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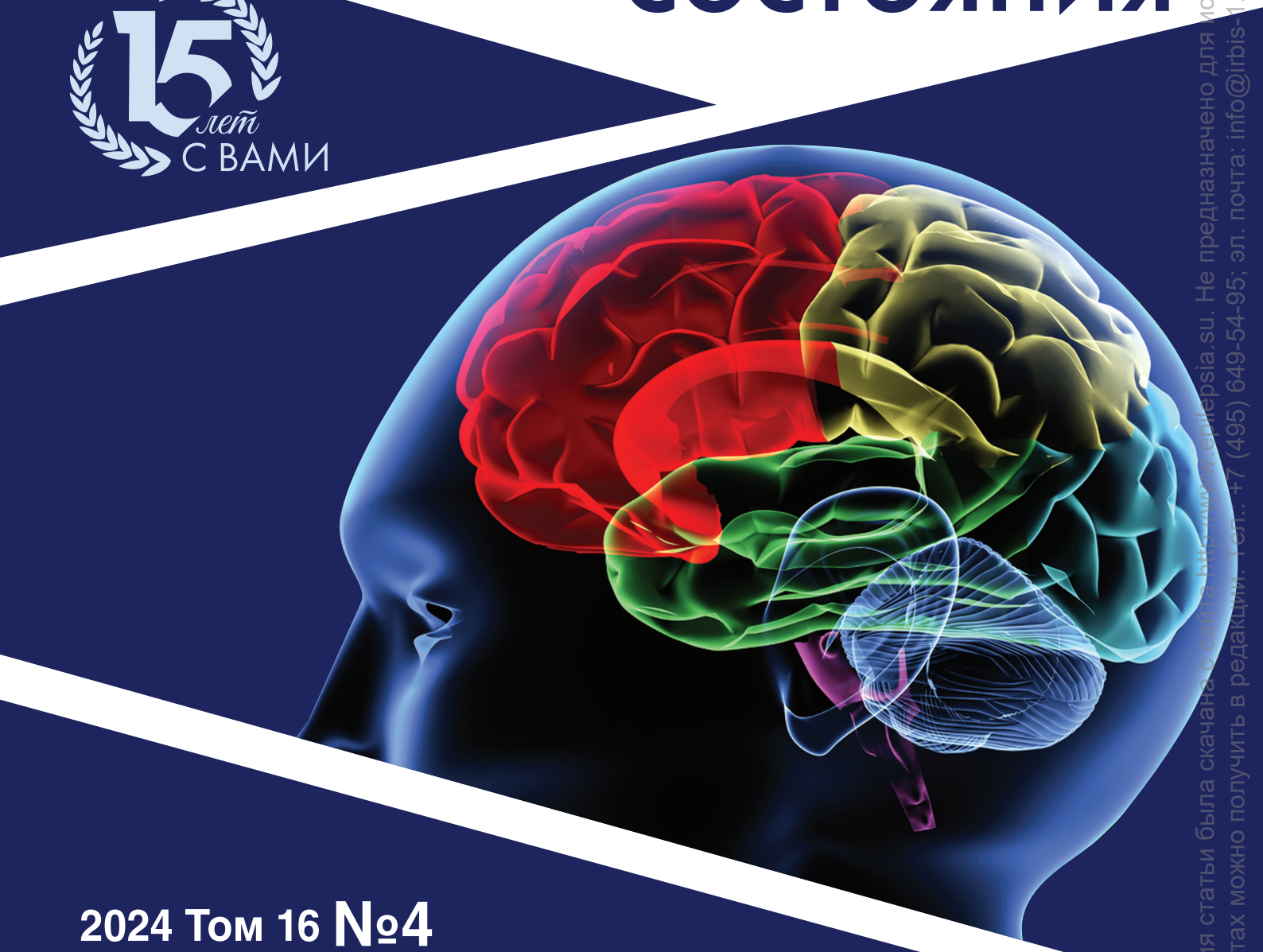

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# Increased postictal creatine kinase in epilepsy patients

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**SUMMARY**

Excessive muscle activity during generalized convulsive seizures in epilepsy patients in some cases can cause significant changes in blood plasma biochemical parameters, increased level of a set of metabolites, particularly, serum creatine kinase, accompanied by azotemia, which leads to prominent diagnostic and therapeutic difficulties. It is necessary to monitor the creatine kinase concentration after seizures, especially in case of electrolyte disturbances. To correct elevated creatine kinase or myoglobin levels, infusion therapy, urine alkalinization along with diuretics administration should be performed.

**KEYWORDS**

Epilepsy, seizures, creatine kinase, acute kidney injury, AKI.

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## Постиктальное повышение креатинкиназы у больных эпилепсией

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**РЕЗЮМЕ**

Избыточная мышечная активность при генерализованных судорожных приступах у больных эпилепсией в ряде случаев может приводить к существенным изменениям биохимических показателей плазмы крови, повышению уровня ряда метаболитов, в частности сывороточной креатинкиназы, сопровождаться азотемией, что вызывает значительные диагностические и терапевтические трудности. Необходимо осуществлять мониторинг концентрации креатинкиназы после судорог, особенно при наличии у пациента электролитных нарушений. Для коррекции повышенного уровня креатинкиназы или миоглобина следует проводить инфузионную терапию, ощелачивание мочи, вводить диуретики.

**КЛЮЧЕВЫЕ СЛОВА**

Эпилепсия, судорожные приступы, креатинкиназа, острое повреждение почек, ОПП.

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## INTRODUCTION / ВВЕДЕНИЕ

Elevated creatine kinase (CK) levels in blood plasma may indicate damage to muscle cells due to injury, excessive physical exertion, infectious diseases, or the use of some medications [1–3]. CK values reversal is often observed in clinical practice in patients with epilepsy (PWE) with seizures and in post-onset period. As a rule, an increased CK level is a clinically insignificant metabolic disorder, but in some cases with its significant increase, it can lead to serious complications and the development of threatening conditions. The nosocomial mortality in PWE after convulsive seizures with CK level more than 5,000 U/l reaches 6% [1].

Excessive motor muscle activity in tonic, clonic and myoclonic seizures can cause rhabdomyolysis [2, 3]. According some authors, seizures can be the cause of rhabdomyolysis in about 4% of PWE, excessive physical activity – in 6.1% [4–6]. In rhabdomyolysis, numerous cytoplasmic components of muscle cells, including myoglobin and electrolytes, enter the interstitial space and bloodstream through a damaged sarcolemma. The breakdown products of myocytes can cause acute kidney injury (AKI) and cardiac arrhythmia [7].

Other factors may be involved in the pathophysiological process associated with muscle damage, in particular electrolyte disorders [8, 9]. The electrolyte imbalance observed in epileptic seizures, for example, decreased blood plasma potassium levels less than 2 mmol/l, may also lead to rhabdomyolysis development [10–12]. An asymptomatic increase in CK is observed in hyponatremia caused by diuretics, as well as in polydipsia and may be complicated by AKI [13].

The situation is aggravated by the fact that general practitioners are not familiar with such a complication of convulsive epileptic seizures, which causes significant difficulties in diagnosing and managing PWE, therefore it is necessary to carry out timely appropriate treatment that can improve the prognosis.

As an illustration, we present our own clinical observation.

## CASE REPORT / КЛИНИЧЕСКИЙ СЛУЧАЙ

Patient S. born in 1997 (27 years old) on September 26, 2023 turned to the neurologist of the clinic with complaints of generalized tonic-clonic seizures (GTCS) with a focal onset in the form of tonic seizures in the right arm.

### History of disease / Анамнез заболевания

In childhood, there were speech disorders, sleepwalking, and rare syncopal conditions, which were regarded as vegetative-vascular dystonia. No specific changes were detected on electroencephalography (EEG) in childhood.

In 2017, the patient suffered a closed craniocerebral injury, a brain contusion (left frontal lobe). In 2022, GTCS and focal motor seizures appeared in the right arm. He was examined at the place of residence. Focal structural epilepsy was diagnosed and lamotrigine was prescribed at a dose of 200 mg/day. Seizure control was achieved.

The patient independently canceled the antiepileptic drug (AED) in June 2023, after which GTCS developed in June and September. In the post-onset period, there was repeated vomiting, blood pressure increased to 160/100 mm Hg. He was hospitalized twice (in June and September 2023) and was monitored by a nephrologist after discharge.

Heredity was not burdened by neuropsychiatric diseases and epilepsy. The patient worked as a ship mechanic.

### Neurological status / Неврологический статус

Patient's mind was clear. Cranial nerves were intact. Tendon reflexes were equal, D=S, there were no paresis, no pathological signs. Muscle tone was normal. There were no sensitive violations. The coordination tests were performed satisfactorily. The patient was stable in the Romberg pose. The gait was not broken. Pelvic organ functions were preserved. In the chest area, under the right breast nipple, a reduced third nipple was revealed (stigma of dysembriogenesis).

### Electrocardiography / Электрокардиография

During electrocardiographic (ECG) monitoring, two episodes of atrial fibrillation lasting no more than 1 sec were recorded. Rhythm variability was slightly increased. The impact of sympathetic division of autonomic nervous system on rhythm regulation was strengthened both during day and at night.

### Brain MRI / МРТ головного мозга

Brain magnetic resonance imaging (MRI) performed on October 9, 2023 on a Discovery MR750W 3.0 T (General Electric, USA) according to the expert protocol yielded 3D FLAIR, 3D SPGR, 3D SWAN, T1, T2 in the axial plane, T2 in the coronal plane (perpendicular to the long axis of the hippocampus), DWI, ASL images. The midline structures were usually formed and not displaced. In the left frontal lobe, in basal-lateral sections, a zone of post-traumatic cystic-glial changes was revealed, surrounded by hemosiderin deposition, 28×26×14 mm in size. The zone of changes was triangular in shape, extending from the cortical surface towards the anterior horn of the lateral ventricle.

When performing non-contrast MR perfusion, a decrease in cerebral blood flow velocity in the area of changes by more than 2 times was revealed compared to a similar area in the right frontal lobe. The size hypoperfusion zone corresponded to the size of the zone of changes. The anterior horn of the left lateral ventricle was moderately dilated. Brain hemispheres were symmetrical. Large brain furrows and gyri were usually formed. Cerebral cortex thickness was normal. The boundary between brain gray and white matters was clearly visible. The hippocampus was symmetrical, with usual configuration and size, internal structure was preserved. There were no foci of pathological signal intensity in the hippocampus and parahippocampal gyri. There was no decrease in the volume of white matter of parahippocampal gyri. The lateral ventricles were not dilated, symmetrical. III, IV ventricles were unremarkable. Subarachnoid space was without visible changes. Brainstem and chiasmal-cellular region structures were not changed. The paranasal sinuses were pneumatized.

Conclusion: Post-traumatic zone of cystic-gliotic changes with hemosiderin deposition in the frontal lobe of brain left hemisphere. No pathological formations or brain abnormalities were identified.

### Video-EEG monitoring / Видео-ЭЭГ-мониторинг

The study was conducted using the Neuron-Spectrum-SM brain electrical activity analyzer (Neurosoft LLC, Russia) with 19 points on the head surface (according to the international 10–20 electrode system). Video-EEG monitoring was performed for 8 hours, in a state of active and passive wakefulness, with certain tests (eye opening and closing, hyperventilation for 3 min, photostimulation), during night sleep, with final forced arousal.

According to EEG data in a state of passive wakefulness before night sleep, the background rhythm was represented by a regular, weakly modulated alpha rhythm in the parietal-occipital regions with a spread to the bifrontal-central regions, frequency 9–10 Hz, amplitude up to 50 mV. The zonal gradient was smoothed. Beta oscillations with an amplitude of up to 20 mV were represented in the frontal-temporal hemispheres.

In functional tests before a night's sleep, the eye opening and closing test was not accompanied by pathological forms of activity. The sample with rhythmic photostimulation was carried out with the frequencies of 3, 5, 10, 15, 21 Hz.

No photoparoxysmal response was received. During the hyperventilation test, an increased amplitude of background activity was noted.

According to night sleep EEG results, the sleep was short with frequent awakenings. When falling asleep, decreased index, fragmentation and subsequent reduction of alpha activity, an increased theta oscillations and the appearance of vertex potentials with maximum amplitude in the central and vertex regions within 30 mV were noted. The second sleep stage itself was characterized by the appearance of rapid forms of "sleep spindles" activity and K-complexes in the form of polyphase diffuse potentials with an amplitude of up to 60 mV. Physiological patterns of the second sleep stage were recorded both in isolation and in combination with each other. In the first sleep cycle, single low-amplitude acute waves were recorded in the left fronto-centro-temporal region.

In passive awake EEG after a night sleep, the background rhythm was represented by a regular, weakly modulated alpha rhythm in the parietal-occipital regions with a frequency of 9–10 Hz spreading to the bifrontal-central regions, with an amplitude of up to 70 mV. The zonal gradient was smoothed out. Periodic accentuation of the main rhythm in the anterior sections was noted. Beta oscillations with an amplitude of up to 20 mV were observed in the fronto-temporal regions of both hemispheres.

During functional tests after a night sleep, the eye opening and closing test was not accompanied by pathological forms of activity. The sample with rhythmic photostimulation was carried out with the frequencies of 3, 5, 10, 15, 21 Hz. Photoparoxysmal response was not obtained. During the hyperventilation test, an increased amplitude of background activity was noted.

Conclusion: The basic rhythm of wakefulness corresponds to age. Diffuse changes in the bioelectric activity of the brain with an emphasis on the anterior regions. Sleep is modulated by phases and stages. No epileptic seizures or patterns of epileptic seizures were recorded. In the first sleep cycle, single low-amplitude acute waves were recorded in the left fronto-centro-temporal region.

### Laboratory examination / Лабораторное обследование

Examination during hospitalization revealed azotemia with creatinine increased to 403–351 mmol/l, CK to 1160 μmol/l, urea to 13–14 mmol/l in combination with dyselectrolythemia. In the urine analysis, there was isolated proteinuria of the nephritic level, maximum 3.5 g/l in a single serving. Azotemia normalized and proteinuria disappeared within a few days due to infusion therapy.

According to the discharge epicrisis: biochemical blood test from September 18, 2023: creatinine 114 μm/l, KCK 412 μm/l, urea 4.1 mmol/l, electrolytes (sodium, potassium, chlorine) within reference values, general urine analysis without pathology.

Blood biochemistry from October 26, 2023: creatinine 11 μm/l, CK 88 μmol/l, urea 4.0 mmol/l, prolactin 414 mIU/l, electrolytes (sodium, potassium, chlorine) within reference values, general urine analysis without pathology.

### Kidney ultrasound / Ультразвуковое исследование почек

Ultrasound revealed diffuse changes in renal parenchyma.

### Diagnosis / Диагноз

As a result of the examination, the diagnosis was established: Focal structural epilepsy with focal non-motor and motor seizures, impaired awareness, evolution into bilateral tonic-clonic seizures. Post-traumatic encephalopathy in the form of cystic-gliotic changes in the left frontal lobe. The stigma of dysembriogenesis. Hyperprolactinemia.

### Therapy / Терапия

The patient was prescribed levetiracetam at a dose of 1000 mg/day and enalapril 5 mg twice a day. Due to therapy, epileptic seizures control and blood pressure normalization were achieved.

## DISCUSSION / ОБСУЖДЕНИЕ

Convulsive seizures in PWE can cause an increase in CK and rhabdomyolysis, therefore, patients after seizures need to monitor the level of CK, electrolytes and perform an ECG [13–16].

K. Wang (2023) described 6 cases of postictal increase in CK: levels exceeded 5,000 U/l in 5 out of 6 patients, and the highest concentration of CK was 39,300 U/l. In all patients, the estimated glomerular filtration rate (eGFR) was below 90 ml/min/1.73 $m^2$. None of the patients developed renal insufficiency and did not require extrarenal blood purification (hemodialysis). The authors recommended that after convul-

sive seizures, a dynamic assessment of CK, myoglobin, eGFR and electrolytes in blood plasma should be carried out. With a significant increase in CK level, infusion therapy, urine alkalinization (pH≥7.5) and diuretics should be prescribed [17].

An increase in CK level was described in hypomagnesemia associated with gastrointestinal tract diseases accompanied by vomiting and diarrhea [18].

Increased urinary pH can prevent lipid peroxidation, oxidative stress development and myoglobin formation. Diuresis is able to prevent the accumulation of decomposition products in renal tubules, increase renal perfusion and improve myoglobin excretion. The use of mannitol in patients with anuria should be avoided and electrolyte levels should be monitored when using loop diuretics [19].

Increased CK level in convulsive seizures can serve as a marker to distinguish epileptic seizures (ES) from non-epileptic seizures (NES). An analysis of four studies, the material for which was a total of 343 ictal events (248 ES and 95 NES), showed that the sensitivity of increased postictal CK levels in ES ranged from 14.6 to 87.5, while the specificity ranged from 85.0 to 100.0. At the 95.7 percentile threshold, the sensitivity ranged from 14.6 to 62.5, and the specificity was 100, therefore, a normal postictal CK level, due to low sensitivity of this marker, still does not exclude ES in patients [20, 21].

It should be noted that along with an increased CK in our observation, the patient maintained an increased prolactin level in postictal period for a long time. According to some authors, the release of this hormone is due to the spread of epileptic activity from temporal lobe to hypothalamic-pituitary axis and is detected in about 60% of PWE with focal seizures. With repeated seizures, there may also be a decrease in the level of postictal prolactin release. This is more common in epileptic status, probably as a result of a decrease in the spread of ictal activity. Prolactin usually does not increase after psychogenic seizures; therefore, the study of postictal prolactin levels can be used for differential diagnosis of ES and psychogenic NES [22]. In addition, in order to exclude NES, neurofilament light chain proteins and glial fibrillar acid protein are considered as potential biomarkers of epilepsy, the content of which in cerebrospinal fluid and blood plasma increases in response to neuroaxonal damage in ES [23].

## CONCLUSION / ЗАКЛЮЧЕНИЕ

Thus, PWE with laboratory CK, myoglobin and dyselectrolythemia deviation in the postictal period require a dynamic assessment of these indicators and correction of disorders.


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## REFERENCES / ЛИТЕРАТУРА


1. McMahon G.M., Zeng X., Waikar S.S. A risk prediction score for kidney failure or mortality in rhabdomyolysis. *JAMA Intern Med.* 2013; 173 (19): 1821–8. https://doi.org/10.1001/jamainternmed.2013.9774.
2. Zimmerman J.L., Shen M.C. Rhabdomyolysis. *Chest.* 2013; 144 (3): 1058–65. https://doi.org/10.1378/chest.12-2016.
3. Bosch X., Poch E., Grau J.M. Rhabdomyolysis and acute kidney

injury. *N Engl J Med.* 2009; 361 (1): 62–72. https://doi.org/10.1056/NEJMra0801327.
4. Alpers J.P., Jones L.K. Jr. Natural history of exertional rhabdomyolysis: a population-based analysis. *Muscle Nerve.* 2010; 42 (4): 487–91. https://doi.org/10.1002/mus.21740.
5. Tong K., Yu G.S. Acute recurrent rhabdomyolysis in a Chinese boy associated with a novel compound heterozygous LPIN1 variant: a case report. *BMC Neurol.* 2021; 21 (1): 42. https://doi.org/10.1186/s12883-021-02050-w.
6. Backer H.C., Busko M., Krause F.G., et al. Exertional rhabdomyolysis and causes of elevation of creatine kinase. *Phys Sportsmed.* 2020; 48 (2): 179–85. https://doi.org/10.1080/00913847.2019.1669410.
7. Nass R.D., Meiling S., Andrié R.P., et al. Laboratory markers of cardiac and metabolic complications after generalized tonic-clonic seizures. *BMC Neurol.* 2017; 17: 187. https://doi.org/10.1186/s12883-017-0965-4.
8. Petejova N., Martinek A. Acute kidney injury due to rhabdomyolysis and renal replacement therapy: a critical review. *Crit Care.* 2014; 18 (3): 224. https://doi.org/10.1186/cc13897.
9. Lee I.H., Ahn D.J. Rhabdomyolysis and acute kidney injury associated with salmonella infection: a report of 2 cases. *Am J Case Rep.* 2022; 23: e936407. https://doi.org/10.12659/AJCR.936407.
10. Horwitz H., Woeien V.A., Petersen L.W., Jimenez-Solem E. Hypokalemia and rhabdomyolysis. *J Pharmacol Pharmacother.* 2015; 6 (2): 98–9. https://doi.org/10.4103/0976-500X.155488.
11. Grifoni E., Fabbri A., Ciuti G., et al. Hypokalemia-induced rhabdomyolysis. *Intern Emerg Med.* 2014; 9 (4): 487–8. https://doi.org/10.1007/s11739-013-1033-8.
12. Jung Y.L., Kang J.Y. Rhabdomyolysis following severe hypokalemia caused by familial hypokalemic periodic paralysis. *World J Clin Cases.* 2017; 5 (2): 56–60. https://doi.org/10.12998/wjcc.v5.i2.56.
13. Khow K.S., Lau S.Y., Li J.Y., Yong T.Y. Asymptomatic elevation of creatine kinase in patients with hyponatremia. *Ren Fail.* 2014; 36 (6): 908–11. https://doi.org/10.3109/0886022X.2014.900600.
14. Chavez L.O., Leon M., Einav S., Varon J. Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice. *Crit Care.* 2016; 20 (1): 135. https://doi.org/10.1186/s13054-016-1314-5.
15. Levey A.S., James M.T. Acute Kidney Injury. *Ann Intern Med.* 2017; 167 (9): ITC66–80. https://doi.org/10.7326/AITC201711070.
16. Barras P., Siclari F., Hugli O., et al. A potential role of hypophosphatemia for diagnosing convulsive seizures: a case-control study. *Epilepsia.* 2019; 60 (8): 1580–5. https://doi.org/10.1111/epi.16090.
17. Wang K., Yang J., Xu W., et al. Characteristics and treatments of patients with significantly elevated creatine kinase levels induced by seizures: case report and literature review. *Clin Case Rep.* 2023; 11 (8): e7788. https://doi.org/10.1002/ccr3.7788.
18. Agus Z.S. Mechanisms and causes of hypomagnesemia. *Curr Opin Nephrol Hypertens.* 2016; 25 (4): 301–7. https://doi.org/10.1097/MNH.0000000000000238.
19. Bragadottir G., Redfors B., Ricksten S.E. Mannitol increases renal blood flow and maintains filtration fraction and oxygenation in postoperative acute kidney injury: a prospective interventional study. *Crit Care.* 2012; 16 (4): R159. https://doi.org/10.1186/cc11480.
20. Brigo F., Igwe S.C., Erro R., et al. Postictal serum creatine kinase for the differential diagnosis of epileptic seizures and psychogenic non-epileptic seizures: a systematic review. *J Neurol.* 2015; 262 (2): 251–7. https://doi.org/10.1007/s00415-014-7369-9.
21. Neufeld M.Y., Treves T.A., Chistik V., Korczyn A.D. Sequential serum creatine kinase determination differentiates vasovagal syncope from generalized tonic-clonic seizures. *Acta Neurol Scand.* 1997; 95 (3): 137–9. https://doi.org/10.1111/j.1600-0404.1997.tb00084.x.
22. Bauer J. Epilepsy and prolactin in adults: a clinical review. *Epilepsy Res.* 1996; 24 (1): 1–7. https://doi.org/10.1016/0920-1211(96)00009-5.
23. Dobson H., Al Maawali S., Malpas C., et al. Elevated plasma neurofilament light and glial fibrillary acidic protein in epilepsy versus nonepileptic seizures and nonepileptic disorders. *Epilepsia.* 2024. https://doi.org/10.1111/epi.18065.

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