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EARLY POSTOPERATIVE SEIZURES IN LIVER AND KIDNEY RECIPIENTS

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Background. Transplantation is presently the only treatment for end-stage liver and kidney failure. Up to 42% of liver transplant recipients and up to 30% of kidney transplant recipients have neurological complications from the transplantation. Acute symptomatic seizures (ACS) occupy an important place in the structure of early postoperative neurological complications. Verification of the causes of seizures and management of the risk of relapse is presently a critical task. **Objective:** to review recent advances in ACS assessment, prevalence, and treatment approaches in liver and kidney transplant recipients. **Materials and methods.** The causes of ACS after liver and kidney transplant are diverse. Nonspecific causes of seizures such as dysmetabolic and volemic changes associated with transplantation are widely known. There are also specific syndromes associated with seizures in liver and kidney recipients, such as posterior reversible leukoencephalopathy syndrome, neurotoxicity of calcineurin inhibitors, hyponatremia in the final stage of liver failure, hypocalcemia in kidney recipients, etc. Diagnosis is made based on general rules, and treatment depends on the identified causes of seizures. Management of acute symptomatic seizures involves prescribing anticonvulsants according to the risk of seizure recurrence; immunosuppression is converted when neurotoxicity is identified. **Results.** The diagnostic algorithm, and often the treatment strategies, in ACS cases in liver and kidney recipients, are not clearly defined. **Conclusion.** Due to the multiple causes of ACS, there are differences in treatment tactics. Further accumulation and generalization of ACS outcome data will help in creating a convenient algorithm for rapid identification of the cause and the most effective treatment tactics.

Keywords: acute symptomatic seizures, seizures, liver recipient, kidney recipient, transplantation, neurological complications.

Organ transplantation is the only therapy for terminal and irreversible kidney and liver failure. Modern advances in surgical techniques, immunosuppression, and perioperative care have raised the 1-year survival rate to 90% [1, 2]. However, postoperative complications continue to occur. Neurological complications of orthotopic transplantation account for 9–42% [3].

Acute symptomatic seizures (ASS) rank second among neurological complications in liver or kidney recipients, second only to post-transplant encephalopathy [4], at 9–36% [5]. In survival studies, seizure syndrome still predicts fatal outcomes in solid organ recipients [6, 7]. In this regard, the issue of timely correction of ASS in the postoperative period of transplantation seems extremely relevant.

As defined by the International League Against Epilepsy, ASS are seizures occurring in close temporal relationship with an acute central nervous system insult, which may be toxic, metabolic, infectious, inflammatory, structural, or due to stroke [8]. The essential difference between ASS and seizures in epilepsy is the prognosis. With the situational nature, the risk of recurrent ASS is low, so long-term treatment with anticonvulsants is not required [8, 9].

ASS semiology can be quite varied. In adult recipients, it is usually represented by bilateral tonic-clonic seizures. In childhood, focal seizures are more common [10, 11]. ASS can recur throughout the day, becoming serial, or follow each other without regaining consciousness, which means development of status epilepticus. In patients with impaired consciousness, nonconvulsive status epilepticus recorded using an electroencephalogram is also possible [7].

Common causes of postoperative seizures include the proconvulsive effect of anesthetics [12], cerebral edema, refeeding syndrome [13], dysmetabolic and volemic changes, neurotoxicity of medications [14], anoxia, and structural brain damage. Liver and kidney recipients have additional causes of seizure syndrome.

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The purpose of this review was to describe the features of ASS and approaches to their correction in patients after orthotopic liver and kidney transplantation.

ASS AFTER ORTHOTOPIC LIVER TRANSPLANTATION

Various authors have reported that the incidence of ASS after orthotopic liver transplantation (OLT) is 2.8–42% [4, 7, 10].

The range of causes of this complication in liver recipients in the early postoperative period is extensive and includes dysmetabolic disorders, neurotoxicity of calcineurin inhibitors, structural and infectious brain damage.

Most cases of ASS in the early post-OTP period are associated with immunosuppressants. For example, according to Derle E. et al. (2015), calcineurin inhibitors are responsible for ASS in 34% of cases [4]. Curiously, no correlation between excess immunosuppressors and occurrence of seizures has been found. ASS can develop even with normal blood levels [4]. Occurrence of a seizure syndrome is more common in the first week after OLT [11].

In 1%–10% of liver recipients, ASS is caused by vasogenic posterior cerebral edema [11, 15, 16]. On brain MRI, this is consistent with the picture of posterior reversible encephalopathy syndrome (PRES), also known as reversible posterior leukoencephalopathy syndrome (RPLS). In the pediatric population, this condition is less common than in adults [6, 10]. PRES is associated with direct neurotoxicity of calcineurin inhibitors [15, 17]. The mechanism of neurotoxicity of calcineurin inhibitors is poorly understood. In a study by Dohgu S. et al. (2004), cyclosporine promoted hyperpermeability of the blood-brain barrier by altering endothelial and astrocyte function [18]. Among the clinical manifestations of PRES are cortical blindness, seizure syndrome, depression of consciousness to coma without increased blood pressure.

In addition to calcineurin inhibitors, other drugs used in liver recipients in the postoperative period can also lead to neurotoxicity and ASS. Among them are isoniazid, methylprednisolone in combination with cyclosporine, imipenem, penicillamine, ciprofloxacin, acyclovir, etc [14, 19].

Metabolic causes of ASS (hypoglycemia, hypocalcemia, hypomagnesemia, hyponatremia, hypophosphatemia), according to Derle E. et al. (2015), were noted in 17.4% of cases [3, 4]. In liver recipients, preoperative hyponatremia is associated with end-stage liver failure. Plasma sodium levels below 115–120 mmol/L are associated with ASS [8, 20]. Rapid perioperative correction of hyponatremia can lead to such severe complications as central pontine and extrapontine myelinolysis (CPM and EPM) [21], the manifestations of which are: impaired consciousness, locked person syndrome, ophthalmoparesis, tetraparesis, and bulbar disorders [22]. An important metabolic cause is refeeding syndrome, when the introduction of parenteral or enteral nutrition after fasting is accompanied by hypophosphatemia, hypomagnesemia, hypokalemia, and thiamine deficiency. Clinical manifestations may include focal neurological symptoms, seizures, cerebral edema, and respiratory disorders.

Structural brain damage as a cause of seizure syndrome occurs in 13% of liver recipients [4]. Among them are hemorrhagic and ischemic cerebrovascular diseases (CVDs), brain abscess, and meningoencephalitis. Hemorrhagic or ischemic CVDs, according to Kim B. et al. (2007), occurs in 2–4% of liver recipients [23]. A higher risk of CVDs was noted in adult patients with pre-transplant diabetes mellitus [24].

Among Central nervous system infections, the herpes virus family is particularly relevant among liver recipients. Specifically, herpesvirus 6 can manifest with limbic encephalitis and seizures [25]. Progressive multifocal leukoencephalopathy (PML), a rare fatal demyelinating disease of the central nervous system caused by reactivation of the John Cunningham virus (JCV); it affects patients with pre-existing immunodeficiency [26–28]. The MRI picture may be similar to PRES, but the condition does not improve when immunosuppression dose is reduced or when immunosuppressants are converted, but continues to progress steadily [29].

Another cause of ASS in the early post-OLT period is sepsis. ASS against the background of sepsis occurs in 8.7% of patients [4]. Sepsis-associated encephalopathy is characterized by acute changes in mental status, cognitive functions, altered sleep/wake cycle, disorientation, impaired attention and/or disorganized thinking in the absence of direct evidence of brain infection [30]. Exaggerated motor activity with agitation and/or hallucinations can sometimes be observed, and agitation and drowsiness can occur alternately. Other but less frequent motor symptoms include asterix, tremor, and multifocal myoclonus [31].

The causes of ASS are often not limited to any one thing. A combination of two or more factors occurs in 26.1% of patients [4].

Diagnosis

There is no standard algorithm yet for identifying the causes of ASS in liver transplant recipients, but Shepard P.W. et al. (2012) suggest the following examinations: assessment of acid-base balance, serum electrolyte composition, including phosphorus and magnesium, neuroimaging to rule out circulatory disorders, electroencephalogram, lumbar puncture [32].

Treatment and prevention

Treatment of ASS in patients after OLT largely depends on the cause. So, in the case of neurotoxicity and

development of PRES, reducing the immunosuppression dose and converting the therapy are carried out [7, 17]. Ismail et al. (2017) describe a successful return of tacrolimus after complete restoration of neurological status in patients with tacrolimus-induced PRES [33].

Correction of metabolic disorders completely stops ASS. Slow correction of hyponatremia no faster than 15 mmol/L in 24 hours or 18 mmol/L in 48 hours avoids CPM and EPM [34].

As for anticonvulsants directly, levetiracetam is preferred because this drug does not affect hepatic enzymes, which allows the use of lower doses of immunosuppressants and avoids drug interactions [35]. In general, levetiracetam, gabapentin, pregabalin and lacosamide are the drugs of choice for the treatment of focal seizures in post-transplant patients. They have been shown to be quite effective and well tolerated [32]. Benzodiazepines, fosphenytoin, intravenous forms of levetiracetam, valproic acid, and lacosamide can be used when it is necessary to stop ASS [32]. Unfortunately, fosphenytoin and lorazepam for injection are not registered in the Russian Federation [36], and lacosamide is contraindicated for children under 16 years of age [37].

Chabolla D.R. et al. (2006) recommend anticonvulsant therapy for 1–3 months in patients without structural brain damage [38, 39]. In cases of structural brain damage, Shepard P.W. et al. (2012) use anticonvulsants for a long time [32] .

In order to prevent seizure syndrome, more authors suggest controlling metabolic parameters and the level of immunosuppressive drugs [4, 39]. When seizures occur before OLT, prescription of antiepileptic drugs is required only if there is a history of neurological disease, such as a history of traumatic brain injury or nontraumatic spontaneous intracranial hemorrhage. The Epilepsy Foundation of America suggests that seizures prior to OLT outside of existing epilepsy be considered acute symptomatic within stage 3–4 hepatic encephalopathy [40].

ASS risk factors in liver recipients

Balderramo D. et al. (2011) confirmed the correlation of calcineurin inhibitors neurotoxicity with hepatic failure before OLT, hyponatremia after OLT, OLT surgery time of more than 7 hours [41].

Later, in 2016, Wu S.-Y. et al. identified additional risk factors for neurological complications after OLT, such as hyponatremia, hepatic insufficiency (high MELD values), bacterial infection suffered the week before OLT, nutritional deficiency (BMI below 21.6 kg/m^2), overweight (BMI above 27.6 kg/m^2), renal failure, Child-Pugh class C cirrhosis, recipient age below 29 and over 60 years [42].

Tacrolimus levels above or equal to 8.9 ng/mL within 7 days were identified by Kumar S.S., Mashour G.A., and Picton P. in 2018 as a separate risk factor [3].

The risk of recurrent seizure in case of cerebrovascular disorders, transplant rejection, and sepsis is high, and anticonvulsants are recommended [32].

ASS AFTER ORTHOTOPIC KIDNEY TRANSPLANTATION

According to Sawhney H. et al. (2020), ASS develops in about 30% of kidney recipients in the early postoperative period [43]. The spectrum of causes of ASS includes, as well as in liver recipients, dysmetabolic disorders, drug neurotoxicity, structural and infectious brain damage. In addition, kidney recipients have specific causes of ASS, namely, hypertensive encephalopathy, disequilibrium syndrome and uremia [43].

Some of the most frequent causes of post-kidney transplant seizure syndrome are dysmetabolic disorders. According to Pochineni and Rondon-Berrios (2018), hypophosphatemia, hypomagnesemia, and hypocalcemia are associated with ASS [44]. According to Meena et al. (2020), hyponatremia developing in the first day after kidney transplantation is manifested as ASS [45]. Electrolyte parameters correlating with ASS are presented in Table 1.

Table 1

Barras P. et al. (2019): Critical values of biochemical indicators of ASS [46]

Indicator	Value
Sodium	<115 mmol/L
Ionized calcium	<5.0 mg/dL (<1.2 mmol/L)
Magnesium	<0.8 mg/dL (<0.3 mmol/L)
Phosphate	<2.5 mg/dL (<0.79 mmol/L)
Creatinine	>884 μmol/L

Malignant hypertension in patients with end-stage renal failure, with hemolytic uremic syndrome before and after kidney transplantation are associated with the development of PRES [47, 48]. The clinical picture is similar to tacrolimus-induced PRES, with high blood pressure additionally recorded. In hypertensive crisis, increased blood pressure level causes autoregulation failure of intracranial vascular tone and vasogenic edema of parietal and occipital brain lobes, manifested on MRI as symmetrical increase in MR signal from parietal and occipital areas in FLAIR and T2 modes [49]. On brain CT, these changes are hypodense [50]. Garg R.K. (2001) notes that the seizure syndrome distinguishes PRES from bilateral occipital infarcts [50].

Disequilibrium syndrome is associated with a sharp decrease in blood urea levels amid hemidialysis with fluid redistribution and occurrence of cerebral edema with depressed consciousness and seizures [51]. Bhandari B., Komanduri S. (2021) singles out the following predisposing factors: high urea nitrogen level above 60 mmol/L,

history of neurological diseases, hyponatremia, hemolytic uremic syndrome, and sepsis [51].

Uremic encephalopathy is characterized by decreased levels of consciousness, motor disorders, ataxia, and convulsions. Motor disorders in uremia, represented by tremor, asterixis and myoclonus, can be confused with ASS [52]. The Epilepsy Foundation of America reports that ASS occurs in one-third of patients with uremic encephalopathy [53]. Video-EEG monitoring allows for differential diagnosis, as there is no epileptiform activity in motor disorders [43].

Diagnosis

The diagnostic algorithm is not standardized; the following examinations are used in practice: blood gas, electrolytes, neuroimaging, and electroencephalography [32].

Treatment and prevention

Treatment of ASS in kidney recipients depends on the cause of the attack. Correction of electrolyte disturbances, stabilization of BP levels, dialysis, and use of benzodiazepines quickly stop the seizures. Stabilization of hypertension completely stops vasogenic cerebral edema in hypertensive PRES. Haughey D., Narsipur S.S. (2014) suggest the use of magnesium sulfate in this case [49], and Medeni S.S. et al. (2018) successfully used calcium channel blockers in a patient with atypical hemolytic uremic syndrome and hypertensive PRES. In the case of disequilibrium syndrome, Doorenbos C.J. (2001) suggests using 5 mL of 23% saline or 12.5 mL of intravenous mannitol to increase plasma osmolarity and reduce further osmotic shift, but this opinion is based on limited data [54]. Mistry K. (2019) recommends increasing dialysis time, reducing urea by 40% within 2 hours at the start of dialysis [55].

Chabolla D.R. et al. in 2006 developed a first aid protocol for ASS in kidney recipients, and in 2020 the protocol was slightly revised by Sawhney H. (2020) [43]. It is presented in Table 2.

Among anticonvulsant therapies, valproic acid is the drug of choice in kidney recipients. It should be noted that the drug is an inhibitor of liver enzymes and can alter the concentrations of immunosuppressants [43].

Valproic acid has several advantages over other anticonvulsants with respect to lever recipients: kidneys are not involved in its metabolism, dose adjustment is not needed depending on glomerular filtration rate (GFR), an additional dose is only required after high-flux hemodialysis, is effective for almost all types of seizures, can be administered intravenously, and can be used in children.

Levetiracetam can be used for ASS in kidney recipients because of its rapid anticonvulsant effect when administered intravenously. However, this drug requires dose adjustment depending on GFR and on the background of hemodialysis. Dose adjustments for anticonvulsants based on GFR are shown in Table 3.

Risk factors of ASS in kidney recipients

Due to the fact that ASS are one of the threatening early post-kidney transplant complications, the search for predictors of their development is of undoubted interest. It is assumed that preoperative EEG data may serve as one of the candidates for the role of a predictor. EEG changes in uremia were detected in 70% of cases and were represented by bifrontal slow-wave activity and 2-sided spike-and-wave activity of 3–6 Hz [56], which

Table 2

Practical approach to the management of bilateral tonic-clonic seizure in a kidney recipient (Chabolla D.R. et al., 2006 [39], modified by Sawhney H., 2020 [43])

<table>
<tr><td colspan="2">Acute onset of generalized tonic-clonic seizure</td></tr>
<tr><td colspan="2">Airway patency assessment, RR, HR</td></tr>
<tr><td colspan="2">Benzodiazepines</td></tr>
<tr><td>Seizure stopped</td><td rowspan="5">Continuous seizure or recurrent seizures without regaining consciousness – follow the epileptic status protocol</td></tr>
<tr><td>Eliminate or correct identified provocative factors</td></tr>
<tr><td>Neurological examination, EEG, brain MRI</td></tr>
<tr><td>If examination reveals no pathology, follow-up without antiepileptic therapy</td></tr>
<tr><td>If the examination reveals a pathology (EEG-epileptic activity or MR-structural lesion) or a spontaneous recurrent seizure occurs during follow-up without antiepileptic therapy – start anticonvulsant therapy</td></tr>
</table>

Table 3

Anticonvulsant doses depending on GFR [43]

GFR (mL/min)	60–90	30–60	15–30	<15	Hemodialysis
Levetiracetam	500–1000 mg twice/day	250–750 mg twice/day	250–500 mg twice/day	500–1000 mg once/day	Additional dose of 250–500 mg after dialysis
Valproic acid	No correction	No correction	No correction	No correction	Correction required for high-flux dialysis

is regarded as part of the existing encephalopathy. The representation of slow rhythms and specific EEG patterns correlates with the stage of CKD and may be a tool for recognizing subclinical uremic encephalopathy [57]. EEG changes are thought to be associated with high urea and chloride levels and low calcium levels [58]. However, EEG findings in studies have not been a reliable predictor of post kidney-transplant seizures but have correlated with developmental abnormalities [58]. Whereas postoperative EEG can be useful in diagnosing and determining treatment strategies when determining the cause of coma: nonconvulsive status epilepticus or encephalopathy, as well as in making differential diagnosis of epileptic and non-epileptic seizures [32]. According to the Lorie DH (2008) single-center study, pre-kidney transplant ASS did not predict pre-transplant recurrent seizure [58].

Since epileptic seizures can be triggered by fluctuations in blood sodium, calcium, magnesium and glucose, regardless of the underlying disease, these indicators may well be considered as predictors. Accordingly, Nardone R. et al. (2016) suggests that routine monitoring of blood electrolyte levels in case of dysmetabolic seizures is crucial for seizure control and prevents irreversible brain damage in patients [59].

Thus, the causes of acute symptomatic seizures developing in children after orthotopic liver and kidney transplantation are very diverse. Approaches to the correction of ASS and assessment of their prognostic significance largely depend on pathogenetic mechanisms. Most of the cases of this early-postoperative complication can be attributed to potentially manageable conditions. At the same time, as it was found out from the analyzed literature, there is currently no standardized diagnostic tactics for ASS. Accordingly, developing such a diagnostic tactic seems very relevant, as it can help to reduce the time for establishing a diagnosis and making decisions on treatment interventions.

The authors declare no conflict of interest.

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