narcolepsy. In the form "narcolepsy without cataplexy", cataplexy is not present and does not appear later. The CSF level of hypocretine is highly variable in these cases and does not aid the diagnostic process. The diagnosis will be confirmed by the multiple sleep latency test (MSLT), which reveals mean sleep latency to be ≤8 minutes (often <5 minutes) and ≥2 SOREMPs. The MSLT is carried out over 4–5 naps, during which sleep-onset latency is measured and sleep recorded over 15 minutes.

A familial pattern has been described for narcolepsy, but the probability of a narcoleptic parent transmitting the disease to his/her children is 1–2 per 100.

Cataplexy should be specifically treated when severe, usually by antidepressants, such as fluoxetine.

Idiopathic hypersomnias

Idiopathic hypersomnias (IHs) are characterised by EDS with long frequent naps, often described as non-restorative. Two different types have been described. 1) IH with long sleep time is defined by the presence of EDS accompanying a long nocturnal sleep time (>10 hours), with difficulties waking up in the morning or after non-refreshing naps. 2) IH without long sleep time associates EDS with normal usual sleep time (6–10 hours per day) and a mean sleep latency of <8 minutes at MSLT. In addition, there should be no SOREMP or no more than one, differentiating IH from narcolepsy without cataplexy. A familial pattern has been described occasionally, but the precise cause of the disease still remains unknown.

The first-line treatment of EDS in narcolepsy and IH is modafinil with a dose ranging 100–400 mg per day.

Behaviourally induced insufficient sleep syndrome

This syndrome occurs when an individual persistently fails to obtain the amount of sleep required to maintain normal levels of alertness or wakefulness. The result is a voluntary but unintentional chronic sleep deprivation. The clinical interview reveals a substantial disparity between

Educational questions

At a clinical interview, if your patient replied "yes" to the following questions, what pathology would you supect if EDS is present?

1. Do you feel strange when you laugh or are emotional?
2. Do you usually sleep ≥10 hours?
3. Do you get less sleep than you need?
4. Do you take sedative treatment on a regular basis?
5. Do you go to bed late and get up late?

sleep needs and the sleep amount actually obtained. During holidays, sleep duration may or may not increase.

Hypersomnias associated with mood disorders

This diagnosis is difficult as hypersomnia *per se* is often associated with depressed mood in obstructive sleep apnoea syndrome or narcolepsy. Therefore, the presence of a depressed mood should not rule out the possible presence of another wake disorder. Hypersomnia is present in ~10% of major depressive disorders, and is associated with prolonged bedtime, daytime naps (usually not refreshing), and objective poor nocturnal sleep, morning fatigue and lack of energy. Compared with hypersomnia and narcolepsy, mean sleep latency as assessed by MSLT is longer, often borderline or even normal. Hyperphagia is more frequent than loss of appetite when hypersomnia is present in mood disorders. Hypersomnia is more frequent in young depressed subjects and bipolar type II (alternation of depression and elation episodes). Seasonal affective disorder usually starts in autumn and improves in spring, and hypersomnia, loss of energy, weight gain and carbohydrate craving are its usual associated clinical features.

Delayed sleep phase syndrome

Delayed sleep phase syndrome (DSPS) is a circadian rhythm disorder, and is characterised by delayed habitual sleep and wake time, usually >2 hours relative to conventional or socially acceptable times. Otherwise, sleep is considered as normal. This pattern appears clearly during holidays. This condition affects mainly young subjects and the first complaint can be severe sleep-onset insomnia with a preference for late wake-up times. When forced to wake up earlier than desired, the patient can be very sleepy and sometimes unable to wake up by himself. When a repeated "early" wake-up time is socially required, the subject becomes sleepy during the daytime due to sleep debt. Nevertheless, sleepiness usually disappears in the evening. A familial pattern has been described, and the origin of the disease is probably genetic combined with psychological and behavioural aspects.

Treatment with phototherapy or chronotherapy is more efficient than hypnotic treatment.

Medical condition- and treatment-related EDS

Table 1 shows some medical conditions where EDS may be present. Table 2 shows the groups of drugs that can cause EDS in patients.

Table 1 *Medical conditions where EDS is presented*

Parkinson's
Post-traumatic hypersomnia
Genetic disorders (e.g. Niemann–Pick, Prader–Willi, myotonic dystrophy)
Tumours, CNS lesions, infections
Hypothyroidism
Metabolic conditions (e.g. renal, hepatic, adrenal, pancreatic)

CNS: central nervous system.

Table 2 *Types of drugs that can cause EDS*

Psychotropic (e.g. hypnotics, neuroleptics, antidepressants)
Mood regulators (e.g. lithium)
Anti-epileptic (e.g. barbiturates)
Anti-histamines
Analgesics
Myorelaxants
Central-acting anti-hypertensives
Migraine
Parkinson's treatment (dopamine agonists)
Alcohol and other toxins

Suggested answers

1. Narcolepsy cataplexy.
2. IH with a long sleep time.
3. Insufficient sleep syndrome.
4. Alcohol or substance abuse.
5. Sleep phase delay.

Suggested further reading

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