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Night-Shift, Risk of Chronic Disesases and Melatonin Rhythm

[Gece vardiyası, kronik hastalıklar ve melatonin ritmi]

ABSTRACT

Industrial Revolution and subsequent changes in lifestyle and diet of contemporary human caused an immense increase for several diseases. Night shift has emerged as an additional health risk affecting over than 100 million induvidials around the planet. Studies revealed that incidence of several health problems such as sleep disturbance, fatigue, cardiovascular disease and certain cancer are higher among night shift workers than that of day workers. Incidence of these diseases may physiologically increase as age, therefore night shift may be accepted as a model of accelerated human aging. One of the pathophysiological mechanisms involved in night shift related diseases is disrupted neurological and hormonal regulations most importantly circadian rhythms of autonomic nervous system and secretion of melatonin from pineal gland. This paper will give a brief outline of the medical problems that general practitioners and occupational physicians can face and common pathways involved increased health risks in night shift.

ÖZET

Günümüz insanının hayat tarzı ve beslenmesindeki değişiklikler ve endüstrileşme çeşitli hastalıkların yoğun bir şekilde artışına neen olmuştur. Gece vardiyası dünya genelinde 100 milyondan fazla insanı etkileyen ilave bir sağlık riski olarak ortaya çıkmıştır. Çalışmalar, uyku bozuklukları, halsizlik, kardiyovasküler hastalıklar ve belirli kanser türlerinin gece vardiyası çalışanlarında gündüz çalışanlarına göre daha sık görüldüğünü ortaya çıkarmıştır. Bu hastalıkların insidansları normalde yaşla beraber artığı için, gece vardiyası hızlandırılmış insan yaşlanması modeli olarak kabul edilebilir. Gece vardiyası ile ilişkili hastalıkların patofizyolojik mekanizmalarından birisi bozulmuş nörolojik ve hormonal düzenlemelerdir, bunlardan en önemlisi de otonomik sinir sisteminin ve pineal bezden melatonin salınımının bozulmasıdır. Bu derleme, pratisyen hekimlerin ve meslek hastalıkları ile ilişkili hekimlerin karşılaşabileceği medikal problemleri genel olarak özetlemekte ve gece vardiyasında artmış sağlık risklerinde yer alan ana mekanizmaları açıklamaktadır.

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Anahtar Kelimeler: Gece vardiyası, kronik hastalıklar ve melatonin ritmi

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INTRODUCTION

Although the human genome has remained unchanged over the last 10,000 years, our diet and lifestyle have become progressively more divergent from those of our ancient ancestors. These maladaptive changes become apparent with Industrial Revolution and have been accelerating in recent decades. Socially, we are people of the 21st century, but genetically we remain similar to our early ancestors (1). In conjunction with this discordance between our ancient, genetically determined biology and the nutritional, cultural, and activity patterns in contemporary Western populations, many of diseases have emerged (2, 3). Only a century ago infectious disease was a major cause of mortality, whereas today non-infectious chronic diseases are the greatest cause of death in the world. Epidemics of diseases of civilization (e.g., cardiovascular diseases, type 2 diabetes, obesity, metabolic syndrome and certain cancers) have become major contributors to the burden of disease and they are presently emerging, or accelerating, in most developing countries (4).

For example, an estimated two thirds of American adults are overweight or obese (5). The lifetime incidence of hypertension is astonishingly 90% (6) and the metabolic syndrome (MS) is present in up to 40% of middle-aged American adults (7). Cardiovascular disease (CVD) remains the number one cause of death, accounting for 41% of all fatalities, and the prevalence of heart disease in the United States is projected to double during the next 40 years (8). Despite remarkable pharmacological and technological advances, the pandemic of diseases

continues. The ultimate factor underlying chronic diseases is possibly the collision of our ancient genome with the new conditions of life in affluent nations, including the nutritional qualities of recently introduced foods. In other words, we are human experiencing the conflict between the unchanged human genome and an enormously altered environment. Consequently, human responses to diurnal changes in the natural photoperiod were more robust prior to the Industrial Revolution and have subsequently been increasingly suppressed by alterations in the physical environment (9). Disruption of these processes is exemplified by the extreme circumstances of reversal of day/night working patterns seen in shift workers. These individuals may be accepted as human model of accelerated circadian disruption and aging.

Population-based studies reveal that 13% of workers in Australia, 15% of workers in the US (estimated 6 million Americans), 22% of workers in the UK and 25% of workers in Greece and Finland regularly work night shifts on regular or rotating basis. They are implemented for economic reasons to increase productivity and decrease production costs; on the other hand it presents high human costs (10).

Night-shift and health consequences

In fact, night shift work, can have a negative impact on health and wellbeing of workers, in particular in four spheres: (a) working: suffering from fluctuated work performance and consequent errors and accidents; (b) social: dealing with difficulties in maintaining the usual relationships both at family and social level, with consequent negative influences on marital relations, care of children and social contacts; (c) biological: due to disturbance of normal circadian rhythms of homeostatic functions, apperently sleep/wake cycle; (d) medical: deterioration of general well-being, acceleration of chronic disease manifestation can be manifested in disturbances of sleeping and excess, continious fatigue (10). More importantly, night shift work may increase cardiovascular risk (e.g., hypertension, ischemic heart diseases) and incidence of certain cancers. This paper will give a brief outline of the medical problems that general practitioners and occupational physicians can face.

Sleep and fatigue

On shifts, particularly night shifts, the main function altered is sleep, which undergoes a reduction in duration and an alteration in its quality. Sleep and wakefulness are frequently disrupted in night-shift workers because the sleep/wake behavior is not aligned with the worker's internal circadian cycle (11). One of the well-recognized consequences of shift work is fatigue, which is a state of tiredness associated with extended periods of being awake and consequently being without sleep. Fatigue is a subjective state that cannot be measured objectively. However, fatigue has significant negative effects on alertness, concentration, judgement, mood and performance (12). These effects can lead to errors and injuries including motor vehicle accidents as frequently occurred in sleep-deprived individuals. Of note is the National Sleep Foundation's estimate that driving under the influence of fatigue is equivalent to driving under the influence of alcohol measured at 0.04-0.05 mg/100 ml of blood (13).

Cardiovascular diseases

Alfredsson et al. (14) conducted a study of 334 cases with myocardial infarction and 882 controls. The shift-work exposure was assessed from the occupational code, and from an interview of 14.500 people belonging to a random sample of households in Sweden. The results showed that shift work was associated with myocardial infarction. Boggild et al. reviewed 17 studies to reveal the connection between shift work and CVD risk and found a 40% higher risk of CVD for shift workers than other workers (15). Kawachi et al. followed 79,000 nurses for 4 years and found a dose–response relationship between years of shift work and CVD (16). The results were controlled for confounders, e.g. smoking, BMI, hypertension, diabetes, hypercholesterolaemia, alcohol intake and physical activity. In a 4-year cohort study of hospitalization, Tuchsen et al. followed more than one million men and reported a higher risk of being admitted to hospital due to ischaemic heart disease in men who have occupations with frequent night and early morning (17). Fujino et al. carried out a large prospective cohort study in Japan. The 233.869 person years of follow-up demonstrated a significant association between rotating-shift work and CVD among Japanese male workers (18). In addition, this association was emphasized among the subjects with coronary risk factors, such as hypertension, overweight, heavy drinking, and smoking, which may draw attention for occupational health policy. Apart from increased cardiovascular risk, several studies reported that maladaption of endogenous circadian rhythms in shift workers was associated with all signs of chronic diseases, in particular increased insulin resistance and elevated postprandial triglyceride levels (19-21).

Cancer

There is increasing interest in the possible role of environmental factors that can alter normal endocrine function, often referred to as 'endocrine disruptors,' in the etiology of cancer. Of particular interest is the potential influence of exposure to light-at-night (LAN), and sleep disruption, on endocrine function and the regulation of hormones that are important in the etiology of some types of cancer. Persons who engage in night shift work are subject to the influence of both factors, and may exhibit altered hormone profiles, most importantly decreased melatonin production and disrupted melatonin rhythm (22) as a result that could increase the risk of hormone-related diseases, including breast and prostate cancer .

Hansen reported an increased risk of breast cancer associated with occupational shift work exposure in over 6000 individuals (23). Similar results were also reported in nurses who worked rotating shifts by Schernhammer et al. (24). Ongoing Denmark and Seattle studies have recently found a strong relation in night-shift and increased breast cancer (25, 26). In the Nurses' Health Study, 78.586 women were followed up from 1988 through 1998 and reported an increased risk of colorectal cancer associated with working rotating night shifts (27). Based on 13 studies, a recent meta-analysis (28) reported an increased breast cancer risk among women who work night shift.

Krstev et al. examined a total of 60.878 men with prostate cancer as underlying cause of death (29). They observed excess risks in some occupations including airplane pilots, firefighters, health practitioners and physicians, police and law enforcement personnel all of which are occupations that typically require some degree of night shift work. Kubo et al. prospectively examined the association between shift work and risk of prostate cancer incidence among 14.052 working men in Japan enrolled in a large-scale cohort. During 111.974 person-years, 31 cases of prostate cancer were recorded. They compared day workers with and reported a significant increased risk for prostate cancer in rotating-shift workers (30).

Possible mechanism of accelerated health detoriation in shift workers

One of the greatest men of science and father of physiology, Claude Bernard (1813-1878) referred "Constance of the internal environment is the condition for a free and independent life" mostly known underlying principle of "homeostasis" coined by Walter Bradford Cannon (1871-1945) from the Greek homoios (same, like, resembling) and stasis (to stand, posture). He wrote "The Wisdom of the Body", a fascinating description of the factors involved in the preservation of the internal equilibrium of the body (homeostasis). To maintain homeostasis, the brain has two avenues of communication: hormones and neurons. Hormones present themselves broadly throughout the body and obtain their specificity by acting on their receptors expressed in specific tissues, whereas neurons deliver their message to a precisely targeted tissue in the body. Neurons are considered for rapid and transient communications; hormones however, cause slow but sustained results.

A crucial part of the neural communication is driven by a special system called as autonomic nervous system (ANS). Because it innervates cardiac muscle, smooth muscle and various endocrine and exocrine glands, the ANS influences the activity of most tissues and organ systems. Hence, the ANS makes a significant contribution to homeostasis. The regulation of blood pressure, gastrointestinal responses to food, regulation the blood levels of several hormones and thermoregulation are just a few of the many homeostatic functions influenced by the ANS. The ANS produces a variety of responses by two anatomically and functionally distinct divisions, the sympathetic nervous sytem (SNS) and the parasympathetic nervous sytem (PNS).

Each system is dominant under certain conditions. Moreover, a clear circadian autonomic rhythm allows for an understanding of which system predominates during different periods of the day. SNS predominates in mentally and physically active part of the day (for human; light period), whereas PNS predominates during quiet, resting conditions (for human; dark period). Under physiologic conditions, the overall effect of SNS is to maintain the organism in a state to optimally perform physical and/or mental work. Thus, SNS activity has the capability of increasing the blood flow to the working tissues, to elevate blood pressure and blood levels of several hormones including adrenaline and glucose, as needed. The overall effect of the PNS, however, is to conserve and store energy.

Shifting of these two systems is strictly dependent on the sun light and works synchronously with central clock located in the hypothalamus. In turn, central clock uses both branches of ANS to tune organs of the body (31). In the preparation for an upcoming active period, pineal melatonin secretions suppresses by sun light, plasma cortisol, glucose, muscular

insulin sensitivity and blood pressure rise known as the "dawn phenomenon" and SNS takes over the autonomic predominancy (32). Before sunset, however, pineal gland spurs melatonin production, plasma cortisol, glucose and blood pressure lower known as the "dusk phenomenon". During dark period, plasma melatonin level remains high reaching a peak level at midnight and PNS manages energy storage, repairment, waste disposal and sleep until sunrise (33).

In the active period, the movement compartment (e.g., skeletal muscles) uses glucose and free fatty acids. As a reaction, the brain facilitates liberation of energy substrate from storage organs, such as liver and fat tissue. In contrast, in the inactive period the brain shifts the body toward an anabolic state of recovery. As a consequence, information from the internal and external environment sets the central clock to run on time and prepares the body for the upcoming tasks (34). In the context of circadian autonomic rhythmicity, LAN is the first to disrupt parasympathetic takeover and pineal melatonin secretion and causes prolonged sympathetic predominance. This abnormal external light information confuses central clock, thereby disrupts internal physiologic mechanism (homeostasis). Ambient light as well as several indoor factors (e.g., personal computers, TV) can also complicate the autonomic rhythm and increase the certain type of diseases (35).

In terms of circadian regulation of homeostasis, it is melatonin that involves in a variety of physiological regulations and governs the shifting of PNS and SNS (36). Melatonin (N-acetyl-5-methoxytryptamine) is a small lipophilic indoleamine generated primarily in pineal gland and secreted in a circadian manner with high levels occurring in all species at night. In mammals including the human, the melatonin rhythm is generated by an endogenous circadian clock in the hypothalamus; via a multisynaptic pathway to the pineal gland thereby stimulating melatonin synthesis. The period of melatonin secretion is proportional to the duration of darkness, and it thus acts as a neuroendocrine transducer of photoperiodic information. Melatonin plays a key role in a variety of important physiological functions, including regulation of circadian rhythms, as well as visual, reproductive, cardiovascular, neuroendocrine, and neuroimmunological actions (37). Recent evidence and several novel mechanisms (38-40) support the idea that melatonin rhythm is core of virtually all physiological process in human and hence reffered as "nature's most versatile biological signal" (41).

Melatonin counteracts many pathologic processes resulting in chronic diseases as an autocrine and paracrine agent, as a versatile anti-oxidant and anti-inflammatory hormone (42). Melatonin has the capability to block several pathways involving disease pathogenesis including nitro-oxidative stress, hyperglycemia, hyperlipidemia (43), high blood pressure (44) and malignancy occurance (45),. Recent medical advencement revealed several nutritional and lifestyle modifications, all correlate of the cancer-protective hormone melatonin and its rhythm (46). Genetically determined biology of human is programmed in accordance with such daily-based (circadian) regulations and adaptation to environmental changes may need generations (47).

CONCLUDING REMARKS

Today most of us dwell in mechanized urban settings, leading largely sedentary lives and eating a highly processed synthetic diet. Chronic illnesses and health problems either wholly or partially attributable to diet and sedentary life style represent by far the most serious threat to public health (48). On the other hand, accumulating evidence suggests a vital role of circadian and particularly melatonin rhythm for being healthy and decelerating metabolic disturbances which normally occur at age. Circadian clock has a profound impression over entire metabolism and peripheral mechanisms are generally reffered as slaves of the circadian mechanisms (49). Melatonin rhythmicity has been suggested to represent one of the first biological signals which appeared on Earth (50), then in turn, it is the rhythm that, once disappeared, homeostasis is disrupted and diseases may readily develop. LAN and particularly night-shift worsen the homeostasis by way of disrupting circadian rhythmicity and function as aging acceletors. Night shift may precede several certain diseases including CVD and cancer and may cause a tremendous human cost beyond economic profits.

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