Hepatic Encephalopathy and Sleepiness: An Interesting Connection?

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Sleep-wake abnormalities in patients with cirrhosis have been traditionally associated with hepatic encephalopathy (HE). In recent years, a certain amount of work has been devoted to the study of this relationship. This has led to a modified picture, with weakening of the association between HE and poor night sleep, and the emergence of stronger links between HE and excessive daytime sleepiness. This brief review focuses on the evidence in favor of the interpretation of HE as a sleepiness syndrome, and on the diagnostic, therapeutic and social implications of such an interpretation. (J CLIN EXP HEPATOL 2015;5:S49–S53)

Sleepiness is the expression of a basic physiological need, not unlike hunger or thirst.¹ Its presence and its intensity can be indirectly measured by how readily sleep occurs, how easily it is disrupted, and how long it lasts. Sleep deprivation/restriction increase sleepiness, and sleep reverses it. Routine access to sleep, not unlike that to food or drink, is not only homeostatic, but is influenced by social and environmental factors. Thus subjective sleepiness and its indicators (yawning, nodding etc.) are reduced under conditions such as social interaction, exercise etc.² However, when sleepiness is severe, our ability to reduce its impact on behavior is reduced, and the likelihood of sleep increases. There is probably some degree of adaptation to chronic sleepiness, and successfully treated patients report that “they had forgotten the experience of complete alertness”.² This could provide an explanation for our observation that induced hyperammonaemia results in significantly more pronounced subjective sleepiness in healthy volunteers compared to cirrhotic patients, who may be used to it.³

The degree of daytime sleepiness is related to both the amount of nocturnal sleep (sleep deprivation/restriction results in increased sleepiness during the following day,⁴) and its quality (night arousals of different etiology, fragmenting sleep, also result in increased daytime sleepiness.⁵) Finally, there is a circadian element to sleepiness. Subjects who are allowed to nap in time-free environments do so in a biphasic pattern, with a nap in the middle of the 24-h cycle (or early in the afternoon).⁶ Such rhythmicity is

preserved in “jet-lagged” conditions, just like that of sleep and feeding.

It is assumed that sleepiness is a central nervous system phenomenon with identifiable neural mechanisms. However, limited information is available on whether: 1) the neurochemistry of sleepiness is different to that of sleep; 2) sleepiness and alertness have common or separate neural and neurochemical correlates. The electroencephalogram (EEG) of behaviorally awake subjects who have been deprived/restricted of sleep documents micro-sleep episodes and increased amounts of theta activity.⁷ These neurophysiological events are considered markers/correlates of sleepiness. Neurophysiological studies have implicated histamine, serotonin, catecholamines, and acetylcholine in the control of wakefulness, and gamma-aminobutyric acid in that of sleep.⁸ Whether these neurotransmitters also control alertness/sleepiness remains unclear. Evidence from animal studies suggests that extracellular adenosine is the main homeostatic sleep neurotransmitter, with brain levels accumulating during wakefulness and declining during sleep.⁹ Of interest, patients with cirrhosis, whose sleep patterns will be described here below, show decreased density of the adenosine receptor A1AR in both cortical and subcortical regions of their brain.¹⁰ Finally, the peptide hypocretin/orexin is considered to be a major wake-promoting hypothalamic neuropeptide and a hypocretin/orexin deficiency has been documented in human narcolepsy.¹¹

Sleepiness is reported as a problem by 10–25% of the population, depending on the definition utilized and the population studied.² The clinical significance of an individual's complaint of excessive sleepiness, and thus the definition of the difference between physiological and pathological sleepiness may not be obvious. The distinction relies on two main factors: chronicity (pathological sleepiness tends to be persistent) and reversibility (i.e. in a healthy individual increased sleep abolishes/decreases sleepiness, which does not happen in patients). An attempt

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Abbreviations: HE: hepatic encephalopathy; EEG: electroencephalogram

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should always be made to translate complaints of sleepiness/its intensity into quantitative, documentable reports. These can be based on scales of reported sleepiness at the time of evaluation, like the Stanford Sleepiness Scale,¹² or scales of reported likelihood/risk of falling asleep in soporific situations, like the Epworth Sleepiness Scale.¹³ Physiological measures of sleepiness can also be obtained: the most commonly utilized tool is the Multiple Sleep Latency Test,¹⁴ which measures sleep latency on repeated opportunities throughout the day by polysomnographic indices.

Although patients in sleep clinics are not representative of the general population, they do provide some indications regarding the clinical impact of sleepiness. Nearly half of patients with excessive sleepiness report road-traffic accidents; half report occupational accidents, and many lose their jobs because of their sleepiness.^{2,15} Occupational consequences of sleepiness are even more common in shift workers, the poorest job performances and the highest rate of industrial accidents occurring over night shifts.¹⁶ These events are partly mediated by the impact of sleepiness on cognition. The literature on this relationship has focused on psychomotor speed and attention, with the main outcomes being response slowing and attentional lapses. Some studies have also documented a relationship between increased sleepiness and poor risk-taking decisions,¹⁷ and memory deficits.¹⁸

SLEEPINESS AND HEPATIC ENCEPHALOPATHY

As early as 1954, in one of the first, organized descriptions of hepatic encephalopathy (HE), Sherlock and co-workers recognized 'sleep-wake inversion' (i.e. the combination of restless nights and excessive daytime sleepiness) as a feature of severe HE.¹⁹ Subsequent, anecdotal evidence suggests that sleep abnormalities worsen following the insertion of portal-systemic shunts,²⁰ and improve after the institution of treatment with ammonia-lowering drugs.²¹ These few findings, together with a tradition of grouping central nervous system complications of cirrhosis, have led to the belief that the pathogenesis of sleep-wake disturbances exhibited by these patients is closely related if not identical to that of HE. While there is evidence for this in animal models, human studies provide a considerably more heterogeneous picture.^{22–26} This may be due to a number of factors, including cultural and environmental confounders, the heterogeneity of the patient populations studied, and a certain tendency of hepato-gastroenterologists and internists to group all kinds of sleep disturbances together, and to study them with tools such as quality of life and psychological well-being questionnaires.²³ In more recent

years, some work has been devoted to defining the sleep-wake disturbances exhibited by these patients in a more formal, systematic fashion, in collaboration with sleep scientists and chronobiologists. This has resulted in a slightly modified picture, with weakening of the association between HE and poor night sleep, and the emergence of stronger links between HE and excessive daytime sleepiness.²⁷ Given the ties between night sleep quality and daytime sleepiness, this is obviously a simplification, but one that maybe helpful for both diagnostic and management purposes.

After the first report by Sherlock and colleagues, excessive daytime sleepiness has also been described in patients with cirrhosis and milder neuropsychiatric impairment.¹⁹ In at least two studies, an association between excessive sleepiness and the presence/degree of HE was also observed.^{24–26} In addition, sleepiness has been shown to be more common in cirrhotic patients with a history of HE and documented portal-systemic shunt,²⁸ and to be positively correlated with the amount of slow activity on the wake EEG.²⁴ This is a well-established marker of HE,²⁹ and one of the neurophysiological correlates of sleepiness.⁷ In a recent, large study, in which habitual daytime sleepiness was qualified as present/absent, its absence had a negative predictive value of 92% in relation to the occurrence of HE-related hospitalizations over the subsequent 8 months.²⁸ Although the number of patients answering "no" to the question was relatively low (29%), it is reasonable to conclude that these may not need formal neuropsychiatric assessment or particularly close monitoring in relation to their risk of HE. Most convincingly, changes in subjective sleepiness were shown to closely parallel changes in blood ammonia levels in both healthy volunteers and patients with cirrhosis in a study of induced hyperammonemia.³ Hyperammonaemia and sleepiness were also associated with changes in both the scalp distribution (spreading over the posterior-anterior axis) and the frequency (slowing) of the wake EEG.³⁰ Of interest, slowing of the background alpha rhythm (9 to 8–8.5 Hz) and an increase in its amplitude along the posterior-anterior axis (anteriorization) are two of the neurophysiological characteristics of the transition from wake-to-sleep.³¹ This would also support the hypothesis that the slow activity which characterizes the wake EEG of patients with HE, while being within the theta frequency band (4–7 Hz) may indeed be a slow alpha rhythm. This hypothesis is in line with the fact that such slow activity often exhibits features which are typical of the background the alpha rhythm, such as responsiveness to eye-opening. There are also behavioral similarities between the wake-sleep transition and HE, which is characterized by sleepiness/lethargy,³ and diminished reactivity to external stimuli.³² All these characteristics seem to place HE at the very border between wakefulness and sleep.

IMPLICATIONS OF THE INTERPRETATION OF HEPATIC ENCEPHALOPATHY AS A SLEEPINESS SYNDROME

The interpretation of HE as a sleepiness syndrome has a number of implications, which are summarized in Figure 1.

First of all there are diagnostic implications, in that tools validated for the detection and the quantification of sleepiness may turn out to be useful also to diagnose and quantify HE. A more profound diagnostic issue relates to the functional hierarchy of attentional networks within the cognitive system. This is pyramidal, in that intact vigilance (i.e. no sleepiness) is required, for example, for adequate orienting and executive function.³³ Therefore, it is possible that some of the neuropsychological deficits which have been documented in patients with HE (which include impairment of orienting and executive function³⁴) may not be specific but rather due to excessive sleepiness/decreased vigilance. Of interest, the sleepiness literature suggests that, for example, memory deficits associated with sleep disorders are not specific to a certain sleep disorder but rather specific to the sleepiness associated with the disorder. When sleepiness is treated, memory and other cognitive deficits tend to improve in parallel.³⁵

Secondly, HE has been associated with both increased risk of road traffic accidents,^{36,37} and with reduced employment and financial status.³⁸ These have been generally attributed to specific aspects of the neuropsychological profile of HE, for example the deficits in attention and inhibition.³⁶ Accidents and reduced employment are com-

mon also in sleepy but otherwise healthy individuals.³⁹ Again, this “parallel” field of research may offer interesting tips both in terms of diagnostic and management algorithms.

Finally, if HE can be interpreted as a syndrome of sleepiness, it might be also treated as such. In this respect, anecdotal evidence is already available in the liver literature. For example, we have reported on the beneficial effect of blue-enriched morning light administration to contain daytime sleepiness in a patient with cirrhosis.⁴⁰ Similarly, modafenil, a drug which improves driving performance in patients with narcolepsy and idiopathic hypersomnia,⁴¹ has also been used to treat daytime sleepiness and fatigue in patients with primary biliary cirrhosis.⁴² On the reverse side, an attempt at correcting night sleep disturbance with the histamine H1 blocker hydroxyzine in patients with cirrhosis and minimal HE was associated with some risk of precipitating severe HE.⁴³ This and other, similar studies remind us that when night sleep is modulated, daytime sleepiness is also modulated, and *vice versa*. While we are generally familiar with the idea that we need a good night sleep for a good, active day, the reverse is also true. As the need for sleep accumulates homeostatically during wakefulness, we also need a good, active day for a good night sleep. The negative effects of daytime napping/inactivity on the quality of the subsequent night become more obvious when, for any reason, we are forced to remain at home, inactive.⁴⁴ Therefore, there is a real possibility that adequate management of daytime sleepiness in patients with cirrhosis may also result in improved night sleep.

Figure 1 Evidence for and implications of the interpretation of hepatic encephalopathy as a sleepiness syndrome.

In conclusion, the connection between HE and sleepiness seems of theoretical and practical interest, and it is worthy of further, formal study.

CONFLICTS OF INTEREST

All authors have none to declare.

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