Delirium in Acute Ischemic Stroke: Risk Factors, Sequelae, and Pathogenetic Treatment

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Abstract

Introduction. *Delirium, or an acute confusional state, is a common complication affecting between 10 and 48% of acute stroke patients. In the acute phase of stroke, delirium contributes to prolonged hospital stays, higher treatment costs and in-hospital and long-term mortality, increased risk of disability, and reduced potential for post-stroke rehabilitation.*

*The **aim** of this study is to identify delirium risk factors in acute stroke patients, to study the effects of delirium on mortality rates, post-stroke cognitive functioning, and to assess treatment options.*

Materials and methods. *One hundred and thirty-eight patients (93 males and 45 females) with a mean age of 71 [69.0; 74.8] years were enrolled in the study. Delirium was assessed using the Confusion Assessment Method (CAM); for initial assessment and repeated measurements of delirium severity, the Delirium Rating Scale (DRS) was used. Pre-stroke cognitive decline was assessed retrospectively using the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE). Neuropsychological testing and assessment of caregiver burden using the Caregiver Burden Scale (CBS) were performed at 3, 6, and 18 months post-stroke onset.*

Results. *An IQCODE score of > 91 is a risk factor for severe delirium in acute stroke patients ($p < 0.001$). Severe delirium in acute stroke was associated with greater cognitive deficits ($p < 0.05$) and greater caregiver burden ($p < 0.01$) at 3 and 6 months post-stroke. DRS score > 15 and delirium duration > 10 days were found to be death risk factors at 18 months after stroke onset (OR = 3.58; 95% CI 1.4–9.19; $p = 0.008$ and OR = 2.56; 95% CI 1.03–6.38; $p < 0.044$, respectively). Central acetylcholinesterase inhibitors reduced the delirium duration ($p = 0.015$), improved cognitive function at 3, 6, and 18 months post-stroke ($p < 0.01$), and decreased caregiver burden at 3 and 6 months post-stroke ($p < 0.05$).*

Conclusion. *Delirium in the acute phase of stroke contributes to post-stroke cognitive decline in the patients and greater burden for their caregivers. Central acetylcholinesterase inhibitors can improve the post-stroke patient's condition and decrease the strain for caregivers.*

Keywords: *delirium, ischemic stroke; risk factors; cognitive decline; caregiver burden; central acetylcholinesterase inhibitors*

Ethics approval. The research protocol was approved by the Ethics Committee of the S.M. Kirov Military Medical Academy (protocol No. 94, July 07, 2009).

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Спутанность сознания в остром периоде ишемического инсульта: факторы риска, последствия, патогенетическая коррекция

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Аннотация

Введение. *Спутанность сознания (СпС)– частое осложнение острых нарушений мозгового кровообращения, возникающее в остром периоде инсульта в 10–48% случаев. Развитие СпС в остром периоде ишемического инсульта (ИИ) способствует увеличению продолжительности госпитализации и стоимости лечения, частоты внутригоспитальных и отсроченных летальных исходов, вероятности инвалидизации, снижению реабилитационного потенциала.*

Цель *исследования – установить факторы риска СпС в остром периоде ИИ, её влияние на вероятность летального исхода, постинсультную динамику когнитивных функций, а также возможности медикаментозной коррекции СпС.*

Материалы и методы. *В исследование были включены 138 пациентов – 93 мужчины и 45 женщин в возрасте 71 [69,0; 74,8] год. Спутанность сознания оценивали по шкале CAM, степень выраженности спутанности сознания и её динамику – по шкале DRS. Доинсультный уровень когнитивных нарушений ретроспективно оценивали по анкете состояния когнитивных функций у пожилого пациента IQCODE. Нейропсихологическое тестирование пациентов и оценку нагрузки на родственников пациента по шкале CBS выполняли через 3, 6 и 18 мес после дебюта ИИ.*

Результаты. *Доинсультные когнитивные нарушения более 91 балла по анкете IQCODE являются фактором риска выраженной СпС в остром периоде ИИ ($p < 0,001$). Развитие выраженной СпС сопровождалось большим когнитивным дефицитом у пациента ($p < 0,05$), а также большей нагрузкой на родственников пациента ($p < 0,01$) через 3 и 6 мес. Факторами риска летального исхода в течение 18 мес после дебюта инсульта явились выраженность СпС более 15 баллов по шкале DRS (ОШ = 3,58; 95% ДИ 1,4–9,19; $p = 0,008$) и продолжительность СпС более 10 дней (ОШ = 2,56; 95% ДИ 1,03–6,38; $p < 0,044$). Применение центрального ингибитора холинэстеразы способствовало уменьшению продолжительности СпС ($p = 0,015$), улучшению когнитивных функций через 3, 6 и 18 мес ($p < 0,01$), уменьшению нагрузки на родственников пациента через 3 и 6 мес после дебюта инсульта ($p < 0,05$).*

Заключение. *СпС в остром периоде ИИ способствует развитию постинсультных когнитивных нарушений и увеличивает нагрузку на родственников пациента. Когнитивные нарушения могут быть скорректированы применением центрального ингибитора холинэстеразы.*

Ключевые слова: *спутанность сознания; ишемический инсульт; факторы риска; когнитивные нарушения; нагрузка на родственников пациента; центральный ингибитор холинэстеразы*

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Introduction

In the International Classification of Diseases (ICD-10), stroke-associated delirium is classified as “Delirium not induced by alcohol and other psychoactive substances” (F05), and in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), as “Delirium Not Otherwise Specified” (780.09) and is defined as an etiologically nonspecific organic cerebral syndrome characterized by concurrent disturbances of consciousness and attention, perception, thinking, memory, psychomotor behavior, emotion, and the sleep-wake cycle [1, 2]. Delirium is a common complication of acute stroke

with an incidence estimated to be between 10 and 48% in the acute phase [3–6]. This wide range of delirium incidence might be explained by considerably different diagnostic approaches and algorithms.

Delirium in the acute phase of stroke is associated with longer hospital stays and increased costs-of-illness, higher in-hospital and long-term mortality, increased risk for disability, and reduced potential for post-stroke rehabilitation [5, 7–10]. There are data indicating that acute stroke patients with delirium are at higher risk of post-stroke cognitive decline [11, 12]. Stroke sequelae have a negative impact on the health of caregivers, reducing their labor potential and compromising social and economic participation in the life of their communities [13].

Delirium is associated with predisposing – anamnestic and social – factors, and precipitating factors, or triggers, which occur during a hospital stay. In neurological patients, the most relevant predisposing factors are advanced age, neurodegenerative diseases, and substance use disorders. The most relevant precipitating factors are meningitis, acute renal failure, or intracranial hemorrhage [14]. Stroke, as an independent risk factor for delirium, exacerbates the effects of the other factors [15–17]. The modern approach to delirium prevention and management suggests a focus on reducing precipitating risk factors, creating comfortable hospital conditions, and pharmacological treatment. To date, central cholinergic deficiency is the leading hypothesized mechanism for delirium [18]. The acetylcholinesterase inhibitor rivastigmine has been shown to be effective [19, 20] and safe [21, 22] in the treatment of stroke patients with delirium.

The **aim** of this study is to identify delirium risk factors in acute stroke patients, to study the possible effects of delirium on mortality rates and post-stroke cognitive functioning changes, and to review treatment options for this condition.

Materials and methods

This prospective study included 138 acute stroke patients (93 males and 45 females) with a mean age of 71 [69.0; 74.8] years and was conducted in three multispecialty hospitals from 2009 to 2024.

Inclusion criteria:
- age > 18 years;
- hyper-acute stroke;
- normal level of consciousness at screening.

Non-inclusion criteria:
- speech impairment, decreased consciousness level, decreased muscle strength, and apraxia, preventing neuropsychological testing;
- history data indicating that the delirium might be a result of alcohol abuse or medication withdrawal;
- reperfusion therapy for acute ischemic stroke;
- previous neurometabolic therapy (including cholinergic agents)
- concomitant disease with life expectancy of less than 1 year;
- previously diagnosed mental illness;
- previously diagnosed brain tumor,
- demyelinating disease of the central nervous system, or epilepsy;
- history of head injury or neurosurgery in the past three years;
- pregnancy;
- clinically significant anxiety or depression;
- for the combined therapy subgroup: contraindications to rivastigmine.

Forty-four non-delirious stroke patients (30 males and 14 females with a mean age of 70 [68.8; 73.2] years) comprised the control group.

Delirium was diagnosed using the Confusion Assessment Method (CAM) [23], an accurate diagnostic algorithm for detecting delirium based on four features:
1) acute onset and fluctuating course;
2) inattention;
3) disorganized thinking;
4) altered level of consciousness.

A diagnosis of delirium requires the presence of features 1, 2, and either 3 or 4. The Delirium Rating Scale (DRS) was used for initial assessment and repeated measurements of delirium severity [24]. Severe delirium (DRS score > 11) in the acute phase of stroke persisting for at least 24 hours was used as a cut-off criterion. In all of the patients, the diagnosis of delirium was verified by a psychiatrist. Ninety-four patients (63 males and 31 females with a mean age of 72 [69; 76] years) with severe delirium were included in the confusion group.

All of the patients received a standard therapy for stroke. The confusion group was divided into two subgroups depending on the therapy administered:
- the standard therapy subgroup (n = 55): delirious stroke patients receiving standard therapy;
- the combined therapy subgroup (n = 39): delirious stroke patients receiving standard therapy + rivastigmine (central acetylcholinesterase inhibitor).

Rivastigmine solution was administered at a target dose of 9–12 mg/day (the route of administration was subsequently switched to transdermal therapeutic system) for 14–25 days (until the hospital discharge).

If the patient became too agitated, haloperidol was administered at a dose of 0.75–5.00 mg/day orally, intravenously, or intramuscularly. The haloperidol dose was reviewed daily by an attending psychiatrist, taking into account the patient's age and severity of delirium.

Pre-stroke cognitive decline was retrospectively assessed using the IQCODE score [25] with the following cut-offs:
- ⩽ 78 – no data indicating pre-stroke cognitive decline;
- 79–103 – moderate pre-stroke cognitive decline;
- ⩾ 104 – pre-stroke cognitive decline up to dementia.

Neuropsychological tests, including the mini–mental state examination (MMSE), the clock drawing test, and the frontal assessment battery (FAB) to screen for frontotemporal

dementia, the 5-word memory test, were performed during the hospital stay and at 3, 6, and 18 months post-stroke onset. The caregiver burden was assessed using CBS (Caregiver Burden Scale) [26] at 3, 6, and 18 months post-stroke onset.

The CBS comprises five factors: general strain, social isolation, frustration, disappointment, emotional involvement, and environment. Depending on the sum score, the results are evaluated as follows:
- 0–21: no to mild burden;
- 21–40: mild to moderate burden;
- 41–60: moderate to severe burden;
- 61–88: severe burden.

The data were analyzed using R.v.4.3.0 and Statistica for Windows v. 10.0 software. The cut-off values were determined using the decision tree analysis. The effects of the calculated cut-offs were determined using an odds ratio. The quantitative variables were compared using the Wilcoxon T-test, and the binary variables were compared using the Fisher's exact test. For contingency tables larger than 2 × 2, a Monte Carlo approximation to Fisher's exact test was used. The false discovery rate (FDR) in multiple comparisons was adjusted with the Benjamini and Yekutieli procedure. Descriptive group statistics are represented as a mean (standard deviation) and a median [Q_{25}; Q_{75}] for the quantitative variables and 95% Clopper-Pearson confidence intervals for binary variables. Inter-group correlations were analyzed using a Spearman's ρ coefficient. The effects of some baseline parameters on the delirium progression, duration, and mortality rates were assessed using logistic regression analysis. Statistical significance of the inter-group differences was determined by the presence of either a 0 (for a difference) or a 1 (for a ratio) in the CI, or by comparing the calculated *p*-value with a cut-off $p = 0.05$.

Results

There were no statistically significant differences in the frequency of stroke subtypes according to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification between patients in the control, standard therapy, and combined therapy groups.

Logistic regression analysis revealed no correlation between the patient's sex and a stroke subtype, and the likelihood to develop delirium. No significant correlation was found between the incidence of delirium and the location and volume of brain infarction.

The IQCODE scores for retrospective assessment of pre-stroke cognitive decline in the confusion group were higher than those in the control group: 93 [89; 99.8] vs 86 [83; 91.2], respectively ($p < 0.001$). The IQCODE cut-off value of 91 for the likelihood of severe delirium in the acute phase of stroke was determined using the decision tree analysis. The odds ratio for the scores > 91 was 5.06 (95% CI 2.72–11.26; $p < 0.001$). We also detected a significant correlation between IQCODE scores and duration of severe delirium in the acute phase of stroke (Spearman's $\rho = 0.24$; $p = 0.018$).

In the combined therapy and standard therapy subgroups, IQCODE scores (93 [86.0; 95.0] and 93 [90.0; 100.0], respectively) and DRS scores 14 [13; 14] and 13 [12; 14], respectively) were similar ($p > 0.05$). At the same time, the duration of delirium in the combined therapy subgroup was less than that in the standard therapy subgroup: 7 [4; 9] and 8 [5; 12] days, respectively ($p = 0.015$).

Neuropsychological assessment at 3 and 6 months revealed greater cognitive decline in post-stroke patients with severe delirium in the acute phase of stroke ($p < 0.05$). Compared with the standard therapy subgroup, neuropsychological tests in the combined therapy subgroup yielded greater MMSE and FAB scores at 3 and 6 months and greater FAB scores at 18 months ($p < 0.01$) (Figures 1 and 2).

Analysis of the CBS scores showed greater caregiver burden at 3 and 6 months post-stroke onset in the confusion group compared with the control group ($p < 0.01$), and less caregiver burden in the combined therapy subgroup compared with the standard therapy subgroup ($p < 0.05$; Figure 3).

Mortality rates during the follow-up period were 30.8% (12 [39]) in the combined therapy subgroup, 45.5% (25 [55]) in the standard therapy subgroup, and 27.3% (12 [44]) in the control group ($p > 0.05$). The cut-offs for increased likelihood of death at 18 months post-stroke onset determined by the decision tree analysis are DRS > 15 and duration of delirium > 10 days. The odds ratio for death likelihood at 18 months post-stroke with a DRS > 15 was 3.58 (95% CI 1.40–9.19; $p = 0.008$), with a duration of delirium > 10 days was 2.56 (95% CI 1.03–6.38; $p < 0.044$).

Frequency of stroke subtypes based on the TOAST classification, *n* (%)

IS subtype	All patients (*n* = 138)	Standard therapy group (*n* = 55)	Combined therapy group (*n* = 39)	Control group (*n* = 44)
Atherothrombotic	38 (27.5%)	17 (30.9%)	9 (23.1%)	12 (27.3%)
Cardioembolic	49 (35.5%)	22 (40.0%)	15 (38.5%)	12 (27.3%)
Lacunar	5 (3.6%)	1 (1.8%)	1 (2.6%)	3 (6.8%)
Other specified etiology	7 (5.1%)	1 (1.8%)	2 (5.1%)	4 (9.1%)
Unspecified etiology	39 (28.3%)	14 (25.5%)	12 (30.8%)	13 (29.5%)

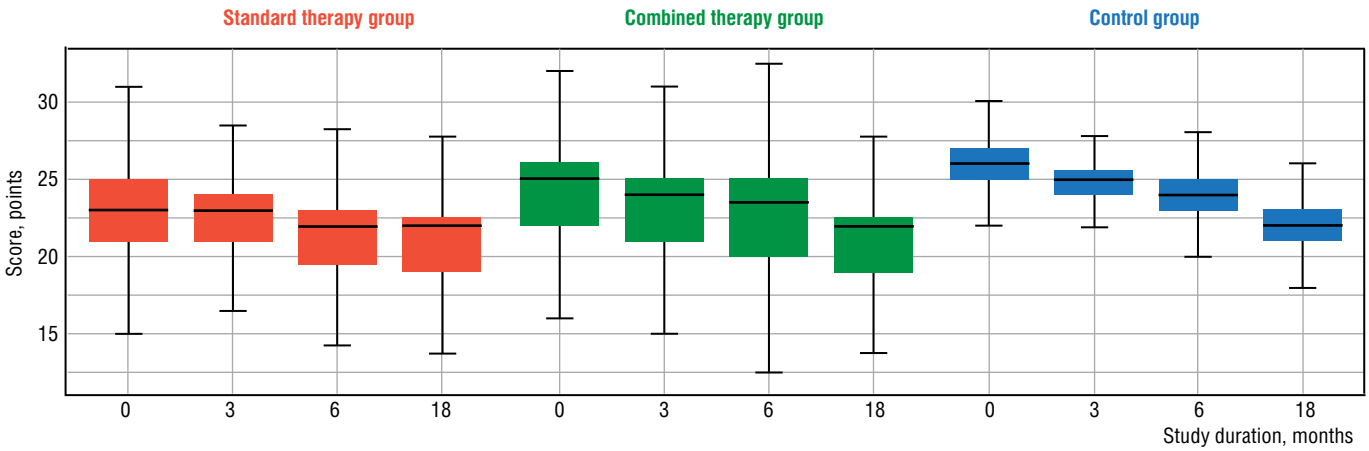

Fig. 1. MMSE scores.

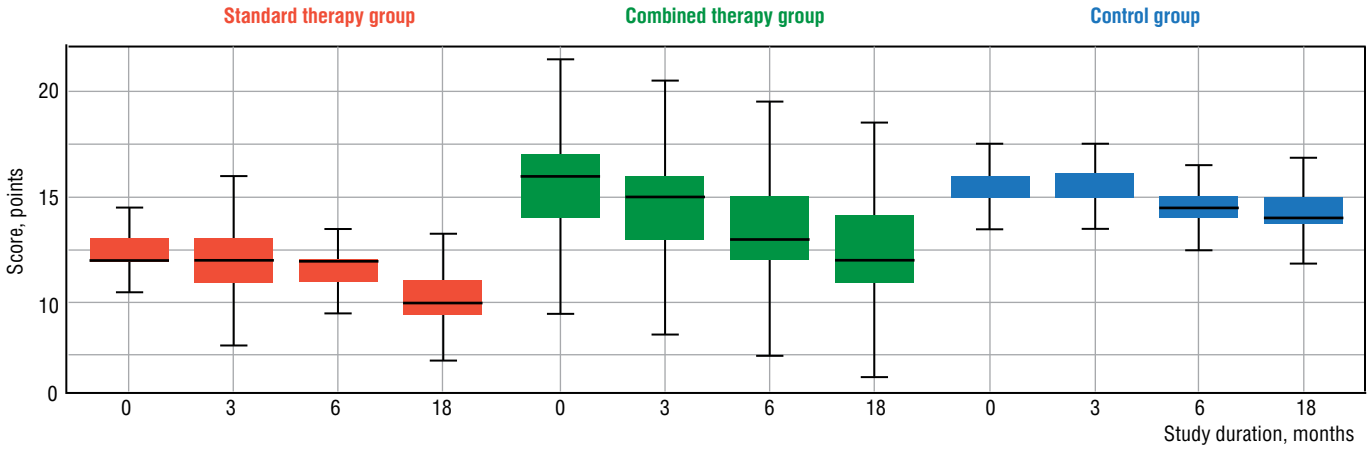

Fig. 2. FAB scores.

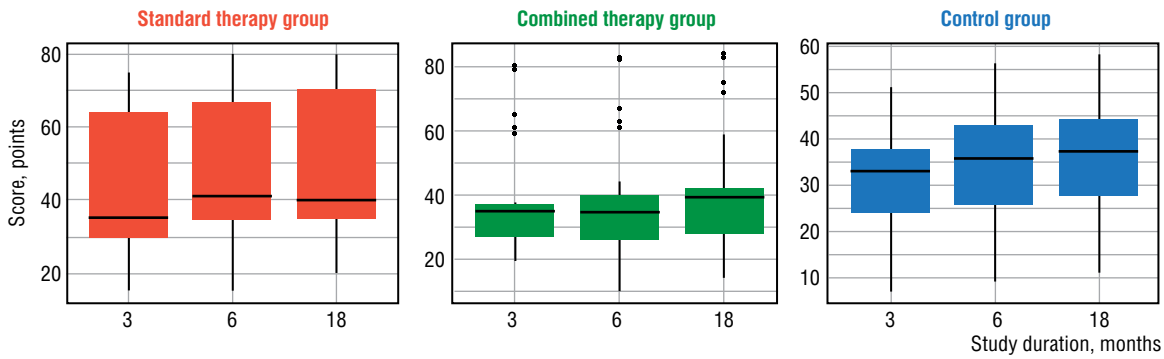

Fig. 3. CBS scores.

Discussion

This study allowed us to evaluate the significance of pre-stroke cognitive decline as a predisposing factor for severe delirium, which also leads to a longer duration of delirium in acute stroke patients. Neither patient's sex nor stroke subtype correlated with the likelihood of delirium onset.

Severe delirium was associated with greater cognitive decline in patients ($p < 0.05$) and greater caregiver burden at 3 and 6 months ($p < 0.01$). DRS > 15 and duration of delirium > 10 days were risk factors for the likelihood of death within 18 months post-stroke.

Treatment with central acetylcholinesterase inhibitor rivastigmine resulted in decreased duration of delirium ($p = 0.015$),

preserved cognitive function at 3, 6, and 18 months post-stroke ($p < 0.01$), and milder caregiver burden at 3 and 6 months post-stroke ($p < 0.05$). The available evidence on the clinical use of rivastigmine in patients with dementia of various etiologies, including those with cognitive decline in the early post-stroke period, suggests that rivastigmine therapy is appropriate for post-stroke patients, especially those with delirium in acute stroke.

Conclusion

Delirium in the acute phase of stroke contributes to post-stroke cognitive decline and increases the caregiver burden. This condition can be managed with central acetylcholinesterase inhibitors. The study results demonstrate the importance of timely diagnosis and appropriate treatment of both the acute stroke delirium and post-stroke cognitive decline.

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