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The influence of circadian variation in ischemic stroke onset on the evolution of cognitive status

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Abstract

Introduction. It is already known and accepted that cerebrovascular disease onset has a temporal variation pattern, the best documented being the circadian variation pattern, with a frequency peak in the morning and a second lower peak during afternoon. The impact of this circadian variation on post-stroke cognitive status has been little studied.

Materials and method. The study included a cohort of 63 patients with ischemic stroke, admitted to the Neurology Departments I and II of the Rehabilitation Hospital in Cluj-Napoca between 1 June 2008 and 1 June 2009, who were evaluated for their cognitive status over 2 years, during 5 successive visits. The onset time of ischemic stroke was assigned to one of the six-hour intervals: 00.01-06.00 (night), 06.01-12.00 (morning), 12.01-18.00 (afternoon), and 18.01-24.00 (evening). Statistical analysis was performed using Excel Microsoft, descriptive and ANOVA test.

Results and conclusions. The circadian variation pattern of stroke onset is confirming in our study the known incidence pattern of ischemic stroke, with the morning peak. There are differences in the evolution during dynamics of the MMSE score depending on the time of the day when stroke occurs. Patients with stroke onset during the night have seems to have a less favorable cognitive evolution in the second year after ischemic stroke compared to patients with stroke onset during the other intervals of the day.

Key words: *ischemic stroke occurrence, circadian variation, cognitive status,*

Introduction

The focus on the need to understand as much as possible of the factors involved in the development of various diseases including stroke, a devastating disorder worldwide due to the severe disability induced, includes the interest in the study of the chronobiological aspects involved (1, 2). It is already known that ischemic stroke onset has a circadian, circaseptan and circannual cyclicity pattern. The best studied and documented pattern, which does not depend on the geographical area, climate or lifestyle, is the circadian variation pattern. This is described as having a morning incidence peak, according to the majority of the literature reports, and a second, less impressive peak, during afternoon, described inconsistently (3-7).

Post-stroke cognitive impairment is frequent. Post-stroke cognitive deterioration represents one of the main causes of dependence in neurovascular patients. It has a multifactorial etiology (vascular lesions, lesions associated with Alzheimer's dementia, white matter changes) and can be assessed by various neuropsychological scores, of which the most widely used and available is MMSE (Mini Mental State Examination) which, along with the degree of disability, correlates with subcortical white matter lesions (8-10). The evolution of cognitive status is closely related to functional status alongside the severity of the clinical picture. There are extremely few data regarding the influence of the circadian variation pattern on the evolution of cognitive status, and the influence on disability is reflected in some studies which suggest that patients with ischemic stroke onset during the night have a less favorable clinical (NIHSS) and functional (mRs, ADL, IADL) evolution compared to other patients with ischemic stroke (11-14).

Materials and method

Our study was based on a cohort of 63 patients who had an ischemic stroke over the past 6 months, admitted to the Neurology Departments I and II of the Rehabilitation Hospital in Cluj-Napoca, in the period 1 June 2008 - 1 June 2009. The diagnosis of ischemic stroke was defined according to updated World Health Organization criteria and was confirmed by neuroimaging. We recorded demographic data for each patient and the time of onset was assigned to one of the four 6-hour intervals of the day: 00.01-06.00 (night), 06.01-12.00 (morning), 12.01-18.00 (afternoon), and 18.01-24.00 (evening).

The 63 patients were assessed for their cognitive status using the MMSE scale during 5 visits over 2 years: at the first visit (time "0"), at 1 month ("1"), 6 months ("6"), 12 months ("12") and 24 months ("24").
Statistical analysis was performed using Excel Microsoft, categorical data were presented as diagrams, and continuous variables were summarized using synthetic centrality, dispersion and location indices. For the analysis of differences between the mean scores at each visit for the 4 time intervals of the day, two-way ANOVA statistical analysis was used.

Results

The circadian cyclicity pattern of ischemic stroke symptom onset in the studied group revealed the highest incidence in the morning, in the 6-12 interval, and the lowest incidence during the night, in the 0-6 interval (Fig. 1).

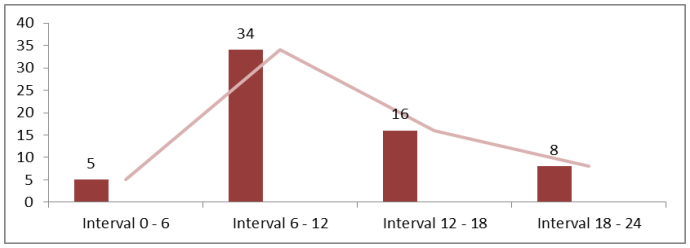

Fig. 1: Circadian cyclicity of ischemic stroke onset in our cohort across the 4 time intervals of the day

Figure 2 represents the descriptive evolution of the arithmetic mean of the MMSE score in patients with stroke onset across the 4 time intervals of the day over the 2 years of follow-up, on the occasion of the 5 evaluations.

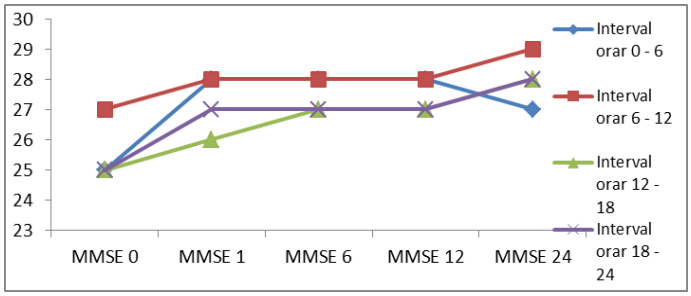

Fig. 2. Temporal evolution of the arithmetic mean of the **MMSE** scores during 2 years, across the four time intervals of the day (5 evaluations).

Following two-way ANOVA statistical processing of MMSE scores across the 4 time intervals of the day and the 5 time points for their evaluation (0,1,6,12,24): statistically significant differences (p<=0.05) were found at each evaluation visit (time point), between the morning and the afternoon time interval, at the first 3 visits (the first 6 months): at time 0 (first visit – MMSE 0), at 1 month (MMSE 1) and at 6 months (MMSE 6). In addition, at the 6-month visit (MMSE 6) there was a statistically significant difference between the morning and the evening intervals (Table 1).

Table 1. Statistically significant differences in the evolution of the MMSE score of patients with ischemic stroke depending on the onset intervals .

- **MMSE 0: 6.01-12.00 ---- 12.01-18.00 (p=0.021)**
- **MMSE 1: 6.01-12.00 ---- 12.01-18.00 (p=0.03)**
- **MMSE 6: 6.01-12.00 ---- 12.01-18.00 (p=0.05)**
- **--- 18.01-24.00 (p=0.04)**

MMSE 12, MMSE 24 - no statistically significant differences

Discussions

The known circadian cyclicity pattern of ischemic stroke onset was confirmed in the case of the cohort of our study, with the incidence peak in the 06.01-12.00 interval and the lowest incidence during the night. (3, 4, 8, 15).
An analysis of the evolution during dynamics of the MMSE score across the 5 evaluations over the 2 years of follow-up shows a favorable evolution for all time intervals in the first month, with a subsequent relative plateau period up to 1 year, followed by a new improvement up to 2 years, except for the night interval of onset (00.00-06.00), for which MMSE worsened again after the first year.
Statistically significant differences between the 4 time intervals of stroke onset by multivariate ANOVA analysis were detected for the MMSE values recorded on the occasion of the first 3 visits (initial time, at 1 month and at 6 months), more precisely between the 6-12 interval and the 12-18 interval, the 18-20 interval, respectively. No statistically significant differences were found regarding the evolution of MMSE values in patients with stroke onset during the night interval compared to patients with stroke onset in the other intervals of the day, despite the differences observed by descriptive analysis, most probably due to the small number of patients.
We found literature data related to the evolution of cognitive status depending on the circadian interval in which stroke occurred. The evolution of the MMSE score correlates with the results of other personal studies, in which the degree of disability

was evaluated using the scores ADL (activities of daily living), IADL (instrumental activities of daily living), mRs (modifed Rankin score) associated with clinical severity assessed by NIHSS, with the least favorable evolution of these for ischemic stroke onset in the 00.00-06.00 night interval and the greatest improvement for all onset intervals during the first year after stroke (13, 14).

The more severe evolution of stroke with onset in the night interval from a clinical, functional and cognitive point of view is due to a number of factors: frequent late discovery on the occasion of wake-up which leads to waste of precious time, favoring endogenous factors such as variability of blood pressure values and autonomic system activity, nocturnal hypercoagulability along with possible sleep-disordered breathing as a risk factor for nocturnal stroke occurrence, and alteration of the post-stroke sleep-wake cycle, maintaining a vicious circle (15,16).

Conclusions

In our study group, the circadian variation pattern was similar to that found in the literature, with the highest incidence in the 6-12 morning interval and the lowest incidence in the 0-6 night interval, the latter seeming to be responsible for the least favorable evolution of cognitive status at 2 years. There are differences in the evolution during dynamics of the MMSE score depending on the time of the day when stroke occurs; more extensive studies in terms of number of patients and length of follow-up are required. Information about the influence of circadian variation in the occurrence of ischemic stroke on the evolution of cognition can help to estimate long-term prognosis and implicitly, the necessary medical and social resources.

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