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Original papers

Circadian rhythm deregulation and thyroid dysfunction: results of an observational study on night shift workers

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Abstract

Context. It has been decades since the circadian variation of the secretion of the thyroid stimulating hormone (TSH) was proven in humans. Even so, there are few studies on human beings that explored the relationship existing between night shift circadian rhythm deregulation and thyroid disorders.
Methods. We have revised the occupational medicine files of all employees in a single speciality hospital to conduct an observational study on the prevalence of thyroid disorders in night shift compared to day shift workers. Age, gender, occupational history, body mass index and specialist diagnosed thyroid disorders were recorded. Numerical variables were compared with ANOVA test, and categorical ones with chi test (StatPlus for Mac version v6).
Results. Obesity was slightly more prevalent in night shift workers, but not statistically significant. Instead, we found a significant increase in the prevalence of thyroid disorders in night shift workers (x= 7.424, p = 0.006). As this is a mere observational study, our results only contribute to the pool of data concerning the relationship between thyroid dysfunction and night shifts.
Conclusions: These results should raise awareness, particularly among occupational physicians and endocrinologists, about the influence of sleep and circadian rhythm deregulation on the raising incidence of thyroid disorders.

Keywords: *circadian rhythm deregulation, thyroid dysfunction, night shift workers*

Introduction

Night shift influence on the homeostasis has become an important direction of the current occupational medicine research. The initial link with fatigue, stress and work related accidents has been extended to an impressive number of studies focused on the investigation of its role in obesity, diabetes, cardio-vascular disorders or neoplasia. As the secretion of TSH has also a circadian variance being highest during the night and having a nadir during the afternoon [1], the possible interruption of this cycle is a reasonable question to rise with regards to night shift workers. This became even more relevant after finding a TSH secretion modulation after the initiation of night sleep and that forced light exposure and sleep deprivation during night-time interrupted this physiological rhythm [2]. Recent research showed night shift workers have higher levels of TSH secretion and a 1.399 fold increased risk of subclinical hypothyroidism [3]. The relation seams to be quantitative, as persistent night shift work for more than 15 years increases almost two fold the relative risk of these diseases [4]. In order to provide supplementary data about this relation, we have analysed if there is a higher prevalence of thyroid disorders in employees working in night shift in comparison with those having only a day shift schedule.

Material and methods

Data recorded during the annual check-up of small, mono-speciality hospital were analysed. We have extracted the following data: age, gender, occupational history, current BMI and presence of absence of a diagnosed thyroid disorder. The employees were divided in two main groups, according to the current program schedule. Nightshift workers were defined by working at least 1 night/week (from 8.p.m to 8 a.m.). For nurses, the scheduling of their shifts was the following: 12 h of activity followed by 24 h recovery period. Technicians worked in a rotating 8h shift. Concerning the day shift, any sort of program except working during the night was considered, no matter if there was regular program (from 8 a.m. to 5 p.m.) or if it also included afternoon shifts (from 2 p.m. to 8 p.m.). The total number of permanent employees of this hospital was 91, from which 35 employees (38.46%) were working in shifts and 56 (61.54%) in dayshifts. Averages, medians and standard deviations were computed with a StatPlus for Mac version v6. The same software was also used for data analysis: numerical variables were compared with ANOVA test and categorical variables with x^2 test. A threshold reflecting a 95% probability was considered as significant.

Results

From the 35 persons working in night shifts, about half were nurses; the rest were assistant nurses, cleaning, technicians and security personnel. The distribution of employees working night shifts according to their occupation is illustrated in the Figure 1. The day shift was a more numerous group, including 56 persons: 3 doctors, 12 nurses, 10 assistant nurses, 7 persons with office and administrative work, 1 pharmacist and 2 pharmacist assistants, 3 cooking personnel, 2 drivers, 8 technicians and 8 cleaning personnel. The average age was slightly higher in the day shift compared to the night shift workers (48.35 versus 47.8 years) but the difference was not statistically significant (p = 0.751). The gender distribution was rigorously the same: 71% women and 29% men in both the night shift and the day shift groups. No age difference between men and women subgroups was noticed. The main characteristics recorded for this analysis are illustrated in Table 1. The average BMI was 27.07 in the night shift compared to 26.37 in day shift workers. Although higher, the difference was not statistically significant (p=0.438). There also no differences in the average BMI in the gender subgroups. Because of low number of cases, we could perform the comparison of BMI by professional category only for the nurses, but neither this comparison gave a significant result (p=0.129). In the whole group, 41% of the subjects were overweight and 22% were obese. In night shift 10 (29%) persons had normal BMI, 17 (50%) were overweight and 7 (21%) were obese. In the dayshift, 41% had normal BMI, 36% were overweight and 23% obese. The difference between groups was not

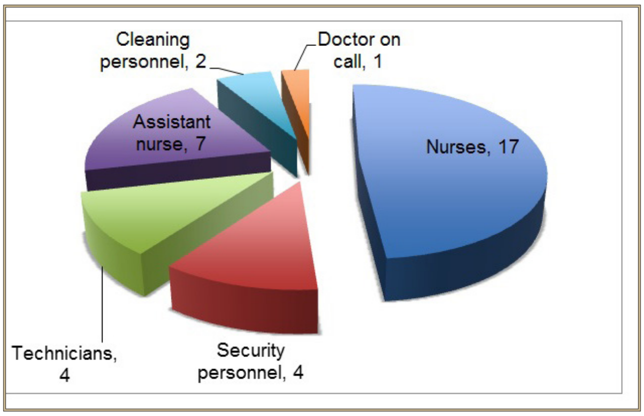

Figure 1. Distribution of the night shift personnel by occupation

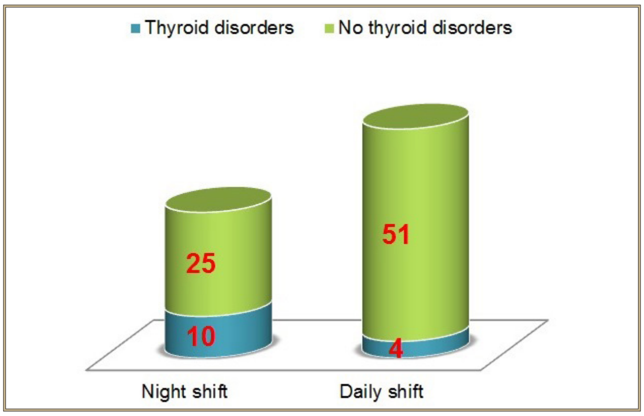

Figure 2. Distribution of thyroid disorders in nightshift and dayshift employees

Table 1. Main characteristics of the study groups

	Nightshift		Dayshift	
	Women	Men	Women	Men
Age (years): average and SD	47.12 (± 7.63)	49.5 (± 6.31)	50.27 (± 7.74)	47.63 (± 8.5)
BMI: average and SD	27.78 (± 3.54)	25.37 (± 5.45)	26.11 (± 4.13)	27.01 (± 3.52)
Thyroid disorders: no. and %	8 (32%)	2 (20%)	3 (10%)	1 (6.3%)

not significant (x=1.9002, p = 0.384). BMI was independent of the frequency of thyroid disease (p=0.423). The prevalence of thyroid disorders was 15.38%. The distribution of cases in the two groups is presented in Figure 2. In the night shift group, the prevalence was 28.57%. The most prevalent form was hypothyroidism (5 cases), followed by 2 cases of hyperthyroidism, 2 small size goitres, and 1 thyroid nodule. In the day shift workers, the prevalence was 7.14%; there were 2 cases of hypothyroidism and 2 thyroid nodules. This prevalence was significantly different in nightshift versus dayshift workers (x= 7.424, p = 0.006).

Discussions

In this observational study, we found a relatively high prevalence of thyroid disorders in night shift workers, comparable with what was found in other studies. [3,5] This finding is particularly relevant for a country in which the number of thyroid disorders is increasing. In fact, according to the National Institute of Public Health, the incidence of thyroid disorders had increased by 69%, from 44785 in 2013 to 75777 in 2017 [6]. The increase in incidence can no more be explained solely by the iodine deficit, the main factor of influence of the incidence, as food supplementation with iodine has been implemented in the last years in Romania, and neither from more readily accessible diagnostic tools. In general population, it is largely accepted that women are more affected than men by all forms of thyroid disease from latent or overt hypothyroidism, autoimmune thyroiditis, latent or overt hyperthyroidism, benign nodules or thyroid cancer [7]. In our study, a higher rate in women was also noticed. Another general risk factor is age. [8] The latent forms of thyroid disorders and the thyroid cancer increase with age, mainly after the 6th decade. We cannot explain the prevalence of our cases in relation to age, as only one person in our group was 60 years old. Instead, more relevant to explain our findings are other two occupational risk factors that have been linked to the prevalence of thyroid disorders: stress and circadian rhythm deregulation. In many occupations, these risk factors co-exist and this is also the case for the medical services.

Epidemiological studies relating medical professions to thyroid diseases continue to accumulate. For example, a large Taiwanese study showed a higher risk of all type of thyroid diseases (OR between 1.27 and 1.89) among physicians [9]. The endocrine profile hours on call activity was initially considered for the cortisol, epinephrine and norepinephrine variations. A recent small study showed that the TSH increase might be an earlier predictor of stress, as its increase was not associated with the expected changes mentioned above [10]. Another study aligns to these findings: a comparison of the TSH levels during the daytime and the night time shifts of nurses showed a significantly higher TSH levels at the end of the nightshift. The TSH increase coexisted with higher levels of triiodothyronine (T3) and thyroxin (T4) [11]. There are plausible biological explanations for these epidemiological findings, due to the circadian variation in relation to the secretion control and to the actions of the thyroid hormones. As mentioned, TSH have peaks between 2 and 4 a.m. and a nadir in the afternoon. The thyroid releasing hormone (TRH) peak, in relation to melatonin secretion, could explain the higher TSH plasma level, but this definitely not the only element of the complex regulatory mechanism, with several feedback controls, that regulates the hypothalamic-pituitary function: among these, positive secretory effects were described for cathecolamines and leptin [12], and negative, inhibitory effects for somatostatin, inflammatory citokines, cortisol, and circulatory T3 and T4 levels, both central and peripheral [1]. Despite the TSH circadian variation, under normal circumstances, the peripheral thyroid hormones do not have significant variations during the day, but we don't know for how long this is a reversible, autoregulated effect and if the long time night shift work has any influence.

Concerning the circadian action of the thyroid hormones, there are at least two directions that have been explored: on one side, is the thyroid clock function, and, on the other side, are the receptor expression variations. In rats, the thyroid clock seams to function independently of the TSH action, as PER1 and BMAL1 clock genes still continue to oscillate after hypophysectomy [13]; the local availability of the thyroid hormones (through the type 2 iodothyronine deiodinase) [14] is also under BMAL1 control. Thyroid receptors are nuclear hormone receptors activated by T4 and T3, acting on the transcription. As other nuclear receptors, they also have nongenomic effects such as angiogenesis, microfilament cytoplasmic architecture, cellular respiration [15] and the immune reaction [16]. Thyroid receptors expression shows circadian variation in hepatocytes and adipose tissue in mice [17] and the interruption of this physiological rhythm is another possible mechanism to be considered when analysing the effect of sleep short duration and or misalignment. Some other experimental data supports that hypo and hyperthyroidism affect the clock genes tissue expression; for example, an experimental study showed a significant effect on myocardial metabolism related to the circadian rhythm [18].

These mechanisms described above constitute other possible effects of the circadian rhythm disruption, which under current knowledge cannot be excluded to be present in night shift workers. However, the main limitations of these proposed mechanisms are that they both rely only on animal experiments, with their limited translation to human biology.

There is definitely a need to initiate well designed, prospective studies, to validate or not these pathophysiological arguments in night shift workers before including this working category in the algorithm of recommendations for thyroid disorders screening. Concerning the screening, international endocrinology societies and preventive task forces are far from reaching a consensus, except for the new born screening in regions with iodine deficit, a screening program that is also implemented in our country. When referring to adults, the American Thyroid Association is in favour of the screening for women > 35 years of age, but the American Association of Clinical Endocrinologists, of Family Medicine and of the College of Physicians would consider it only for older persons [19]. The more clinical orientated approach is better accepted: this includes a history (personal or family) of autoimmune disorders, including pernicious anaemia, thyroid mass reduction (neck radiation, surgical), medication that interferes with thyroid function (e.g. amiodarone, lithium), diseases that might be significantly influenced by thyroid hormones levels such as: cardiac diseases, including prolonged QT interval, myopathies, dysmenorrhea, obesity, type 1 diabetes and dyslipidaemia. Alopecia, changes in skin texture, constipation, vitiligo, malaise and fatigue, cold intolerance should also be considered [19].

In order to assure the evidence for considering night shift as risk factor for thyroid disorders and to include it in screening recommendations is a long way. Occupational physicians might contribute to the understanding of the thyroid effects of circadian deregulation by reporting their statistics and by initiating occupational cohorts to conclude is that such a risk does happen in night shift workers.

Our study has limitations that can not give, under any circumstances, conclusive remarks on the effects of night shift on thyroid functions: first, it is a descriptive study that can not, by its intrinsic design, lead to a cause-effect relation. Second, the study did not consider other factors that cause the thyroid dysfunction, such as the iodine concentration or immune status. Meantime, a demonstration of the thyroid dysfunction after night shift exposure can not be emphasized by this cross sectional analysis.

Conclusion

In practical terms, occupational physicians should carefully check for symptoms and signs of thyroid disorders in night shift workers. In what concerns the screening programs for thyroid disorders, a the exact role of the disrupted circadian rhythm remains to be established and occupational cohorts could give important clue in solving this topic.

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