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Refractory Status Epilepticus After the Middle Cerebral Artery Aneurysm Clipping (a Case Report)

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ABSTRACT We present the management features for the refractory epileptic status in a patient after surgical treatment of unruptured cerebral aneurysm and no epileptic prehistory. The role of continuous electroencephalographic monitoring in adjusting the rate of drugs administration for general anesthesia in the treatment of this condition is also described.

Keywords: refractory epileptic status, brain aneurysm clipping, continuous EEG monitoring

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BP — blood pressure
CVEM — continuous video encephalographic monitoring
EEG — electroencephallogram
HR — heart rate
VA — valproic acid

INTRODUCTION

Epileptic seizures in the early postoperative period after planned neurosurgical interventions on the brain are not uncommon. According to various authors, their incidence is 8–20% [1–3]. However, the incidence of the extreme form of such attacks, epileptic status, refractory to treatment with first and second line drugs, is low. In the literature, these conditions are mainly presented in the description of a clinical case or a series of cases [4–8]. Authors point out the extremely high resistance of epileptic activity during treatment and the absence of significant neurological effects after treatment.

The frequency of epileptic seizures after open interventions for cerebral aneurysms varies [9, 10]. The role of prophylactic anticonvulsant therapy, given the extracerebral localization of the pathological process, is not defined in this category of patients [11]. The same is about the management of the patient during the development of a refractory epileptic status after the operation [12]. The absence of any specific recommendations significantly complicates the problem and forces specialists to apply general approaches for epilepsy, which effectiveness in patients after surgery without epileptic anamnesis is also not determined.

The purpose of the article is to demonstrate and discuss the features of patient management with refractory epileptic status after surgical treatment of unruptured brain aneurysm.

Clinical case

A 39-year-old female patient K. was admitted to the clinic for the surgical treatment of aneurysmal brain disease. The manifestation of the disease occurred 3 months before admission, when she noted a periodic headache mainly in the occipital region against the background of complete well-being. The spiral computed tomographic angiography revealed saccular aneurysm (6x8x5 mm, neck diameter up to 4 mm) of M2 segment in the left middle cerebral artery. Upon admission to the clinic, the condition was satisfactory, no concomitant somatic pathology was detected, blood pressure (BP) was 120/70 mm Hg, heart rate (HR) was 72 beats per min, height 170 cm, weight 60 kg. No focal and cerebral pathological bioelectric activity was revealed during examination by a neurologist or a 15-minute electroencephalogram (EEG) with stress tests. No anticonvulsants in history. Considering the size and location of the aneurysm, the patient under general combined anesthesia underwent osteoplastic craniotomy in the left front-temporal region, clipping the aneurysm. For induction and intubation of trachea propofol 100 mg, fentanyl 0.2 mg, rocuronium 50 mg were used. Medication sleep was maintained with sevoflurane (MAC 0.8–1), analgesia with Fentanyl intravenous bolus 0. mg every 30 minutes. The duration of preventive temporary clipping of the middle cerebral artery became necessary due to intraoperative the rupture of the cupula of the aneurysm and was 18 min, the aneurysm was put of the bloodstream with

three clips. Retraction of the brain with automatic retractors and spatulas during the operation was not performed. During the entire period of temporary clipping, medical protection of the brain against ischemia was carried out. Few minutes before applying the clip sevoflurane introduction was ceased, bolus intravenous injections of 150 mg of propofol and adjusted the infusion rate of 60 ml/h. At the same time, according to *BIS* monitoring, the appearance of a flash-suppression pattern was observed, which was 50–80% of the analysis. To maintain an average blood pressure above 65 mm Hg during anesthesia and drug protection, we performed microinfusions of norepinephrine at a rate of 0.08–0.14 μg/kg/min.

At the end of the surgical intervention which lasted 190 minutes, selective cerebral angiography was performed. The aneurysm of the left middle cerebral artery was not contrasted. No pathological changes he left carotid system. No vascular zones and cerebral vascular spasm.

Upon admission to the wake-up ward, the patient's condition was considered satisfactory. Ten minutes after admission with the background of residual medical sedation, rhythmic contractions of the muscles of the right neck, mouth, tongue were observed. BP was 110/70 mm Hg without vasoinotropic support, heart rate was 68 beats per min. Hemoglobin oxygen saturation was 99%, exhaled carbon dioxide gas 34 mm Hg with assisted ventilation with FiO_2 0.3 and minute ventilation 5 l/min. The axillary temperature was 36° C. The episode of contraction was regarded as a focal motor epileptic seizure. Intravenously, 50 mg of propofol, 10 mg of diazepam and 500 mg of valproic acid were added. Episodes of focal convulsions repeated twice, during which we additionally introduced 10 mg of diazepam and adjusted infusion of valproic acid at a rate of 100 mg/h. An hour after the last episode, focal epileptic seisure generalized. The infusion of propofol was increased to 300 mg/h, 500 mg of sodium thiopental were injected intravenously. According to the results of urgently performed computed tomography, hemorrhagic complications in the surgical area are absent (figure). In the biochemical (total blood protein, glucose, electrolytes, urea, creatinine, total bilirubin and liver enzymes activity in the blood) and general blood tests there were no deviations from the reference values. In general, the condition was regarded as a series of convulsive seizures and we decided to delay the patient's awakening until the next morning. For medication sleep we continued the introduction of propofol at the rate of 300 mg/h.

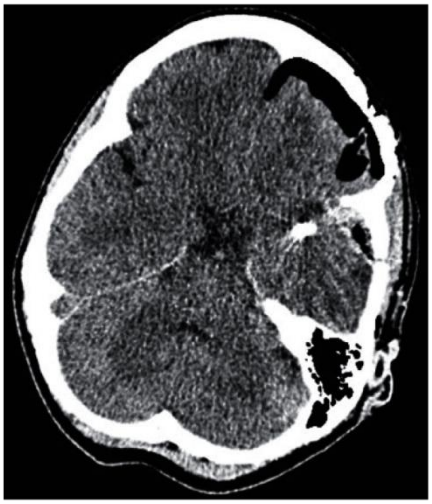

Figure. Computed tomography of the head in the earliest hours after surgery on the background of a series of convulsive seizures

When canceling sedation in the morning on the following day, convulsive contractions of the right face, neck and tongue were again observed. In order to monitor bioelectric activity and select adequate therapy, continuous video electroencephalographic monitoring (CVEEM)was initiated with Encephalan-EEGR-19/26 device by Medicom MTD (Russia) (silver cup electrodes with adhesive paste *Ten* 20), which showed long (more than 30 sec) episodes of rhythmic acute theta-alpha waves with a typical progression of frequency and morphology, mainly in the left paratemporal leads without clinical manifestations. Under the conditions of CVEEM, another attempt was made to awaken the patient. When the infusion of propofol was stopped, the epileptiform bioelectric activity observed earlier changed the morphology and frequency and generalized within a few minutes, which was accompanied by a generalized tonic-clonic seizure, arrested by the administration of propofol 100 mg. It has been suggested that the tactic used earlier (double dose of benzodiazepine, single administration of sodium thiopental, continuous administration of propofol and sodium valproate) may not have led to the relief of brain epileptic activity, which with a high probability persisted overnight in a non-convulsive form. Based on this assumption, the condition was regarded as epileptic status. Given the duration of epistatus more than 12 hours, refractory to the administration of medicines, including the long-term administration of general anesthetic propofol at a dose of 5 mg/kg, it was decided to replace it with sodium thiopental and add levetiracetam (3 g/day to sodium valproate (100 mg/h).

With the introduction of sodium thiopental at a rate of 300 mg/h (5mg/kg/h) with the CVEEM monitoring reached the flash-suppression pattern with suppression periods up to 7–10 sec. At the same time, with a frequency of 1–2 times within 5–10 min after the glash-suppression, epileptiform activity similar to the previously recorded epileptic activity

was observed for a duration from 30 s to 2 min, which underwent changes in frequency and morphology. Within 3 hours, this activity did not show a tendency to decrease in frequency and duration, as a result, despite the EEG effect achieved at the recommended dose in the form of a flash-suppression pattern, we decided to increase the dose of sodium thiopental to 500 mg/h (8mg/kg/h). Within 30 minutes it caused an increase in the duration of the periods of suppression to 15–20 sec without episodes of epileptic activity. The high rate of barbiturate administration led to arterial hypotension, as a result, invasive monitoring of blood pressure and noradrenaline infusion (0.1–0.3 μg/kg/min) were established to maintain mean blood pressure in the range of 65–80 mm Hg.

The following morning, the administration of sodium thiopental was stopped. The total time of the introduction of barbiturate was about 20 hours. Over the next several hours of observation, the EEG pattern of flash-suppression was leveled. The epileptic activity was not observed, as a result, the CVEEM monitoring was stopped. The administration of norepinephrine was rejected 10 hours after the withdrawal of sodium thiopental. Despite all the available preventive measures, non-severe (*Clinical Pulmonary Infection Score* 3) ventilator-associated pneumonia developed in the patient on day 3 after admission to the intensive care unit. The minimum consciousness was restored by day 5 after the cancellation of sodium thiopetal. The recovery from mechanical ventilation took another 3 days. In total, the patient stayed 10 days in the intensive care unit. Then, she was transferred to a specialized department with a recommendation to continue taking oral forms of dual anticonvulsant therapy (valproic acid 1.5 g/day and levetiracetam 1.5 g/day) in a satisfactory condition without neurological disorders, and another 5 days later she was discharged from the hospital.

DISCUSSION

Practically, there are a number of unresolved problems in the management of patients with epileptic seizures after a planned neurosurgical intervention. Without affecting the features of the prophylactic use of anticonvulsants, these problems mainly appear when such a patient enters the wake-up room and episodes of rhythmic muscle contractions appear in different areas of the body. The simplest variant is rare focal attacks without evolution in semiotics and severity. As a rule, anticonvulsants are prescribed to such patients if they did not take them before the operation. Otherwise, the therapy does not undergo any changes at all. For those patients where the frequency, duration and severity of focal seizures are increasing, and without significant morphological, metabolic and infectious causes, according to additional examination methods, the first difficulty arises. There is no certainty in the question: when an epileptic seizure or a series of epileptic seizures in such patients should be considered as epileptic status? The answer depends on the tactics and intensity of treatment in a particular patient. According to the current *operational* definition, the time *t*1 for focal simple and complex seizures should be considered 10 min, for generalized tonic-clonic primary and secondary - 5 min [13, 14]. The probability of an independent termination of an attack beyond this time is negligible. From a practical point of view, it is precisely such a prolonged attack that requires urgent treatment, namely, the prescription of a first-line drug, the parenteral form of benzodiazepine. It is not known how these recommendations are suitable for patients in the immediate postoperative period after brain surgery. It is not clear whether the waiting tactics are justified in such a situation, since studies in this category of patients in this area have not been found in the available literature.

Formally, the postoperative series of epileptic seizures with increasing frequency, with recovery in the interictal period to the initial level does meet the definition of status and does not require urgent treatment. At the same time convulsive phenomena themselves may in theory provoke unfavorable conditions for the healing of an operative wound or even hemorrhagic complications. The latter makes experts fear seizures in the immediate postoperative period and, in some cases, insist on a delayed awakening of the patient. In turn, the drug sedation itself, most often carried out by propofol, with delayed awakening, further complicates the process of interpretation and decision making in the event of the development of convulsive seizures. The clinical observation cited in the article is anexample of such a situation. A series of focal seizures, ending with a generalized seizure, took place in the coming hours after surgery in conditions of deep sedation by propofol (5 mg/kg/h), fractional administration of benzodiazepine and barbiturate, and continuous infusion of the anticonvulsant. The question remains, whether the series of convulsive epileptic seizures against the background of the actual use of the whole recommended spectrum of status therapy (benzodiazepine, anticonvulsant, general anesthesia) should be considered as refractory epileptic status. In addition to the increasing intensity of drug treatment, such an interpretation of the clinical situation would automatically require the patient to be treated under conditions of continuous EEG monitoring, which this patient only underwent on the following day. It is possible that the earlier EEG-oriented treatment could significantly shorten the patient's period in the epikeptic status and reduce the intensity of the treatment.

Currently ongoing status after the introduction of benzodiazepine is considered *established epileptic status* and as a next step it is suggested use intravenous anticonvulsants [15]. Of the latter, valproic acid (VA), levetiracetam and lacosamide are on the domestic market. In the above clinical observation, VA was initially applied, however, departing from recommendations in the instruction for the drug for urgent achievement and maintenance of the required plasma concentrations (15 mg/kg intravenous bolus, then infusion 1 mg/kg/h). It should be noted that in scientific studies, the authors use several options for the introduction of VA, differing both in the total dose of the bolus (from 20 to 40 mg/kg) and in the method of further administration (continuous infusion or periodic boluses) [16, 17]. Also today, the role of plasma concentration of the free and bound fraction of this drug is not clear. Reference values of total VA concentration (40–100 mg/l), determined in patients with epilepsy, are considered effective. At the same time, patients with well-established epileptic status may require higher concentrations due to

the apparently developing resistance to epileptic activity. Unfortunately, in the literature there was not a single study devoted to testing the hypothesis of the need to change the reference interval of plasma concentrations of VA. Probably, the absence of scientifically confirmed data in this matter leads to different approaches to the choice of dosage, method of administration, and, in general, the need to determine plasma concentrations when arresting established epileptic status. We hope that the current *ESETT* study, which has a well-defined goal and design, contains a description of the pharmacokinetic aspects of VA, levetiracetam and phosphoenitoin in established epileptic status [18]. However, there is no doubt that it is necessary to measure the level of anticonvulsants used during the maintenance of the refractory and superrefractive status (usually 24 hours after the start of the administration), to avoid reaching toxic concentrations (150 mg/ml for VA) or to identify an inappropriate amount of the administered drug on the background of polypragmasy and insufficiency of organs and systems common for patients in the intensive care unit. In the described clinical case, unfortunately, there was no technical possibility to determine the concentration of VA and levetiracetam, which limited the certainty of clinical judgments in the course of management of this patient.

Separately, it is necessary to discuss the methods of treatment recommended for refractory status. Currently, the existing recommendations on this topic relate to the level of evidence "the opinion of consensus of experts" [19, 20]. As a result, researchers treat them differently: from using a combination of enteral and parenteral forms of anticonvulsants to applying a combination of general anesthetics with or without the flash-suppression pattern. In the above clinical case, the most vigorous method was ultimately applied — high doses of sodium thiopental (before the appearance of the flash-suppression pattern on the EEG). The appropriateness of thiopental can be criticized by many doctors due to various negative effects on the organs and poor pharmacokinetics during long-term administration. However, propofol, which is preferred according to these characteristics, may cause "propofol infusion syndrome" complication with a high level of mortality [21]. In addition, this drug, unlike recommended Midazolam (benzodiazepine) and sodium thiopental (barbiturate), it does not belong to any of the groups of anticonvulsants. Also, an important role in selecting the drug was played by the fact that there is no epileptic status as an indication for administration in the instructions for use of propofol.

Another important point that should be considered separately is the dosage of the selected general anesthetic. As the presented clinical case convincingly showed, even the prescription of such a drug in the maximum recommended dosages (for sodium thiopental — 3-5 mg/kg/h) with the achievement of the "flash-suppression" pattern did not lead to the relief of relatively frequent non-convulsive focal epileptic seizures recorded only with using the EEG. This fact required to significantly exceed the infusion rate (up to 8 mg/kg/h), while contributing to a rapid decrease in the frequency and, ultimately, the cessation of epiactivity. Thus, a preliminary conclusion can be made that continuous EEG monitoring is an essential part of the treatment of refractory epileptic status .

FINDINGS

1. Despite the formally extracerebral type of most brain aneurysms, the postoperative period after clipping may be accompanied by the development of refractory epileptic status, which may be associated with direct (dissection, traction, coagulation, resection of the cortex) and indirect (focal ischemia, pneumocephaly) operational injury .

2. The recommended dosages of anesthetics for general anesthesia as third-line treatment drugs for refractory epileptic status does not guarantee the relief, even in the absence of external motor manifestations and achieving an electroencephalographic pattern of "flash-suppression".

3. Continuous video electroencephalographic monitoring should be considered an essential component of monitoring in the management of patients with refractory epileptic status as an objective method of control, allowing to evaluate the sufficiency of measures for its relief.

REFERENCES

1. Al-Dorzi H.M., Alruwaita A.A., Marae B.O., et al. Incidence, risk factors and outcomes of seizures occurring after craniotomy for primary brain tumor resection. *Neurosciences (Riyadh)*. 2017; 22(2): 107–113. PMID: 28416781. DOI: 10.17712/nsj.2017.2.20160570.
2. Gokhale S., Khan S.A., Agrawal A., et al. Levetiracetam seizure prophylaxis in craniotomy patients at high risk for postoperative seizures. *Asian J Neurosurg*. 2013; 8(4): 169–173. PMID: 24550999. DOI: 10.4103/1793-5482.125658.
3. Wu A.S., Trinh V.T., Suki D., et al. A prospective randomized trial of perioperative seizure prophylaxis in patients with intraparenchymal brain tumors. *J Neurosurg*. 2013; 118(4): 873–883. PMID: 23394340. DOI: 10.3171/2012.12.JNS111970.
4. Devarajan J., Siyam A.M., Alexopoulos A.V., et al. Non-convulsive status epilepticus in the postanesthesia care unit following meningioma excision. *Can J Anaesth*. 2011; 58(1): 68–73. PMID: 21061109. DOI: 10.1007/s12630-010-9405-2.
5. Al-Mefty O., Wrubel D., Haddad N. Postoperative nonconvulsive encephalopathic status: identification of a syndrome responsible for delayed progressive deterioration of neurological status after skull base surgery. Clinical article. *J Neurosurg*. 2009; 111(5): 1062–1068. PMID: 19326988. DOI: 10.3171/2008.12.JNS08418.
6. Aver'yanov D.A., Lukash A.A., Prokudin M.Yu., et al. Non-convulsive epileptic seizure in patient with delayed awakening after supratentorial tumor removal. *Anesteziologiya i reanimatologiya.* 2016; 61(2): 143–146. PMID: 27468507. DOI: 10.18821/0201-7563-2016-61-2-143-146 (In Russian).
7. Jang J.H., Song K.S., Bang J.S., et al. What Should Be Considered to Cause the Early Post-Craniotomy Seizure: Antibiotics (Cefazolin) Irrigation. *J Korean Neurosurg Soc*. 2015; 58(5): 462–466. PMID: 26713147. DOI: 10.3340/jkns.2015.58.5.462.
8. Sokolova E.Yu., Golovteyev A.L., Savin I.A., et al. Comatose state caused by seizure-free status epilepticus in postoperative period. *Zhurnal Voprosy neyrokhirurgii im NN Burdenko.* 2010; (2): 39–45. PMID: 20825081.
9. Hoh B.L., Nathoo S., Chi Y.Y., et al. Incidence of seizures or epilepsy after clipping or coiling of ruptured and unruptured cerebral aneurysms in the nationwide inpatient sample database: 2002–2007. *Neurosurgery*. 2011; 69(3): 644–650. PMID: 21499155. DOI: 10.1227/NEU.0b013e31821bc46d.

10. Wong J.M., Ziewacz J.E., Ho A.L., et al. Patterns in neurosurgical adverse events: open cerebrovascular neurosurgery. *Neurosurg Focus*. 2012; 33(5): E15. PMID: 23116095. DOI: 10.3171/2012.7.FOCUS12181.
11. Raper D.M., Kokabi N., McGee-Collett M. The efficacy of antiepileptic drug prophylaxis in the prevention of early and late seizures following repair of intracranial aneurysms. *J Clin Neurosci*. 2011; 18(9): 1174–1179. PMID: 21724398. DOI: 10.1016/j.jocn.2010.12.042.
12. Zeiler F.A., Kaufmann A.M., Gillman L.M., et al. Ketamine for medically refractory status epilepticus after elective aneurysm clipping. *Neurocrit Care*. 2013; 19(1): 119–124. PMID: 23702695. DOI: 10.1007/s12028-013-9858-6.
13. Trinka E., Cock H., Hesdorffer D., et al. A definition and classification of status epilepticus-Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia*. 2015; 56(10): 1515–1523. PMID: 26336950. DOI: 10.1111/epi.13121.
14. Dobesberger J., Ristić A.J., Walser G., et al. Duration of focal complex, secondarily generalized tonic-clonic, and primarily generalized tonic-clonic seizures-A video-EEG analysis. Epilepsy Behav. 2015; 49: 111-117. PMID:25935513 DOI: 10.1016/j.yebeh.2015.03.023
15. Trinka E., Kälviäinen R. 25 years of advances in the definition, classification and treatment of status epilepticus. Seizure. 2017; 44: 65–73. PMID: 27890484. DOI: 10.1016/j.seizure.2016.11.001.
16. Grover E.H., Nazzal Y., Hirsch L.J. Treatment of Convulsive Status Epilepticus. *Curr Treat Options Neurol*. 2016; 18(3): 11. PMID: 26920416. DOI: 10.1007/s11940-016-0394-5.
17. Cook A.M., Zafar M.S., Mathias S., et al. Pharmacokinetics and Clinical Utility of Valproic Acid Administered via Continuous Infusion. *CNS Drugs*. 2016; 30(1): 71–77. PMID: 26715390. DOI: 10.1007/s40263-015-0304-5.
18. Cock H.R.; ESETT Group. Established status epilepticus treatment trial (ESETT). *Epilepsia*. 2011; 52 (Suppl 8): 50–52. PMID: 21967363. DOI: 10.1111/j.1528-1167.2011.03237.x.
19. Brophy G.M., Bell R., Claassen J., et al. Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care*. 2012; 17(1): 3–23. PMID: 22528274. DOI: 10.1007/s12028-012-9695-z.
20. Glauser T., Shinnar Sh., Gloss D., et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. *Epilepsy Curr*. 2016; 16(1): 48–61. PMID: 26900382. DOI: 10.5698/1535-7597-16.1.48.
21. Krajčová A., Waldauf P., Anděl M., Duška F. Propofol infusion syndrome: a structured review of experimental studies and 153 published case reports. Crit Care. 2015; 19: 398–407. PMID: 26558513. DOI: 10.1186/s13054-015-1112-5.

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