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CEREBRAL HEMISPHERES – CEREBELLUM – KIDNEY INTERACTION IN PATIENTS WITH ACUTE CEREBRAL ISCHEMIA

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Key words: *acute ischemic stroke, lateralization of brain function, cerebellum, renal concentration-filtration function*
Ключові слова: *гострий ішемічний інсульт, міжпівкульна асиметрія, мозочок, концентраційно-фільтраційна функція нирок*
Ключевые слова: *острый ишемический инсульт, межполушарная асимметрия, мозжечок, концентрационно-фильтрационная функция почек*

Abstract. Cerebral hemispheres – cerebellum – kidney interaction in patients with acute cerebral ischemia. Kononets O.M., Tkachenko O.V., Kamenetska O.O. *The nervous system, in particular the autonomic one, is well known to constantly regulate the internal functioning of the body, adapting it to changeable external and internal environmental parameters. In particular, there is a close multiple-vector correlation between the nervous system and the kidneys. The aim of this study was to specify the mechanisms, clinical and paraclinical characteristics of the concomitant lesions of the nervous system and the kidneys in patients with acute stroke. This paper presents the case report of 215 patients, aged 70 ± 8.44, who suffered from ischemic stroke. Among them, we examined 144 women and 71 men. The patients underwent a comprehensive examination, including a detailed clinical and neurological check-up (evaluating the patients' condition severity with the National Institutes of Health Stroke Scale (NIHSS) and the Barthel index on admission and on the 21st day of the disease), laboratory analysis (electrolyte balance, nitrogen metabolism (on admission and on the 21st day of the disease) and instrumental examination (CT scan of the brain, the follow-up brain magnetic resonance imaging). The statistical methods were used to analyze the data. In the 1st day of the disease, all the surveyed patients with right hemispheric carotid stroke and the overwhelming majority of the patients with left hemispheric carotid stroke and ischemic stroke in the vertebrobasilar system had cerebral renal syndrome, represented by renal concentration-filtration dysfunction, accompanied by the reduced glomerular filtration rate. A reliable relationship was found between the renal concentration and filtration function and the right hemispheric ischemic focus in patients with ischemic stroke, the characteristics are to be specified.*

Реферат. Взаємодія півкуль головного мозка та мозочку з нирками в умовах гострої церебральної ішемії. Кононець О.М., Ткаченко О.В., Каменецька О.О. *Загальновідомим є той факт, що нервова система, зокрема автономна, постійно моніторує і контролює роботу внутрішніх органів, регулюючи та адаптуючи їх роботу до мінливих параметрів зовнішнього і внутрішнього середовищ. Між нервовою системою та нирками існує тісний полівекторний взаємозв'язок. Метою дослідження стало уточнення механізмів, клінічних та параклінічних характеристик асоціативного ураження структур нервової системи та нирок при гострих порушеннях мозкового кровообігу. Наведено результати одного з фрагментів комплексного обстеження 215 пацієнтів з гострим порушенням мозкового кровообігу за ішемічним типом. Середній вік хворих був 70±8,44 року. Серед них було 144 жінки та 71 чоловік. Комплексне обстеження пацієнтів включало: детальне клініко-неврологічне обстеження (з оцінкою ступеня тяжкості стану пацієнтів за шкалою NIHSS та шкалою Бартела на 1-й та 21-й день захворювання), лабораторне (з визначенням параметрів електролітного балансу, азотного обміну в динаміці на 1-й і 21-й день захворювання) та інструментальне дослідження (комп'ютерна томографія головного мозку, магнітно-резонансна томографія головного мозку). Для обробки даних було використано відповідні статистичні методи. У всіх пацієнтів з гострим ішемічним інсультом в правому каротидному басейні та в переважної більшості пацієнтів з гострим ішемічним інсультом у лівому каротидному басейні та у вертебробазилярному басейні в першу добу захворювання мав місце церебро-ренальний синдром у вигляді порушення фільтраційно-концентраційної функції нирок зі зниженням швидкості клубочкової фільтрації. Виявлено достовірний зв'язок показників концентраційно-фільтраційної функції нирок з правопівкульною локалізацією ішемічного вогнища в пацієнтів з ішемічним інсультом, характеристики якої вимагають уточнення.*

The nervous system, in particular the autonomic one, is well known to constantly regulate the internal functioning of the body, adapting it to changeable external and internal environmental parameters.

For example, neuroendocrine and renal interactions regulate osmolarity with vasopressin. The systemic changes in osmolarity are detected by osmoreceptors in the specific areas of the central nervous system. Neuronal activity in these areas regulates vasopressin secretion in the hypothalamus and posterior pituitary gland, and also stimulates or inhibits thirst and sodium intake. Circulating vasopressin acts upon Vasopressin 2 receptors, expressed in renal collecting tubules and increases the number of Aquaporin 2 channels in the apical membrane, resulting in the increased water reabsorption in the kidneys [2, 5].

One more example of cerebro-renal interaction is the functioning principles of renal afferent (sensory) and efferent (sympathetic) nerves, which maintain sodium balance as well as the kidneys. The renal afferent nerve, which innervates mainly the pelvic wall, but does not innervate the renal parenchyma vessels, is activated by the increased pressure level on the renal pelvis wall and its stretching. The sympathetic nerves innervate all renal vessels, including the renal tubule epithelium [5].

Stimulating renal sensory afferent nerve reduces the contralateral efferent renal nerve sympathetic activity, consequently reducing contralateral sodium excretion [2]. An inhibitory reno-renal reflex should be mentioned, whereby the increased activity of the renal afferent nerve inhibits the efferent renal sympathetic nerve activity. In case of kidney disease, the renal afferent sensory nerve activation can provoke an impaired inhibitory reno-renal reflex. The mechanism of the inhibitory reno-renal reflex conversion to the excitatory one in kidney disease has not been studied yet (nowadays, exciting renal chemosensitive nerves with the enhanced

concentration of adenosine is considered to be a possible mechanism). The cerebellum has been shown by experiments to regulate arterial pressure [8, 11].

The brain-kidneys strong correlation is derived from the fact that the structure of their vascular system has a number of anatomical and physiological features: the both organs have the "strain vessels" (afferent arterioles in the kidneys and perforating arterioles in the brain), which are short and small-diameter arterioles; the arterioles branch out from larger diameter arteries and this in itself autonomously regulates tissue perfusion. Both cerebral and renal blood vascular territories are evaluated in terms of low vascular resistance, accompanied by a high perfusion level with a high blood flow velocity in them, and they have similar autoregulatory systems. By virtue of such blood flow peculiarities the both organs are very sensitive to fluctuations in the systemic blood flow velocity and change in the systemic blood pressure. The reason for this is that strain vessels are constantly subject to large pulse pressure, which directly spreads from the strain large arteries [2].

In view of this, cerebrovascular diseases (both stroke (or cerebrovascular accident) and chronic ischemia) and kidney diseases have many cardiovascular risk factors in common, and such risk factors as elderly age, smoking, arterial hypertension, diabetes mellitus, hyperlipidemia can cause small vessel-related lesions [3]. In addition, the both organs can be affected by arteriolosclerosis and atherosclerosis. Silent brain ischemia has been established to be an important prognostic factor for kidney damage progression in patients with chronic kidney disease [4, 7]. Moreover, a number of the follow-up studies showed stroke to be a significant independent predictor for the whole gamut of chronic kidney disease, including its onset and progression, as well as the development of end-stage renal disease [1, 9, 10]. Thus, patients with stroke are at high risk of both disability and mortality, and chronic kidney disease onset and progression. The objective of this study was to specify the mechanisms, clinical and paraclinical characteristics of the concomitant lesions of the nervous system and the kidneys in patients with acute stroke.

MATERIALS AND METHODS OF RESEARCH

This paper presents the case report of 215 patients, aged 70±8.44, who suffered from ischemic stroke. Among them, we examined 144 women, aged 71±8.65 and 71 men, aged 67±8.49. The patients underwent a comprehensive examination, including a detailed clinical and neurological check-up, laboratory analysis (electrolyte balance, nitrogen metabolism) and instrumental examination (CT scan of the brain, the follow-up brain magnetic resonance imaging).

All the surveyed patients with acute stroke were divided into three groups: the 1st group included the patients with ischemic stroke in the right carotid territory (50 people, aged 73±7.75); the 2nd group consisted of the patients with ischemic stroke in the left carotid territory (103 people, aged 72±7.86); the 3rd group included the patients with ischemic stroke in the vertebrobasilar system (62 people, aged 62.6±6.7). All the mentioned patient groups were followed-up for neurologic deficit (the 1st, the 3rd, 7th and 21st days of the disease), creatinine and blood urea levels (the 1st and 7th days of the disease), glomerular filtration rate (the 1st and 7th days of the disease). The patients also underwent neurovisualization. The severity of patients' condition was evaluated with the National Institutes of Health Stroke Scale (NIHSS) and the Barthel index on admission and on the 21st day of the disease [12]. Statistical analysis of the results of the study was carried out on personal computer using the Microsoft Excel software (Microsoft Office 2016 Professional Plus, Open License 67528927), and Statisitica 6.1 (StatSoft Inc., serial N AGAR909E415822FA). Such statistical methods, including the following indices, were used to analyze the data: average, average ± statistical uncertainty, average ± statistical deviation, Student's t-test, correlation coefficient. A correlation coefficient, often denoted by "R", tells us how close is the linear relationship between the two variables. Negative values indicate a negative linear relationship. Positive values indicate a positive linear relationship; R=[3-5] indicates a weak relationship; R=[5-7] indicates a moderate strong relationship. R=[>7] indicates a strong relationship [6].

RESULTS AND DISCUSSION

When measuring creatinine in serum, we found those values to be within 0.057-0.165 mmol/l, the mean value =0.088±0.02 mmol/l, in the 1st patient group; to be within 0.018-0.18 mmol/l, the mean value =0.115±0.07 mmol/l, in the 2nd patient group and to be within 0.062-0.121 mmol/l, the mean value =0.082±0.01 mmol/l, in the 3rd patient group.

When measuring blood urea, we found those values to be within 3.1-10.2 mmol/l, the mean value =8.2±4.93 mmol/l, in the 1st patient group; to be within 3.0-13.9 mmol/l, the mean value =6.7±1.57 mmol/l, in the 2nd patient group and to be within 3.1-10.1 mmol/l, the men value =5.75±4.92 mmol/l, in the 3rd patient group.

The glomerular filtration rate was observed to be within 25-101 ml/min/1.73m^2, the mean value =67.4±15.13 ml/min/1.73m^2, in the 1st patient group; to be within 5-135 ml/min/1,73m^2, the mean

value =64±19,72 ml/min/1,73m^2, in the 2nd patient group; and to be within 41-120 ml/min/1.73m^2, the mean value =74.6±11.71ml/min/1.73m^2, in the 3rd patient group.

Having evaluated over time the severity of patients' condition with the NIHSS on the 1st and 21st day of the disease, we obtained the following results. On the 1st day of the disease, the NIHSS scores averaged 12±4.3 (the range =2-23) in the 1st patient group (Fig. 1), the NIHSS scores averaged 11.17±4.58 (the range =2-30) in the 2nd patient group (Fig. 2), the NIHSS scores averaged 5.24±2.4 (the range =1-15) in the 3rd patient group, respectively.

As of the 21st day of the disease, the NIHSS scores averaged 7.94±4.58 (the range =0-20) in the 1st patient group (Fig. 1), the NIHSS scores averaged 7.72±5.04 (the range =1-25) in the 2nd patient group (Fig. 2), the NIHSS scores averaged 3.0±2.0 (the range =0-13) in the 3rd patient group, respectively.

Having assessed over time the patients' activities of daily living with the Barthel index on the 1st and 21st days of the disease, we obtained the following results. On the 1st day of the disease, the Barthel index averaged 36.8±19.49 (the range =0-85) in the 1st patient group, the Barthel index averaged 43.4±21.74 (the range =2-98) in the 2nd patient group, and the Barthel index averaged 63.45±19.51 (the range =20-100) in the 3rd patient group, respectively.

As of the 21st day of the disease, the Barthel index averaged 53.08±21.25 (the range =0-98) in the 1st patient group, the Barthel index averaged 59.39±22.89 (the range =5-100) in the 2nd patient group, and the Barthel index averaged 83.68±13.24 (the range =25-100) in the 3rd patient group, respectively.

Thus, the following patterns were detected: on admission (the 1st day of stroke), the patients with acute vertebrobasilar stroke were observed (according to the NIHSS) to have the easiest neurological dysfunction among all the mentioned above. The patients with acute carotid stroke (both in the left hemisphere and in the right one) were observed to have more severe neurological dysfunction. The same patterns were observed over time in all the patient groups on the 21st day of the disease. At the same time, the reduced neurological dysfunction was observed more in the patients with acute left and right hemispheric carotid strokes, than that in the patients with acute vertebrobasilar stroke: during the average specified period, the neurological dysfunction in the 1st two patient groups was rated 5 points lower on the NIHSS; for the same period, in the third patient group it was rated only 2 points lower. The similar pattern was observed in the mentioned patients' activities of daily living, according to the Barthel index.

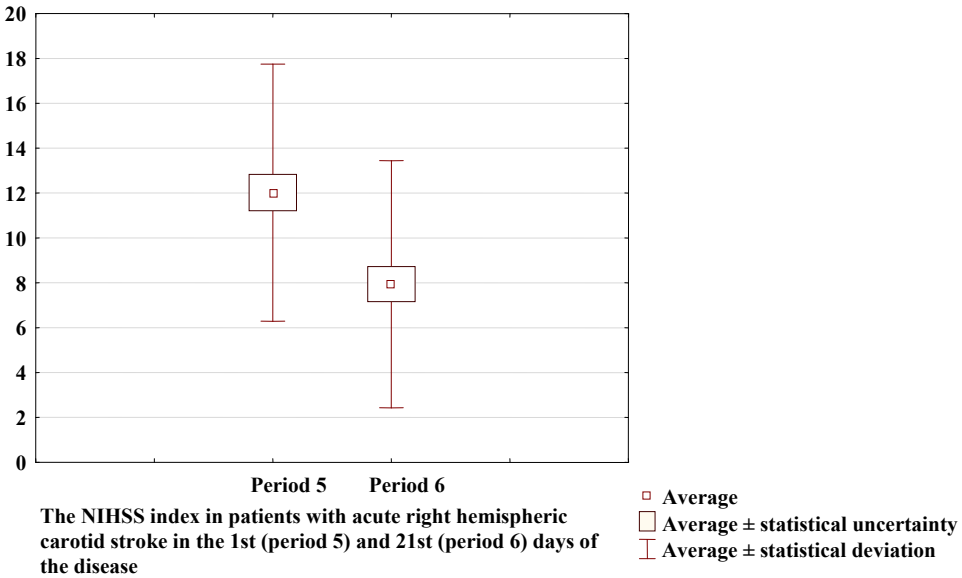

Fig. 1. The NIHSS index box plot in patients with acute right hemispheric carotid stroke in the 1st and 21st days of the disease

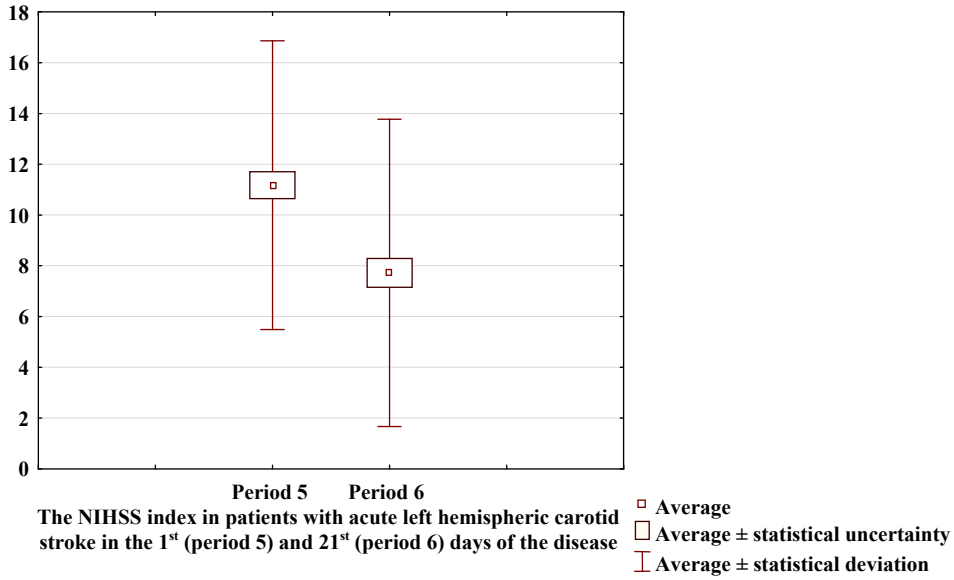

Fig. 2. The NIHSS index box plot in patients with acute left hemispheric carotid stroke in the 1st and 21st days of the disease

In the 1st day of acute ischemic stroke, the patients with mild neurological deficit (the NIHSS scores ranged from 3 to 8) were noted to predominate over all the surveyed ones. Moderate (the NIHSS scores ranged from 9 to 12) and severe (the NIHSS scores ranged from 13 to 15) neurological deficits were predominantly observed in the patients with acute left and right hemispheric carotid strokes, (within 20%) (Fig. 3). The severe neurological deficit (the NIHSS scores ranged from 16-34 or >) was observed only in the patients with hemispheric strokes.

No severe neurological deficit (according to the NIHSS) was observed in the patients with acute brain-stem and cerebellar ischemia, the overwhelming majority of the patients (70%) was detected to have a mild neurological deficit. In the 1st day of the disease, coma (>34 scores, according to the NIHSS) was detected only in patients with left hemispheric carotid stroke (4.8%).

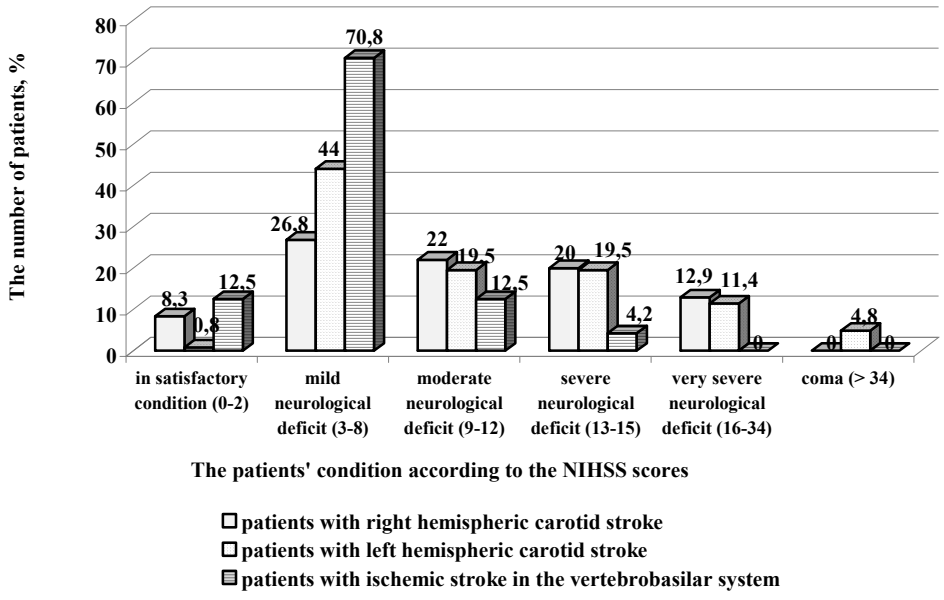

Fig. 3. Neurological deficit severity in patients with acute stroke in the 1st day of the disease (according to the NIHSS)

Having evaluated over time the patients' condition by means of the NIHSS on the 21st day of the disease, and stratified the patients depending on the neurological deficit severity, we obtained the following results: the patients with ischemic stroke in the vertebrobasilar system predominated over all the surveyed ones (63.9%). Furthermore, the patients with acute brain-stem and cerebellar ischemia were found to have no very severe neurological deficit on the 21st day of the disease as well, according to the NIHSS (Fig. 4).

In the 1st and 2nd groups, the surveyed patients with mild neurological deficit (the NIHSS scores ranged from 3 to 8) were detected to prevail over all the rest: 35.8% and 40%, respectively. The very severe neurological deficit cases (the NIHSS scores ranged from 16 to 34) went up in the 2nd group from 11.4% to 15.4%, however, due to the decrease in the number of neurological deficit (>34 scores) cases within the group.

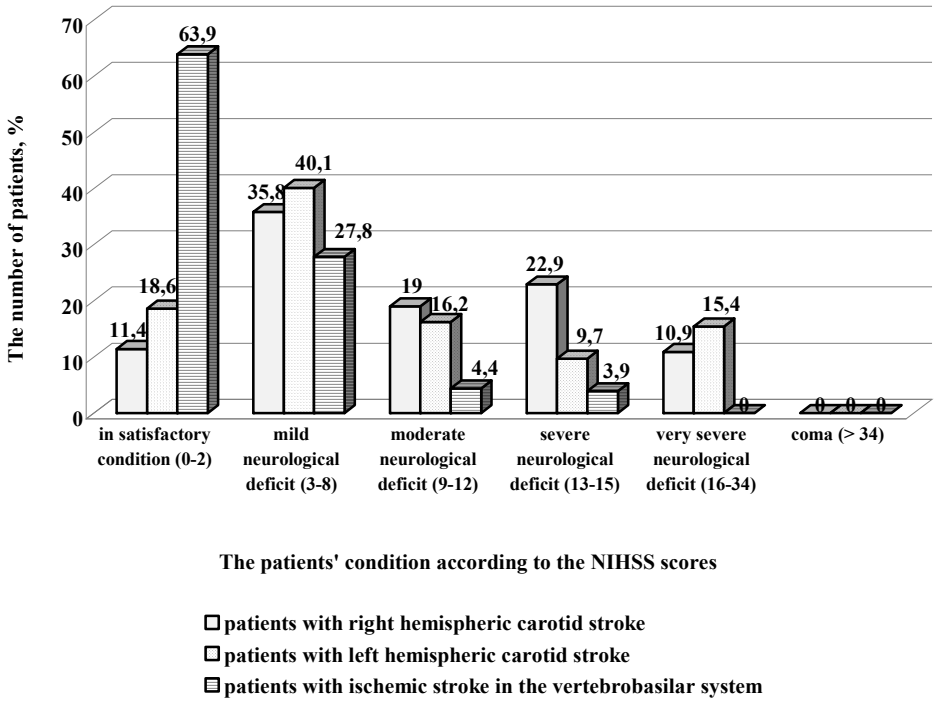

Fig. 4. Neurological deficit severity in patients with acute stroke in the 21st day of the disease (according to the NIHSS)

In all the patients, we followed up renal function, more specifically, we monitored both urea and creatinine levels in the serum, and the glomerular filtration rate. It's worth paying attention to an important fact: in the 1st day of the disease, only 5.8% of patients with right and left hemispheric carotid strokes and 6.85% of patients with ischemic stroke in the vertebrobasilar system were observed to have normal glomerular filtration rate, namely 100 ml/min/1.73 m² and more (Fig. 5). No patient with hemispheric carotid stroke had a normal glomerular filtration rate. The vast majority of patients was found to have moderate impairment in the renal filtration-concentration function, the glomerular filtration rated 61-90 ml/min/1.73 m². The number of severe impaired filtration-concentration renal function cases (the glomerular filtration rate was 30-60 ml/min/1.73 m²) was the highest among the patients with right hemispheric carotid stroke, and it made 26%. The number of very severe and end-stage renal dysfunction cases (the glomerular filtration rate was <29 ml/min/1.73 m²) was also prevalent among those with right hemispheric carotid stroke, and it made 4%. The patients with acute brain-stem and cerebellar ischemia were found to have no very severe and end-stage renal dysfunction.

The correlation coefficient between NIHSS neurological deficit severity in the 1st day of the disease and the glomerular filtration rate in the 1st patient group accounted for R= +3.18 ($p<0.005$), i.e. a weak positive relation was found (Fig. 6).

The correlation coefficient between neurological deficit severity (according to the NIHSS) in the 1st day of the disease and the glomerular filtration rate in the second patient group accounted for R= -1.38 ($p<0.001$), i.e. no relation was found.

The correlation coefficient between NIHSS neurological deficit severity in the 1st day of the disease and the glomerular filtration rate in the 3rd patient group accounted for R= +0.71 (p<0.001), i.e. no relation was found.

The correlation coefficient between the presence of foci and glomerular filtration rate in the patients with acute brain-stem and cerebellar ischemia in the 1st day of the disease accounted for R= -0.57 (p<0.001), i.e. no relation was found.

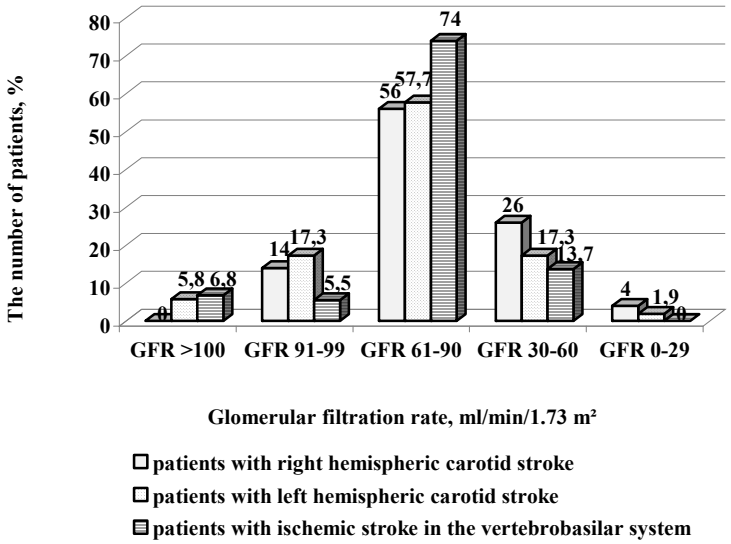

Fig. 5. Glomerular filtration rate indices in patients with acute stroke in the 1st day of the disease

Thus, the neurological deficit severity was detected to correlate to the glomerular filtration rate in the patients with right hemispheric ischemic stroke, as confirmed by hemispheric asymmetry role in renal filtration functioning. Moreover, our findings showed that the more severe was neurological deficit in patients with right hemispheric ischemic stroke, the better was the renal concentration-filtration capacity (the higher glomerular filtration rate). Thus, the right hemisphere of the brain has been found to be superior for regulating renal function under acute cerebral ischemia. In such a case, the compensatory mechanisms can be better done, even if the patients have cerebral renal syndrome. No relationship between the cerebellar structures lesion and the renal concentration-filtration capacity regulation was detected in patients with acute ischemia.

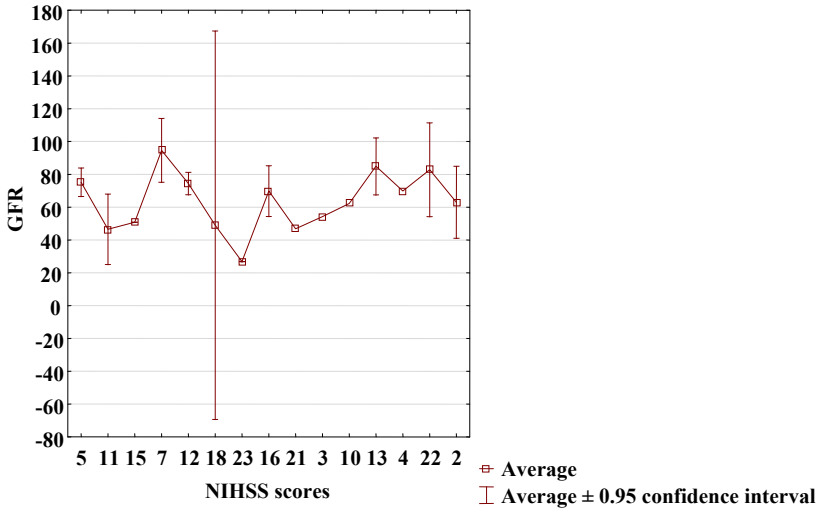

Fig. 6. Neurological deficit severity (according to the NIHSS) – Glomerular filtration rate relationship

CONCLUSIONS

1. In the 1st day of the disease, all the patients with right hemispheric carotid stroke and the overwhelming majority of the patients with left hemispheric carotid stroke and ischemic stroke in the vertebrobasilar system had cerebral renal syndrome, represented by renal concentration-filtration dysfunction, accompanied by the reduced glomerular filtration rate.
2. A reliable relationship was found between the renal concentration and filtration function and the right hemispheric ischemic focus in patients with ischemic stroke, the characteristics are to be specified.

Conflict of interests. The authors declare no conflict of interest.

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