проти 8,1%, р<0,05). Таким чином, додавання МД+γ-БД до комплексної терапії пацієнтів з ХСН та ЦД 2 типу покращує клініко-гемодинамічні і глюкометаболічні показники та коригує дисбаланс оксидантно-антиоксидантної системи.

Ключові слова: хронічна серцева недостатність, цукровий діабет 2 типу, структурно-функціональні зміни лівого шлуночка, перекісне окислення ліпідів, фіксована комбінація мельдонію дигідрату та γ-бутиробетаїну дигідрату.

Стаття надійшла 28.06.2019 р.

против 8,1%, р <0,05). Таким образом, добавление МД+γ-БД в составе комплексной терапии пациентов с ХСН и СД 2 типа улучшает клинико-гемодинамические и глюкометаболи-ческие параметры и корригирует дисбаланс оксидантно-антиоксидантной системы.

Ключевые слова: хроническая сердечная недостаточность, сахарный диабет 2 типа, структурно-функциональные изменения левого желудочка, перекисное окисление липидов, фиксированная комбинация мельдония дигидрата и γ-бутиробетаина дигидрата.

Рецензент Шепітько В.І.

A.O. Volosovets, I.S. Zozulya, O.P. Volosovets[1], D.S. Savchenko[1], O.G. Kramareva
Shupyk National Medical Academy of Postgraduate Education – NMAPE, Kyiv
[1]Bogomolets National Medical University - NMU, Kyiv

INFLUENCE OF EXCESSIVE NIGHTTIME ACTIVITY ON THE RISK OF ISCHEMIC CEREBRAL STROKE EVENT AND ITS COURSE FEATURES

e-mail: healermaster@gmail.com

Clinical neurological and neuroimaging examination of 300 patients with ischemic stroke was performed. The control group included 40 patients without signs of acute cerebral stroke (men - 21, women - 19) aged 46 to 76 years (mean age being 62.6 ± 10.2 years). The data obtained confirmed that the important role of excessive nighttime activity (ENA) is characteristic of all groups of patients, but 100% correlation is observed in patients with nocturnal strokes. In patients with ENA there are two peaks of blood pressure increase: - 9:00 and 21:00. Patterns of blood pressure disorders at night were as follows: 68.4% (n = 13) - night peaker, 26.3% (n = 5) - non dipper, 5.2% (n = 1) - dipper subtype. Against the background of an optimized stroke prevention program, the incidence of recurrent ischemic strokes was by 2.09 times lower than in the control group within 2 years. The present study results show the importance of ENA for the diagnosis and pathogenesis of acute ischemic stroke.
Key words: stroke, excessive nighttime activity, onset time, stroke risk, prevention.

The problem of acute ischemic stroke remains one of the main issues in modern medicine, being one of the main causes of disability and mortality of people in Ukraine and in the world. The issue of ischemic stroke treatment, regardless of the economic status of the country, remains expensive, therefore, the world's organizations focus on the therapeutic strategy to combat ischemic stroke, precisely on the prevention of this disease [6].

Importance of the ischemic stroke prevention brings to the forefront identification and unifying the whole variety of risk factors for cerebral ischemia [1]. However, at this stage, researchers have only agreed concerning unmodified (age, gender, race, etc.) and "internal" modified risk factors for cerebrovascular catastrophe (arterial hypertension, hypercholesterolemia, diabetes, etc.) [1, 2]. As for the "external" risk factors, researchers have not yet come to a single conclusion, separately identifying only the factors of bad habits [3, 5].

One of the important predictors of cerebral ischemia, which, however, is poorly described in modern literature, remains excessive nighttime activity (ENA). Excessive nighttime activity is a habitual permanent deformation of the day regime (social risk groups are doctors, taxi drivers, night shift workers). This factor plays a significant social role in many people's lives and can seriously affect the incidence of cerebrovascular pathology in many groups of population [4]. Studies have already confirmed that excessive nighttime activity shows a pronounced association with cardiovascular disease [7], diabetes mellitus and cancer, but the question of the impact on patients with acute ischemic stroke remains understudied [9].

The purpose of the work was to determine the extent and nature of the excessive nighttime activity factor's influence on the incidence of ischemic stroke and to study the efficacy of ENA prevention in association with the recurrent ischemic strokes incidence.

Materials and methods. To achieve this purpose, we performed a clinical neurological and neuroimaging examination of 300 patients who had acute ischemic stroke (men - 196, women - 104) aged 42 to 84 years (mean age - 65.2 ± 8.7 years). The inclusion criteria for this study were: the patients' age from 40 to 85 years; ischemic stroke focus verified by MRI; consent of the patient or his legal representative.

The control group consisted of 40 patients with no signs of acute stroke (men - 21, women - 19) aged 46 to 76 years (mean age being 62.6 ± 10.2 years) who were enrolled in the study to develop a social risk assessment scale for the cerebral stroke onset.

To assess the risk of a patient with acute ischemic stroke, preference was given to clinical examination methods directly at the patient's bedside. In this case, the patient with acute stroke (or his relatives in case of inability to contact) subject to a detailed survey and collection of premorbid anamnesis, followed by the use of the stroke social risk scale, which presents the severity of such cerebrovascular ischemia social risk factors in the patient as sleep disturbance, stress inducing environment, excessive nighttime activity, prolonged work with monitors, low physical activity, poor nutrition, bad habits (alcohol, tobacco smoking).

Assessment of the excessive nighttime activity severity was performed by collecting information on the nature and timing of the patient's work and rest according to the following criteria:

• 3 points - one or more of the following symptoms are observed: permanent work at night shift or work ending later than 3:00; severe nocturnal physical or mental activity more than 3 nights per week.

• 2 points - one or more of the following symptoms are observed: periodic work at night shift or end of work ending after 00:00; severe nocturnal physical or mental activity more than 1 night per week.

• 1 point - one or more of the following symptoms are observed: rarely work at night shift or end of work after 9:00 pm; severe nocturnal physical or mental activity more than 1 night per month.

• 0 points - work ends no later than 6:00 pm, severe nocturnal physical or mental activity is observed less frequently than 1 night per month.

According to the severity of one or another factor, each predictor is scored in points, denoting the highest grade of the score being 3 points, complete absence - 0 points. In the case of several signs indicating different degrees of the factor severity, the one considered to be of the highest risk is taken into account.

Statistical analysis was performed using Microsoft Excel. Average values (M) were calculated to provide adequate evaluation of the data. Statistical processing of absolute values was carried out according to conventional methods with the calculation of intensive and extensive indicators. The relationship between qualitative variables was determined using the Fisher's exact test, the difference between the average values was estimated using the non-parametric Mann-Whitney U-test. The difference at $p < 0.05$ was considered statistically significant (using the Bonferroni amendment).

Results of the study and their discussion. To identify the most important risk factors for ischemic stroke and the place of ENA among them, we analyzed the occurrence frequency of the most common stroke predictors not only among the main A1 group patients (n = 300) but also among the A2 control group (n = 40), which representatives had no ischemic stroke (table 1).

Table 1

Social risk factors and their incidence in patients with and without acute cerebral stroke (%)

Social factors	Patient groups	
	A1 n=300) %	A2 (n=40 %
Stress inducing environment	98.3*	10
Sleep disturbance	96.0*	5
Low physical activity	86.0*	11
Excessive nighttime activity	83.3*	5
Prolonged work with monitors	80.0*	35
Poor and irregular food intake	75.0*	5
Bad habits (alcohol, tobacco smoking)	71.0*	10
Marital status	70	84
Physical overload	62	45
Hyperthermia	57	40
Past lung infection	55	58
Unsystematic intake of antihypertensive drugs	54	39
Frequent voyages by train, air travels	46	23
Absence of sexual activity	37	18
Depression	18	10

* - statistically significant difference (p <0.05).

The results of the analysis indicate a high diagnostic value of such a predictor as ENA, which ranked fourth (83.3%) in the list of the most frequently diagnosed risk factors for cerebral ischemia, while among the representatives of the control group the frequency of this factor detection did not exceed 5% (p <0.05).

The mean ENA severity among the patients in the main group who showed this risk factor (n = 249) was 2.22 ± 0.16 points.

Having obtained confirmation of the ENA factor diagnostic value, we continued studying the effect of this predictor on the ischemic stroke course. In particular, we analyzed variants of the cerebral ischemia onset time against the background of excessive nighttime activity detected in patients of the main group (table 2). To optimize the analysis of the data obtained, all patients were divided into 3 groups according to the of day when the ischemic stroke occurred:

- group 1, which patients suffered from cerebral ischemia during the day (8: 00-14: 59);
- group 2, which patients had a stroke in the evening (15: 00-21: 59);
- group 3, which patients underwent ischemic stroke at night (22: 00-7: 59).

Table 2

Influence of ENA on the daytime period of ischemic stroke onset

Index	Patient groups		
	Daytime stroke (n=146)	Evening stroke (n=107)	Nocturnal stroke (n=47)
Excessive nighttime activity	123 (84.2 %)	80 (74.7 %)	47 (100 %)

The data obtained confirmed that excessive nighttime activity played an important role in all patient groups, however, there was a 100% correlation for patients with nocturnal strokes.

Based on the above information, we analyzed the ENA influence on the patterns of blood pressure (BP) fluctuations in patients within the day and night periods (fig. 1).
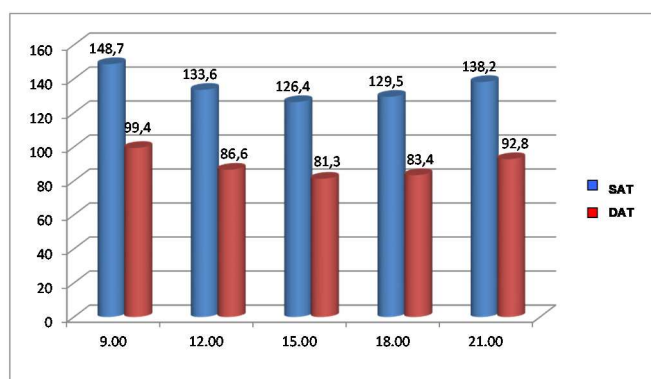

Fig. 1. Characteristics of systolic (SAT) and diastolic blood pressure (DAT) fluctuations among patients with acute ischemic stroke in whom ENA was observed.
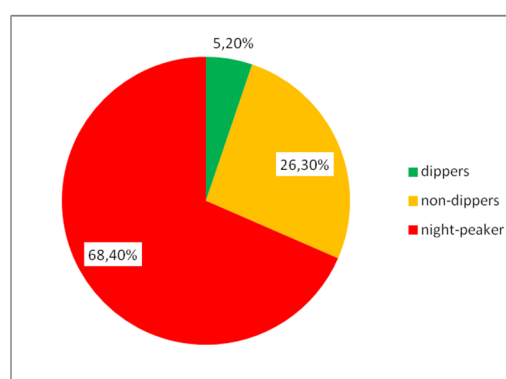

Fig. 2. Variability of nocturnal of blood pressure oscillation in patients with stroke that occurred against the ENA background (22: 00-7: 59)

The features of the blood pressure dynamics in patients with ENA lied in the fact that such patients had two peaks of blood pressure increase - 9:00 and 21:00 respectively. It is noteworthy, that such a model of blood pressure variability, according to our observations, is largely associated with the disturbance of the sympathetic system circadian activity and its forced stimulation in the night period due to excessive night activity, sleep disorders and active night consumption of alcohol in the history of the ischemic stroke social risk. Such a shift leads to a high risk of increased blood pressure during sleep and causes a pathological background for the cerebrovascular catastrophe onset during the night period.

Observation of nocturnal blood pressure oscillation in such patients only confirms our findings, since the spectrum of blood pressure oscillation patterns was as follows: 68.4% (n = 13) - night-peaker, 26.3% (n = 5) - non- dipper, 5.2% (n = 1) - dipper subtype (fig. 2).

The obtained data permit to conclude that for patients with ENA, in whom stroke was mostly observed at night, the main internal risk factor for the cerebral ischemia onset is arterial hypertension, which is confirmed by the results of the study on the influence of circadian rhythm disturbance on heart disease risk performed by Shanmugam V. with co-authors [7].

However, it should be emphasized that the peak of blood pressure in such patients occur during the night period, which contradicts the standard daily blood pressure fluctuations and, most likely, are associated with patients' lifestyle, which requires them to be excessively active during the night time of day (security, night duty, dispatcher's service, active nightlife, etc.) and thus causes the body to maintain a sufficient level of vigor and functionality due to chronic unnatural stimulation of the sympatho-adrenal system.

Important is the fact that, even after a person returns to normal daytime work and activity, such a pathological pattern of BP fluctuation continues to persist for a long time and, as a result, can lead to the

ischemic stroke onset at night. Similar trends are consistent with the findings of a research team led by Yadegarfar G., although the focus of their study was related to cardiovascular rather than cerebrovascular diseases [9].

Given the identified trends in the ENA impact on the ischemic stroke course, the following algorithm for the ischemic stroke prevention is possible for the following patients:

1) Antihypertensive therapy with assignment of complex (2 or more drugs) therapeutic regimens according to individual features. Given the subtype of "night-peaker" daily BP fluctuation, evening antihypertensive medication is mandatory and the main thing is that the drugs are given at a high dose before bedtime. In the absence of counterindications, the calcium antagonist group is preferred;

2) Continuous control over the patient's own heart rate;

3) Adequate antiplatelet therapy (100 mg of protected acetylsalicylic acid form in the evening after meals);

4) Prescription of statins in standard (20 mg) dosage according to the scheme "1 month of admission - 1 month without drug" under the control of liver sampling;

5) Use of drug-free (autotraining, exercise, meditation, swimming) and medicamentous (antidepressants, anxiolytics, sedatives) methods of stress relief, avoidance or elimination of stress inducing environmental elements;

6) Adequate oxygenation of the office space where the office equipment is located. Periodic breaks every 45 minutes (it is advisable to do exercises to remove the spasm of accommodation or just staying with eyes closed). During breaks it is necessary to perform a set of exercises for the neck;

7) Changing working conditions to adapt to the usual biorhythm with daytime activity and nighttime sleep, reducing episodes of nighttime activity, and a mandatory after-work rehabilitation period. Avoiding the use of stimulants to enhance activity at night;

8) Complete refusal of alcohol intake or a significant restriction on its consumption. It is permissible to consume alcohol in small or moderate amounts, which makes - 2 units of alcohol per day for men and - 1 unit for nonpregnant women;

9) Prevention of night hypoxia by room ventilation or oxygen therapy. Removal of the elements that can excite the nervous system at bedtime (stimulants, alcohol, videos, etc.). Normalization of sleep by physical methods (gymnastics, warm baths, autotraining) and medication (sleeping pills, sedatives). It is recommended to administer melatonin as a hypnotic and neuroprotective drug at the dose of 1-2 mg before going to bed with a gradual transition to the dose of 3-6 mg in case of failure in the circadian rhythms normalization.

Considering the ability of melatonin (N-acetyl-5-methoxytryptamine) and its metabolites to absorb a wide range of free radicals, researchers consider this compound as one of the most important antioxidants in the body. Acting as the mechanism of direct acceptor, this neurohormone is able to neutralize the effect of free radicals on the cell wall of neurons [8].

Assessment of the described prevention scheme efficacy in patients with stroke, which occurred against the background of the ENA, was performed according to a comparative data assessment of the main group, which included 24 patients with stroke against the ENA background, aged 52 to 83 years (mean age – 63. 6±1.3 years), who received prevention treatment according to the algorithm described above.

To control the prophylactic treatment efficacy, the control group was also formed including 23 patients with acute stroke, which also occurred in association with ENA, aged 51 to 84 years (mean age 64.1±1.5 years), but who were assigned a standard prophylactic regimen.

The efficacy of the presented preventive regimen was studied during the observation period of 2 years. During this period, only 2 recurrent cerebrovascular catastrophes occurred in the main group (8.3%). However, in the control group the situation with recurrent episodes of ischemia was worse - 4 cases (17.4%). Thus, in this case, the specialized scheme had a positive effect in reducing the incidence of recurrent ischemic strokes by 2.09 times compared to the control group, which confirms the results obtained by Wirtz P.H. and co-authors concerning the positive effect of melatonin use on blood coagulation properties [8] and the respective prevention of thrombosis.

In general, the results of our study are concordant with the general scientific trends outlined in the work of Douma et al. [3], but our data indicate a more pronounced dependence of daily fluctuations in blood pressure both on the complex effects of internal risk factors and excessive nighttime activity, which also was reflected in our other scientific works [1].

At the same time, a data from Fodor et al. [4] supports our findings that excessive nighttime activity has a particularly pronounced negative impact on the nocturnal time of onset of ischemic stroke, which has a more severe clinical course and a special nature of complications [1].

Conclusion

The results of the presented study indicate that ENA has significant diagnostic and informational value for determining the risk of ischemic stroke. The study of the excessive nighttime activity effect on the ischemic stroke course showed that this risk factor had a pronounced association with the stroke onset at night and led to a characteristic disturbance of blood pressure daily fluctuations patterns in patients with ischemic stroke. Preventive measures that included ENA correction resulted in a decrease of the recurrent ischemic strokes incidence by 2.09 times compared to the control group.

References

1. Zozulya I, Zozulya A, Volosovets A. Complications of ischemic stroke: Diagnostics, treatment, prevention and rehabilitation. Psychiatry, Psychotherapy and Clinical Psychology 2017, T. 8, №3:375-381 [in Ukrainian]
2. Mishchenko TS. Epidemiologiya tserebrovaskulyarnykh zabolevaniy i organizatsiya pomoshchi bolnym s mozgovym insultom v Ukraine. Ukr. vísn. psikhonevrolohiyi. 2017; 25(1):22-4. [in Russian]
3. Douma LG, Gumz ML. Circadian clock-mediated regulation of blood pressure. Free Radic Biol Med. 2018;119:108–114.
4. Fodor D. M., Gonganau-Nitu D., Perju-Dumbrava L. "Circadian pattern of ischemic stroke onset," in Human Vet Med Bioflux, vol. 6, pp. 132–139, 2014.
5. Choi Y. I., Seo I.-K., Kim D.-E. et al., "Same pattern of circadian variation according to the season in the timing of ischemic stroke onset: preliminary report," Sleep Medicine Research, vol. 6, no. 2, pp. 72–76, 2015.
6. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Blaha MJ. Heart disease and stroke statistics – 2014 update: a report from the American Heart Association. Circulation. 2014 Jan 21;129(3):e28-e292.
7. Shanmugam V, Wafi A, Al-Taweel N, Busselberg D. Disruption of circadian rhythm increases the risk of cancer, metabolic syndrome and cardiovascular disease. J Local Global Health Sci. 2013; 2013:3.
8. Wirtz PH, von Känel R. et al. Psychological Stress, Inflammation, and Coronary Heart Disease. Curr Cardiol Rep. 2017 Sep 20;19(11):111
9. Yadegarfar G, Shahabi J, Garakyaraghi M, The association of anthropometric indices and cardiac function in healthy adults. ARYA Atheroscler. 2019 Jan;15(1):9-13.

Реферати

ВПЛИВ НАДМІРНОЇ НІЧНОЇ АКТИВНОСТІ НА РИЗИК ВИНИКНЕННЯ ТА ОСОБЛИВОСТІ ПЕРЕБІГУ ІШЕМІЧНОГО МОЗКОВОГО ІНСУЛЬТУ
Волосовець А.О., Зозуля І.С., Волосовець О.П., Савченко Д.С., Крамарева О.Г.

Проведено клініко-неврологічне та нейровізуалізаційне обстеження 300 хворих, що перенесли ішемічний інсульт. Контрольну групу склали 40 пацієнтів без ознак гострого мозкового інсульту (чоловіків - 21, жінок - 19) у віці від 46 до 76 років (середній вік 62,6 ± 10,2 року). Отримані дані підтвердили, що важлива роль надмірної нічної активності характерна для всіх груп пацієнтів, однак для пацієнтів з нічними інсультами спостерігається кореляція 100 %. У пацієнтів з ННА спостерігається два піки підвищення АТ - 9:00 і 21:00. Паттерни порушення артеріального тиску в нічний час виглядали наступним чином: 68,4% (n = 13) – night peaker, 26,3% (n = 5) – non dipper, 5,2% (n = 1) - підтип dipper. На тлі оптимізованої програми профілактики інсульту протягом 2 років серед пацієнтів у основній групі спостерігалося зменшення частоти повторних ішемічних інсультів у 2,09 рази в порівнянні з контрольною групою. Результати представленого дослідження показують важливість ННА для діагностики та патогенезу гострого ішемічного інсульту.

Ключові слова: інсульт, надмірна нічна активність, час початку, ризик інсульту, профілактика.

Стаття надійшла 25.04.2019 р.

ВЛИЯНИЕ ЧРЕЗМЕРНОЙ НОЧНОЙ АКТИВНОСТИ НА РИСК ВОЗНИКНОВЕНИЯ И ОСОБЕННОСТИ ТЕЧЕНИЯ ИШЕМИЧЕСКОГО МОЗГОВОГО ИНСУЛЬТА
Волосовец А.А., Зозуля И.С., Волосовец О.П., Савченко Д.С., Крамарева О.Г.

Проведены клинико-неврологическое и нейровизуализационное обследования 300 больных, перенесших ишемический инсульт. Контрольную группу составили 40 пациентов без признаков острого мозгового инсульта (мужчин - 21, женщин - 19) в возрасте от 46 до 76 лет (средний возраст 62,6 ± 10,2 года). Полученные данные подтвердили, что важная роль чрезмерной ночной активности характерна для всех групп пациентов, однако для пациентов с ночными инсультами наблюдается корреляция 100%. У пациентов с чрезмерной ночной активностью (ЧНА) наблюдается два пика повышения АД - 9:00 и 21:00. Паттерны нарушения артериального давления в ночное время выглядели следующим образом: 68,4% (n = 13) - night peaker, 26,3% (n = 5) - non dipper, 5,2% (n = 1) - подтип dipper. На фоне оптимизированной программы профилактики инсульта в течение 2 лет среди пациентов в основной группе наблюдалось уменьшение частоты повторных ишемических инсультов в 2,09 раза по сравнению с контрольной группой. Результаты представленного исследования показывают важность ЧНА для диагностики и патогенеза острого ишемического инсульта.

Ключевые слова: инсульт, чрезмерная ночная активность, время начала, риск инсульта, профилактика.

Рецензент Дельва М.Ю.