



SLEEP AND FATIGUE IN PATIENTS WITH LIVER COMPLICATIONS

Acquiline Cladius*, Qumre Alam, Rajendra Sandur V, Vidya Banakar, Veena S, Pooja Laxman, Meghana NK

Department of Pharmacology, Krupanidhi College of Pharmacy, Bangalore

*Corresponding author E-mail: acqu96@gmail.com

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ABSTRACT

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Liver complications are very common in the present world and the most concerned issue faced by modern life style is sleep disorders and fatigue, which affects the quality of living and also increases the mortality. There are various factors that cause sleeplessness and fatigue which can be due to unhealthy life style or a medical (diseased) condition. Similarly, there are various signs and symptoms due to various liver impairment issues but among them the commonly reported are sleep and fatigue issues by patients irrespective of the type of liver disorder. Here we are drawing the relationship between liver complications with sleep and fatigue. Various statistical data stands as a strong evidence for increased mortality rate among people who are face sleep disorders. Lack of sleep or excessive fatigue can tremendously affect the personal and social life of an individual, which can give rise to psychological problems like suicidal tendency, depression and many more. The coexistence of liver disorders with sleep and fatigue can increase the mortality by many folds. Sleeplessness, insomnia, difficulty in falling asleep, poor- quality of sleep during the night-time and day-time sleepiness with increases drowsiness are the most commonly reported by the patients with impaired liver functions.

INTRODUCTION

Liver is considered to be a busy organ in our body because it is constantly involved in purifying the blood, around 6 cups of blood passed through the liver which is to be purified. When liver is diseased or damaged it cannot function to its optimal capacity, which leads to the overrunning of toxins in the blood. This can give rise to various symptoms which affect the quality of health, sleep disorders and fatigues are among them. These symptoms are not specific to liver impairment, as it does not indicate the intensity of liver impairment and it is reported among people with no liver complications. Majority of the liver complications like fatty liver, metabolic disorders, hepatitis B and C, jaundice, and hepatic encephalopathy, when left untreated or

If sever leads to liver cirrhosis. These causative factors are the major reason for the prevalence of cirrhosis in the world population. Patients with liver complications commonly show high fatigue and sleep disorders when compared to healthy individuals. The impaired sleep cycle affects the circadian rhythm which in turns affects the quality of life¹⁻⁵. The common sleep complications reported are prolonged sleep latency; short durations of sleep, somnolence, and frequent awakenings during the sleep, and thus poor sleep quality⁵⁻⁸.

LIVER DISEASE AND SLEEP:

The process of falling asleep is classes into different levels

- Consciousness
- Unresponsiveness to the surroundings
- Movement of voluntary muscles

For a deeper understanding sleep is divided based on polysomnography into rapid eye movements sleep (REM) and non-rapid eye movement sleep (NREM). REM accounts to 20% to 25% of total sleep and the remaining 75% to 80% being the NREM⁹. Cortisol and melatonin are two main hormones responsible for sleep-wake cycle. Cortisol is a hormone that is released during stress conditions and at the time of waking up which gives a refreshed feel, whereas melatonin is released to feel relaxed and right before bedtime. During stress the blood levels of cortisol is high which increases the work load of liver in metabolising cortisol, which can be overwhelming to the liver and certain amount of cortisol can still remain in blood without undergoing deactivation, which can keep the body feeling restless and difficulty in falling asleep, this also affects the melatonin levels in the blood. Similarly, the levels of melatonin can also show elevated blood levels when the liver is impaired, where the breakdown of melatonin is not done fully and certain amount of melatonin still remains in the blood which results in day-time sleep. The circadian rhythm of sleep is regulated by two processes, one to promote sleep (Process S) and other one to maintain wakefulness (Process W), these processes determines the sleep duration¹⁰. Process S responsible for the homeostatic sleep, also inhibits the hypothalamic neuronal communication, which minimises the arousal during sleep⁹. When process S is disturbed due to any disorders it results in insomnia¹⁰. Process W is responsible for increased alertness thus promotes wakefulness. The suprachiasmatic nucleus regulates the melatonin, cortisol and core body temperature, alteration of which lead to sleep abnormalities³. Thus, abnormalities in the circadian rhythm are responsible for sleep disorders in patients with liver diseases¹²⁻¹⁴. Impaired melatonin metabolism in cirrhosis leads to an increased level of melatonin and causing increased day time sleep¹⁵. The inversed sleep-wake cycle that is excessive sleep during day time and

struggle to fall asleep during night time is been documented among patients with liver complications and is thought to be one of the early signs. There are various studies which supports the fact that patients with cirrhosis have difficulty in having adequate sleep, which was studied using actigraphy^{3,17-18}.

LIVER DISEASE AND FATIGUE:

Fatigue due to liver impairment can due to glucose supply and modified release of neurotransmitters. Liver is involved in storing glucose and releasing when required, by which liver plays an important role in preventing muscle fatigue. The glucose obtained through diet is converted to glycogen and stored in liver and when body is in need of energy the glycogen in the liver breaks down to release glucose, also when body is running short of carbohydrates, the liver provides it by break down of certain fats and proteins. When the liver is damaged its functioning ability is decreased along with its storage capacity. A long term of liver impairment can cause emotional and physical stress which will activate immune system which signals the brain over the release of certain neurotransmitter as a defence response. The alterations in the neurotransmitter pathways in the brain are the ultimate cause for central fatigue. Those neurotransmitters that are involved in behavioural activation, arousal and locomotion are linked in causing central fatigue¹⁹⁻²⁵. Corticotropin-releasing hormone (CRH) and noradrenaline are two of the main neurotransmitter systems in the genesis of central fatigue.

CRH:

A defective release of CRH in the brain can be an important factor for the central fatigue development²⁵⁻²⁷. The decreased release of CRH with behavioural and physiological responses has shown a direct relationship²⁸⁻³⁰. Patients with primary biliary cirrhosis (PBC), demonstrate augmented adrenocorticotrophic hormone release after intravenous CRH infusion, consistent with an upregulation of pituitary CRH receptors in these patients, possibly secondary to defective endogenous CRH stimulation of their anterior pituitary glands³¹.

NORADRENALINE:

Noradrenaline's hypo-functioning nerve pathway in the brain is known for causing central fatigue³². The beta-blockers and alpha-2 agonists are adrenergic blockers which will cause hypo-functioning of noradrenaline by blocking its activity³³. Majority of the cirrhotic patients are prescribed betablockers for variceal bleeding³⁴.

CONCLUSION:

Sleep disorders and fatigue are not the obvious symptoms of liver dysfunction but are commonly seen among a large number of patients with liver impairment. Since liver plays a major role in metabolism of majority of the compounds in the body, when the liver doesn't meet its optimum function can cause accumulation of various compounds, majorly melatonin which causes sleep inversions and day time drowsiness or fatigue. There are modifications of neurotransmitters that occur due to the impaired liver function. When the neurotransmitters that are responsible for behavioural and locomotory function gets affected causes central fatigue.

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