The influence of circadian variation in ischemic stroke onset on the evolution of the severity of the clinical picture and disability

Dana Marieta Fodor¹, Marius Marian Fodor², Ioana Cristina Stănescu¹, Gabriela Dogaru³, Lăcrămioara Perju-Dumbravă¹

Abstract
Introduction. The chronobiology of ischemic stroke describes an occurrence pattern with the highest incidence in the morning according to most literature reports, but its influence on the evolution of the severity of the neurological picture and functional status is little studied. Materials and method. This cohort study included 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 followed up for 2 years by 5 successive evaluations. The onset time of ischemic stroke was assigned to one of the six hours intervals: 00.01-06.00 (night), 06.01-12.00 (morning), 12.01-18.00 (afternoon) and 18.01-24.00 (evening). For each patient, the National Institute of Health Stroke Scale (NIHSS) and Modified Rankin Scale (mRS) scores were recorded on the occasion of each evaluation. Statistical analysis was performed using Excel Microsoft, descriptive and ANOVA test. Results and conclusions. Our study confirms the incidence pattern of ischemic stroke with a morning peak, which is more obvious in the case of patients aged less than 65 years. Patients with stroke onset in the nocturnal interval have a less favorable neurological and functional evolution during the second year after ischemic stroke.

Key words: ischemic stroke occurrence, circadian variation, NIHSS, mRS,
Statistical analysis was performed using Excel Microsoft software. Categorical data were presented as diagrams, absolute and relative frequencies, and continuous variables were summarized using synthetic centrality, dispersion and location indicators or frequency histograms and linear diagrams. For the analysis of the differences between the mean scores at each visit across the 4 time intervals of the day, two-way ANOVA statistical analysis was used.

Results
In our study, ischemic stroke onset had the highest frequency in the 06.01-12.00 interval, followed by the 12.01-18.00 interval (Figs. 1 and 2), and the lowest frequency in the 00.01-06.00 interval. Patients were divided into two age groups (<65 years, ≥65 years) – Fig. 3, with the predominance of patients aged less than 65 years in the morning interval. Figures 4 and 5 show the descriptive evolution of the arithmetic mean of NIHSS and mRS scores across the 4 time intervals of the day during the 2 years (5 evaluations).

Following one-way ANOVA statistical analysis, statistically significant differences were found regarding patients’ age (descriptively represented in Fig. 2) and the time interval of stroke onset (F (3.59)=3.18 (Welch), p=0.011), but the relationship between age and the stroke occurrence interval was of low intensity ($\omega^2=0.12$). Post-hoc data analysis evidenced a significant difference between the 06.01-12.00 and 00.01-06.00 intervals.

Two-way ANOVA statistical processing of NIHSS and mRS scores across the 4 time intervals of the day for the 5 evaluations (0, 1, 6, 12, 24 months) showed the following: no statistically significant differences were observed for NIHSS (but for NIHSS 6, p=0.073), while for mRS score, statistically significant differences were found for mRS1 (F (3.55)=5.6 (Welch), p=0.028). Post-hoc analysis indicated statistically significant differences between the 00.01-06.00 and 12.01-18.00 intervals, as well as between the 00.01-06.00 and 18.01-24.00 intervals.
Discussions
In the case of the studied group, the circadian variation pattern of ischemic stroke is confirmed, having the highest incidence in the 06.01-12.00 interval and the lowest incidence during the night (00.01-06.00) (Fig. 1), according to literature data derived from both retrospective (5-8,14) and prospective studies (15-17). This pattern is more obvious for patients aged less than 65 years.

By analyzing the diagrams for the evolution of NIHSS and mRS scores across the 5 evaluations during the 2 years of follow-up, it can be seen that NIHSS (reflecting the severity of the neurological picture) had a favorable evolution for all time intervals, excepting the nocturnal one (00.01-06.00), which was associated with its worsening after 6 months of resolution. This aspect was correlated with the evolution of the mean mRS score (reflecting the degree of disability or functional status), which also only for the nocturnal interval, after a rapid improvement by 2 points during the first month after stroke, remained unchanged for the rest of the first year, then started to worsen slowly by 1 point during the following 12 months. The highest mean NIHSS score at onset (NIHSS 0) was found for the 12.01-18.00 interval (7), but its evolution was favorable (decreasing by 3 points during the first year), similarly to that of the 06.01-12.00 and 18.01-24.00 intervals (5→2). The greatest disability (mRS) at onset was found for the 18.01-24.00 interval, along with the 00.01-06.00 interval mentioned before, but its evolution was favorable and similar to that of ischemic strokes with onset in the 06.01-12.00 and 12.01-18.00 intervals.

It can be concluded that these scores, reflecting clinical severity on the one hand and the degree of disability on the other hand, had an almost parallel evolution (Figs. 3 and 4).

Statistically significant differences between the 4 time intervals of stroke onset were found by multivariate ANOVA analysis only for mRS values at 1 month (mRS1), while for NIHSS the differences in values at 6 months (NIHSS 6) between the 4 time intervals of the day came close to statistical significance, most probably due to the small number of patients in the study group.

There are very few literature data on the evolution of NIHSS and mRS scores depending on the circadian interval in which stroke has occurred, the available data being derived only from the initial admission of patients with ischemic stroke (values at admission versus discharge), not from evolution during a longer follow-up period. However, the results are concordant, describing the best evolution of the functional score (mRS) from admission to discharge for patients with ischemic stroke onset in the 04.01-08.00 interval and the lowest score in the 20.01-24.00 interval, without statistically significant differences for NIHSS (8,11). The evolution of the mRS score is also consistent with the results of another study performed by us, in which the degree of disability was assessed based on ADL (activities of daily living) and IADL (instrumental activities of daily living) scores, with their least favorable evolution for ischemic stroke occurring in the nocturnal interval 00.01-06.00 and the greatest improvement for all time intervals during the first year after stroke (18).

Conclusions
This study confirms the circadian variation pattern for stroke of ischemic etiology, with the highest incidence in the morning and the lowest incidence during the night, our results being statistically significant for patients aged less than 65 years. The evolution of NIHSS (reflecting the severity of the neurological picture in stroke) and mRS (reflecting the degree of disability) scores during the 2 years of follow-up, depending on the circadian interval of stroke onset, is similar for our study group, with the greatest improvement during the first year after stroke and relatively no changes during the second year, except for onset in the nocturnal interval (00.01-06.00), associated with a slight worsening after 12 months. The difference in the evolution of the functional status of patients with nocturnal stroke onset compared to patients with onset in the other time intervals of the day is statistically significant for the evaluation visit at 1 month.

Knowing the influence of the circadian variation in ischemic stroke onset on the evolution of the neurological and functional picture can be important in assessing long-term prognosis, which involves different degrees of use of medical and social resources.

Informed consent
An informed consent was obtained from the patients included in this study.

Declaration of conflict of interests
The authors declare that there is no conflict of interest regarding the publication of this paper.
References