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Predictive value of melatonin and serotonin levels in early recovery period of cerebral ischemic hemispheric stroke

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The aim was developing of criteria for prediction of the early recovery period outcome of cerebral ischemic hemispheric stroke (CIHS) on the base of the identification of serum concentration of melatonin and plasma level of serotonin.

Materials and methods: complex clinical and paraclinical investigation was carried out in 77 patients (the average age of patients was 57.9 ± 0.9 years) on early recovery period of CHIS using of clinical scales (National Institute of Health Stroke Scale, Barthel Index, modified Rankin Scale) on the 10th, 30th, 90th and 180th day of disease, and visualization of cerebral structures by CT scan, and identification of the serum concentration of melatonin and serotonin plasma level on the 10th, 30th day of disease, and also by the calculation of the melatonin/serotonin ratio (MSR) as serum concentration of melatonin divided by serotonin plasma level.

Results. Using the comparative ROC-analysis it was defined that the most informative parameters for prediction of moderate and severe disability as for value according to mRS ≥ 3 points on the 180th day are the level of MSR on the 30th day (AUC = 0.78, p < 0.05), serotonin plasma level on the 30th day (AUC = 0.74, p < 0.05), dynamics of serum concentration of melatonin on the 30th day (AUC = 0.67, p < 0.05), dynamics of serotonin plasma level on the 30th day (AUC = 0.67, p < 0.05), dynamics of MSR on the 30th day (AUC = 0.66, p < 0.05) and serum concentration of melatonin on the 30th day (AUC = 0.66, p < 0.05).

Conclusions. The level of MSR >212,0 on the 30th day was the predictor of moderate and profound disability for modified Rankin's scale ≥3 points on the 90th (AUC = 0.81, p < 0.05; sensitivity = 100.0 %, specificity = 75.0 %) and on the 180th day of disease was (AUC = 0.78, p < 0.05; sensitivity = 100.0 %, specificity = 73.3 %); the serotonin plasma level ≤0.15 mcmol/l on the 30th day of CIHS was the predictor of moderate and profound disability for modified Rankin's scale ≥3 points on the 180th day of disease (AUC = 0.74, p < 0.05; sensitivity = 60.0 %, specificity = 86.7 %).

Key words: cerebral infarction, serotonin, melatonin, prognosis.

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Прогностичне значення рівнів мелатоніну та серотоніну в ранньому відновному періоді мозкового ішемічного півкульового інсульту

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Мета роботи – розробка критеріїв прогнозування виходу раннього відновного періоду мозкового ішемічного півкульового інсульту (МІПІ) на підставі визначення сироваткової концентрації мелатоніну та рівня серотоніну у плазмі крові.

Матеріали та методи. Здійснили комплексне клініко-параклінічне дослідження 77 хворих (середній вік 57,9 ± 0,9 року) в ранньому відновному періоді МІПІ з використанням клінічних шкал (National Institute of Health Stroke Scale, Barthel Index, modified Rankin Scale) на 10, 30, 90 та 180 добу захворювання, візуалізації церебральних структур методом комп'ютерної томографії, визначення сироваткової концентрації мелатоніну, рівня серотоніну у плазмі крові на 10, 30 добу захворювання, а також розрахунком співвідношення мелатоніну та серотоніну (СМС) = сироваткова концентрація мелатоніну/рівень серотоніну у плазмі крові.

Результати. На підставі порівняльного ROC-аналізу встановили, що найінформативнішими параметрами для прогнозування помірної та вираженої інвалідизації у вигляді значення по mRS ≥ 3 бали на 180 добу є рівень СМС на 30 добу (AUC = 0,78, p < 0,05), вміст серотоніну в плазмі крові на 30 добу (AUC = 0,74, p < 0,05), динаміка сироваткової концентрації мелатоніну на 30 добу (AUC = 0,67, p < 0,05), динаміка рівня серотоніну в плазмі крові на 30 добу (AUC = 0,67, p < 0,05), динаміка СМС на 30 добу (AUC = 0,66, p < 0,05) і сироваткова концентрація мелатоніну на 30 добу (AUC = 0,66, p < 0,05).

Висновки. Рівень СМС >212,0 на 30 добу МІПІ є предиктором помірної та глибокої інвалідизації у формі значення за модифікованою шкалою Ренкіна ≥3 бали на 90 (AUC = 0,81, p < 0,05; чутливість = 100,0 %, специфічність = 75,0 %) та 180 добу захворювання (AUC = 0,78, p < 0,05; чутливість = 100,0 %, специфічність = 73,3 %); вміст серотоніну у плазмі крові ≤0,15 мкмоль/л на 30 добу МІПІ виступає предиктором помірної та глибокої інвалідизації у вигляді значення за модифікованою шкалою Ренкіна ≥3 бали на 180 добу захворювання (AUC = 0,74, p < 0,05; чутливість = 60,0 %, специфічність = 86,7 %).

Ключові слова: інфаркт мозку, серотонін, мелатонін, прогноз.

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Прогностическое значение уровней мелатонина и серотонина в раннем восстановительном периоде мозгового ишемического полушарного инсульта

С. А. Медведкова

Цель работы – разработка критериев прогнозирования исхода раннего восстановительного периода мозгового ишемического полушарного инсульта (МИПИ) на основании определения сывороточной концентрации мелатонина и уровня серотонина в плазме крови.

Материалы и методы. Проведено комплексное клинико-параклиническое исследование 77 больных (средний возраст 57,9 ± 0,9 года) в раннем восстановительном периоде МИПИ с использованием клинических шкал (National Institute

Ключевые слова: инфаркт мозга, серотонин, мелатонин, прогноз.

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of Health Stroke Scale, Barthel Index, modified Rankin Scale) на 10, 30, 90 и 180 сутки заболевания, визуализации церебральных структур методом компьютерной томографии, определения сывороточной концентрации мелатонина и уровня серотонина в плазме крови на 10, 30 сутки заболевания, а также расчётом соотношения мелатонина и серотонина (СМС) = сывороточная концентрация мелатонина/уровень серотонина в плазме крови.

Результаты. На основании сравнительного ROC-анализа установлено, что наиболее информативными параметрами для прогнозирования умеренной и выраженной инвалидизации в форме значения по mRS ≥ 3 балла на 180 сутки являются уровень СМС на 30 сутки (AUC = 0,78, p < 0,05), содержание серотонина в плазме крови на 30 сутки (AUC = 0,74, p < 0,05), динамика сывороточной концентрации мелатонина на 30 сутки (AUC = 0,67, p < 0,05), динамика уровня серотонина в плазме крови на 30 сутки (AUC = 0,67, p < 0,05), динамика КИБМ на 30 сутки (AUC = 0,66, p < 0,05) и сывороточная концентрация мелатонина на 30 сутки (AUC = 0,66, p < 0,05).

Выводы. Уровень СМС >212,0 на 30 сутки МИПИ является предиктором умеренной и глубокой инвалидизации в форме значения по модифицированной шкале Рэнкина ≥3 балла на 90 (AUC = 0,81, p < 0,05; чувствительность = 100,0 %, специфичность = 75,0 %) и 180 сутки заболевания (AUC = 0,78, p < 0,05; чувствительность = 100,0 %, специфичность = 73,3 %); содержание серотонина в плазме крови ≤0,15 мкмоль/л на 30 сутки МИПИ выступает предиктором умеренной и глубокой инвалидизации в форме значения по модифицированной шкале Рэнкина ≥3 балла на 180 сутки заболевания (AUC = 0,74, p < 0,05; чувствительность = 60,0 %, специфичность = 86,7 %).

Introduction

Diagnostics and treatment of the patients with cerebral stroke is one of the main problems in modern neurology. Medical and social significance of this problem is caused by the high morbidity, disability and mortality for above mentioned pathology [7]. Cerebral stroke is the main reason of disability among surviving patients. Post-stroke disability takes the first place among the reasons of disability concerning adults in the majority countries of the world. 80 % of people after brain stroke become disabled, 25 % of people need the nursing care [3]. Differentiated determination of optimal structure and number of medical therapies based on the individual prognosis is one of the ways for improvement of functional outcome among the patients with cerebral ischemic stroke [2].

In recent clinical and experimental investigations the role of serotonin [1] and melatonin [4–6,8] has been persuasively proved in pathogenesis of acute focal cerebral ischemia. This fact is the basis for suggestion about the possibility to use the humoral markers with aim to predict the outcome of cerebral ischemic stroke.

Its aim was developing criteria for prediction of the outcome during the early recovery period of CIHS on the base of the identification of serum concentration of melatonin and the level of serotonin in the plasma.

Material and methods of investigation

In order to achieve the aim, complex clinical and paraclinical investigation was carried out in 77 patients (55 men and 22 women, the average age was 57.9 ± 0.9 years) on early recovery period of CIHS. The inclusion criteria were: men and women at the age from 33 to 74 years old with the confirmed cerebral hemispheric ischemic stroke according to the data of clinical and computer tomography study; hospitalization during the first 24 hours from the beginning of disease. The patients with the following criterion were excluded from the investigation: acute disorders of cerebral circulation in anamnesis; haemorrhagic transformation of cerebral infarction; combined stroke; ≥2 lesions; somatic pathology on the stage of decompensation; cancer pathology.

The evaluation of the level for neurological deficit was carried out in all the patients according to the National Institute of Health Stroke Scale (NIHSS), the level of functional independence according to Barthel Index (BI) and disability according to modified Rankin Scale (mRS) on the 10th, 30th, 90th and 180th day of disease. Visualization of cerebral structures was done using the CT scanner Siemens Somatom Spirit (Germany).

Blood samples were collected into 2 vacutainer tubes (one – with clot activator, the next – with EDTA) by venipuncture from median cubital vein on the anterior forearm in the morning (7–7.30 AM) on the 10th and 30th day from CHIS onset. Melatonin serum level was measured using an immunoassay (IBL, Germany, Cat. No. RE54021) at Scientific Medical Laboratory Center (head – prof. A. Abramov) of ZSMU. Serotonin plasma level was measured using a fluorescent spectrophotometry (λex = 300 nm, λem = 540 nm) at Laboratory Diagnosis and General Pathology Department (head – prof. A.Trailin) of the Zaporizhzhia Medical Academy of Postgraduate Education. Melatonin/Serotonin ratio (MSR), dynamic coefficients of melatonin (ΔME), serotonin (ΔSE) and MSR (ΔMSR) changes from the 10th day to the 30th day as compared to the 10th day were calculated.

Statistical data processing was done using the Statistica 6.0 (StatSoft Inc., USA, serial number AXXR712D-833214FAN5) application. Descriptive statistics are presented as median and interquartile range – Me [Q1; Q3]. The criteria of Mann–Whitney and Kruskal–Wallis were used for the estimation of intergroup differences, binary logistic regression and ROC-analysis were used for development of the predicting criteria.

Results and their discussion

On the 10th and 30th day of disease essential differences of serum concentration of melatonin, plasma concentration of serotonin and their correlation among the patients with CIHS depending on the age and sex were not revealed.

Distribution of patients with CIHS depending on the mRS index on the 90th and 180th day of disease is revealed in the *Table 1*.

As the primary endpoints, the cases of moderate and profound disability on the 90th and 180th day of the disease according to the indexes of mRS ≥ 3 points were registered respectively in 14 (18.2 %) and 12 (15.6 %) patients.

Using the comparative ROC-analysis we defined that the most informative parameters for prediction of moderate and severe disability for mRS ≥ 3 points on the 90th day of CIHS are the following (in decreasing order of predictive value): the level of MSR on the 30th day (AUC = 0.81, p < 0.05), the serotonin plasma level on the 30th day (AUC = 0.69, p < 0.05), dynamics of MSR level on the 30th day (AUC = 0.67 p < 0.05), the serotonin plasma level on the 30th day (AUC = 0.65, p < 0.05) and dynamics of serum concentration of melatonin on the 30th day (AUC = 0.64, p < 0.05) (*Table 2*).

In accordance with the date from the *table 2*, the most informative parameters for prediction of moderate and severe disability for mRS ≥ 3 points on the 180th day are also MSR level on the 30th day(AUC = 0.78, p < 0.05), the serotonin plasma level on the 30th day (AUC = 0.74, p < 0.05), dynamics of serum concentration of melatonin on the 30th day (AUC = 0.67, p < 0.05), dynamics of the serotonin plasma level on the 30th day (AUC = 0.67, p < 0.05), dynamics of MSR on the 30th day (AUC = 0.66, p < 0.05) and the serum concentration of melatonin on the 30th day (AUC = 0.66, p < 0.05).

On the basis of ROC-analysis the definitions of above mentioned indexes for prediction of moderate and severe disability for mRS ≥ 3 points on the 90th day (*Table 3*) and on the 180th day of CIHS (*Table 4*) with the optimal correlation of sensitivity and specificity were determined.

It was defined that prognostic criterion of moderate and severe disability for mRS ≥ 3 points on the 180th day of CIHS were: MSR level on the 30th day >212.0, MSR dynamics on the 10th–30th day >1.019, the serum concentration of melatonin on the 30th day ≤29.1 pg/ml and dynamics of serum concentration of melatonin on the 10th–30th day ≤0.382, whereas the level of serotonin in blood plasma on the 30th day is >0.15 mcmol/l and its dynamics on the 10th–30th day ≥-0.318 were associated with the mRS ≤2 points on the 180th day of disease.

So, decreasing of serum concentration of melatonin on the 30th day or its increasing no more than 38.2 % from the level on the 10th day of disease are prognostically unfavorable for the functional outcome during early recovery period of CIHS. It allows considering mentioned options of melatonin dynamics as the markers of insufficiency in the system of endogenous antioxidant protection. At the same time it is the base for more intensive neurometabolic and antioxidant therapy among the patient of such a group.

Moreover, decreasing of serotonin level in blood plasma on the 30th day more than 31.8 from its level on the 10th day of the disease is also prognostically unfavorable factor. The availability of correlation interaction between plasma serotonin concentration and its level in brain was proved earlier by T. Audhya with co-authors [9]. Received data is also coordinated with the results of I. V. Shilonosova's investigation (2012), where inverse correlation between the content of humoral serotonin on the 16th–24th day of CIHS and the level of neurological deficit was defined [1]. Taking into consideration the ability of serotonin to play the role of angiogenesis inductor [4] and revealed by us interconnection between its concentration in blood and forecast of CIHS treatment, we can affirm about the pathogenetic significance of serotonin in the realization of sanogenesis mechanisms during early recovery period of CIHS.

Among the studied indexes the highest information value for prognosis of functional outcome of early recovery period of CIHS as for the results of this research was set for the ratio of melatonin and serotonin on the 30th day of disease (AUC = 0.81 against 0.45 и 0.69 for melatonin and serotonin respectively). It defines the practical usage of mentioned criterion as surrogate marker of objectification of interconnection of melatonin and its metabolic precursor – serotonin among the patients with CIHS as

Table 1. Distribution of patients with CIHS depending on the mRS index on the 90th and 180th day of disease

mRS score	the 90th day, n (%)	the 180th day, n (%)
0	13 (16.9 %)	21 (27.3 %)
1	21 (27.3 %)	20 (26.0 %)
2	29 (37.7 %)	24 (31.2 %)
3	13 (16.8)	11 (14.2 %)
4	1 (1.3 %)	1 (1.3 %)

Table 2. Comparative analysis of informational content as for melatonin and serotonin levels, MSR on the 10th and 30th day of CIHS for prediction of moderate and severe disability for mRS ≥ 3 points on the 90th and 180th day of disease on the basis of calculations of Area Under the Curve index (AUC)

Options	End point, AUC	
	mRS ≥ 3 the 90th day	mRS ≥ 3 the 180th day
The serotonin plasma level on the 10th day, mcmol/l	0.41	0.42
The melatonin serum level on the 10th day, pg/ml	0.53	0.54
MSR level on the 10th day	0.54	0.55
The serotonin plasma level on the 30th day, mcmol/l	0.69*	0.74*
The melatonin serum level on the 30th day, pg/ml	0.45	0.66*
MSR level on the 30th day	0.81*	0.78*
ΔSE	0.65*	0.67*
ΔME	0.64*	0.67*
ΔMSR	0.67*	0.66*

mRS: modified Rankin Scale score; *: significance of differences with the value of AUC = 0.5; p < 0.05.

Table 3. Criteria for prediction of moderate and severe disability for mRS ≥ 3 points on the 90th day of CIHS

Criterion	Sensitivity	Specificity
MSR level on the 30th day of CIHS >212.0	100 %	75.0 %
The serotonin plasma level on the 30th day ≤ 0.15 mcmol/l	50.0 %	86.4 %
ΔMSR > 0.658	66.7 %	72.1 %
ΔSE ≥ -0.318	50.0 %	83.7 %
ΔME ≤ 0.513	100 %	45.2 %

Table 4. Criteria for prediction of moderate and severe disability for mRS ≥ 3 points on the 180th day of CIHS

Criterion	Sensitivity	Specificity
MSR level on the 30th day of CHIS > 212.0	100 %	73.3 %
The serotonin plasma level on the 30th day ≤0.15 mcmol/l	60.0 %	86.7 %
ΔSE ≥ -0.318	60.0 %	84.1 %
ΔME ≤ 0.382	100 %	48.4 %
ΔMSR > 1.019	60.0 %	79.5 %
The melatonin serum level on the 30th day ≤ 29.1 pg/ml	60.0 %	79.7 %

for prognosis of outcome during the early recovery period of disease.

Conclusions

Conducted investigation allows us to draw out the following conclusions:

1. The level of MSR >212.0 on the 30th day of CIHS is the predictor of moderate and profound disability for modified Rankin's scale ≥3 points on the 90th (AUC = 0.81, p < 0.05; sensitivity = 100.0 %, specificity = 75.0 %) and on the 180th day of disease (AUC = 0.78, p < 0.05; sensitivity = 100.0 %, specificity = 73.3 %).

2. The serotonin plasma level ≤0.15 mcmol/l on the 30th day of CIHS is the predictor of moderate and profound disability for modified Rankin's scale ≥3 points on the 180th day of disease (AUC = 0.74, p < 0.05; sensitivity = 60.0 %, specificity = 86.7 %).

Perspective for further scientific investigations is the development of differential approach for arranging treatment and rehabilitation in patients with CIHS, taking into account the individual prognosis of outcome on the early recovery period of disease, based on the identification of the serum concentration of melatonin and the serotonin plasma level.

References

[1] Shilonosova, I. V. (2012) Serotonintransportnaya sistema v ostrejshem periode tyazhologo aterotromboticheskogo ishemicheskogo insul'ta [Serotonin a transport system in an acute period jf a serious atherothrombotic ischemic stroke]. *Vrach-aspirant*, 51(2.2), 335–339. [in Russian].

[2] Reuter, B., Gumbinger, C., Sauer, T., Wiethölter, H., Bruder, I., Diehm, C., et al. (2016) Access, timing and frequency of very early stroke rehabilitation - insights from the Baden-Wuerttemberg stroke registry. *BMC Neurol*, 16, 222. doi: 10.1186/s12883-016-0744-7.

[3] Wu, L., Wang, A., Wang, X., Zhao, X., Wang, C., Liu, L., et al. (2015) Factors for short-term outcomes in patients with a minor stroke: results from China National Stroke Registry. *BMC Neurol*, 15, 253. doi: 10.1186/s12883-015-0505-z.

[4] Qin, L., Zhao, D., Xu, J., Ren, X., Terwilliger, E. F., Parangi, S., et al. (2013). The vascular permeabilizing factors histamine and serotonin induce angiogenesis through TR3/Nur77 and subsequently truncate it through thrombospondin–1. Blood, 121(11), 2154–2164. doi: 10.1182/blood-2012-07-443903.

[5] Juan, W. S., Huang, S. Y., Chang, C. C., Hung, Y. C., Lin, Y. W., Chen, T. Y., et al. (2014) Melatonin improves neuroplasticity by upregulating the growth-associated protein-43 (GAP-43) and NMDAR postsynaptic density-95 (PSD-95) proteins in cultured neurons exposed to glutamate excitotoxicity and in rats subjected to transient focal cerebral ischemia even during a long-term recovery period. *J Pineal Res*, 56(2), 213–223. doi: 10.1111/jpi.12114.

[6] Chumboatong, W., Thummayot, S., Govitrapong, P., Tocharus, C., Jittiwat, J., & Tocharus, J. (2017) Neuroprotection of agomelatine against cerebral ischemia/reperfusion injury through an antiapoptotic pathway in rat. *Neurochem Int*, 102, 114–122. doi: 10.1016/j.neuint.2016.12.011.

[7] Parada, E., Buendia, I., León, R., Negredo, P., Romero, A., Cuadrado, A., et al. (2014) Neuroprotective effect of melatonin against ischemia is partially mediated by alpha-7 nicotinic receptor modulation and HO-1 overexpression. *J Pineal Res*, 56(2), 204–212. doi: 10.1111/jpi.12113.

[8] Sangha, R. S., Caprio, F. Z., Askew, R., Corado, C., Bernstein, R., Curran, Y., et al. (2015) Quality of life in patients with TIA and minor ischemic stroke. *Neurology*, 85(22), 1957–63. doi: 10.1212/WNL.0000000000002164.

[9] Audhya, T., Adams, J. B., & Johansen, L. (2012) Correlation of serotonin levels in CSF, platelets, plasma, and urine. *Biochim Biophys Acta*, 820(10), 1496–501. doi: 10.1016/j.bbagen.2012.05.012.

[10] Paterniti, I., Cordaro, M., Esposito, E., & Cuzzocrea, S. (2016) The antioxidative property of melatonin against brain ischemia. *Expert Rev Neurother*, 2016, 16(7), 841–848. doi: 10.1080/14737175.2016.1182020.

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