Seizure: European Journal of Epilepsy 61 (2018) 177–185

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure

Review

Seizures after transplantation

Peijia Lin[a], Xin Tian[a], Xuefeng Wang[a,b,*]

[a] Department of Neurology, Chongqing Key Laboratory of Neurology, The First Affiliated Hospital of Chongqing Medical University, No.1 Youyi Road, Chongqing 400016, China

[b] Center of Epilepsy, Beijing Institute for Brain Disorders, Beijing 100871, China

ARTICLE INFO

Keywords:
Seizure
Transplantation
Epilepsy
Immunosuppressant
Clinical character
Treatment

ABSTRACT

Purpose: To summarize information on the history, incidence, clinical manifestation, best treatment, as well as prognosis of seizures in transplant recipients.

Methods: In October 2017, we searched the literature on PubMed in English with the search terms: "transplantation" AND "seizure", "transplantation" AND "epilepsy", "transplantation"AND "status epilepticus", "immunosuppressant" AND "seizure", "immunosuppressant" AND "epilepsy". Publications not based on new data and original research were not included in this article.

Results: Seizures including generalized seizures, focal seizures and status epilepticus are a common central nervous system complication after transplantation. The incidence of seizures varied between different kinds of transplantations. The reported incidence of seizures was 7%–27% in association with solid organ transplantations and 1.6%–15.4% with hematopoietic stem cell transplantation. Most of seizures appeared in the early post-transplantation period. Patients often had a favorable prognosis, however, in some conditions, recurrent or intractable seizures may occur.

Conclusions: The underlying pathogenesis of new-onset seizures or epilepsy in recipients of transplantation needs to be further elucidated. In addition, more information is required from prospective studies and research focusing on therapeutic strategies.

1. Introduction

With the development of medical technology, transplantation has prevailed and become an important tool in the treatment of disease. According to the WHO's statistics, as of 2015, approximately 120,000 cases of solid organ transplantation have been performed globally. Renal transplantation is the most common, followed by liver transplantation, heart transplantation, lung transplantation, hematopoietic stem cell transplantation, etc. [1]. And, in recipients of transplantation, seizures usually occur during the postoperative period [2,3].

2. History

In 1965, Tyler et al. [4] found that some patients experience seizures after transplantation and thought they might be caused by electrolyte abnormalities. In 1982, Gross et al. [5] put forward the concept of rejection encephalopathy, noting that, in recipients of transplantation, convulsions, changes in mental status and focal neurological signs may be related to the use of cyclosporine A(CsA), hormone therapy, high blood pressure or organ rejection. In 1989, Estol et al. [6] found that most patients who experienced seizures after liver transplantation had brain lesions, such as hemorrhagic stroke, central pontine myelinolysis, etc.

3. Incidence

Approximately 30–60% of patients who have received hematopoietic stem cell transplantations or solid organ transplantations have central nervous system complications [7]. Senzolo et al. [3] found that the incidence of seizures is approximately 2–24% in recipients of solid organ transplants. In addition, in a study by Zivkovi et al. [8], the incidence of seizures in recipients of solid organ transplants was found to be approximately 7–27% and approximately 5–7% in recipients of hematopoietic stem cell transplants.

Abbreviations: AEDs, antiepileptic drugs; CNIs, calcineurin inhibitors; CsA, cyclosporine A; GABA, gamma aminobutyric acid; GTCS, generalized tonic-clonic seizure; MRI, magnetic resonance imaging; NAA, *N*-acetylaspartate; PRES, reversible posterior encephalopathy; SE, status epilepticus; FK506, tacrolimus

* Corresponding author at: Department of Neurology, Chongqing Key Laboratory of Neurology, The First Affiliated Hospital of Chongqing Medical University, No.1 Youyi Road, Chongqing 400016, China.

E-mail addresses: linpeijia123@163.com (P. Lin), 649820863@qq.com (X. Tian), xfyp@163.com (X. Wang).

https://doi.org/10.1016/j.seizure.2018.08.010
Received 11 February 2018; Received in revised form 9 August 2018; Accepted 11 August 2018
1059-1311/ © 2018 British Epilepsy Association. Published by Elsevier Ltd. All rights reserved.

4. Seizure type

Currently, there are hardly any prospective studies that have investigated seizure types in recipients of transplantation. Both focal seizure and generalized seizure have been reported, and generalized tonic-clonic seizure (GTCS) is common. Status epilepticus (SE) is relatively rare and is more common in pediatric patients [3,9–11].The terminology of seizures in this text is in accordance with Classification of International League Against Epilepsy [12,13].

4.1. Generalized seizure

Generalized seizure is common, particularly in drug-related seizure [10,14,15]. Seizures that are related to calcineurin inhibitors (CNIs, such CsA) are usually generalized seizures, especially GTCSs, and there are always mental and behavioral abnormalities before their onset [10,14]. Sevmis et al. [10] conducted a retrospective study and found that out of approximately 130 patients who had used tacrolimus (FK506) after liver transplantation, 12 of them experienced postoperative seizures, all of which were characterized as generalized seizures, and the seizures stopped after the replacement of immunosuppressive agents. Additionally, Caselli et al. [15] found that in recipients of hematopoietic stem cell transplantation, generalized seizures are often related to the use of busulfan.

4.2. Focal seizure

It is usually associated with focal, structural abnormalities such as meningitis, intracranial hemorrhage, encephalitis, brain abscess, and so on [2]. Some scholars believe that the mechanism of the first seizure after transplantation often may be due to focal onset [16]. Navarro et al. [11] observed focal onset in five of eight recipients of transplantation who had shown postoperative seizures, which included focal impaired awareness seizure, limb tic, visual impairment, etc. Loar et al. [17] reported a case of a heart transplant patient who showed focal impaired awareness seizure on the tenth day after the survey and then developed to bilateral tonic–clonic seizure, which may have been related to the use of FK506.

5. Etiology and risk factors

5.1. Immunosuppressive agents

The use of immunosuppressive agents (such as CNIs) is a common risk factor for seizures. The incidence of FK506-related seizures is approximately 5–11% [18,19]. McDiarmid et al. [20] conducted a study of patients using FK506 or CsA after transplantation and found that seizures were only observed in the patients who were using FK506. However, in the studies by Freise et al. [21] and Lewis et al. [22], an analogous phenomenon was rarely observed.

Studies found that CsA can inhibit the concentration of GABA, the activity of GABAergic neuron and binding property of the GABA receptor, while this kind of damage of GABAergic transmission plays an important role in increasing the susceptibility of seizure [23–25]. In addition, it has been reported that the side effects of CsA may be related to the decrease of the concentration of *N*-acetylaspartate (NAA), and the decrease of NAA may increase the frequency of seizure [23,26]. CNIs-induced seizures may also be related to increased neuronal excitability, brain lesion, genetic polymorphisms and some other factors [27–31]. There are more details in Table 1. However, Jung et al. [32] and Setkowicz et al. [33] found that CsA and FK506 can reduce seizures in animal model. Therefore, the function of CNIs in the nervous system remains to be further studied.

Table 1
The potential mechanism of CNIs-induced seizure.

Immunesuppressant	The type of transplantation	The type of study	Dosage	Result	Reference
CsA, SRL and RAD	N/A	Vitro study	CsA (500 μg/L), SRL (100 μg/L), RAD (100 μg/L)	CsA inhibit the metabolism of Krebs cycle. SRL and RAD suppress cytosolic glycolysis.	Klawitter et al. [23]
CsA	N/A	Vitro study	500 mg/kg	CsA inhibit activity of GABAergic neurons and binding property of the GABA receptor	Shuto et al. [24]
CsA and FK506	HSCT	Genotyping of patients	N/A	Gene polymorphisms of CYP3A5 or ABCB1	Yanagimachi et al. [27]
FK506 and Rapamycin	N/A	Vitro study	FK506 (10, 50, 100 nmol/L), Rapamycin (1, 10, 50, 100, 250, 500, 1000, 2000 nmol/L)	FK506 elicit epileptiform burst discharges and increased the amplitude of field excitatory post-synaptic potentials, while rapamycin can hardly exert the same influence.	Daoud et al. [28]
CsA	N/A	Vitro study	1,000–10,000 ng/ml	CsA can exert a direct effect on the excitability of neuron and the transmission of synapse	Wong et al. [29]
CsA	HSCT	Clinical imaging study	initial dosage is 2 to 3 mg/kg/d	CsA may induce brain lesions	Trullemans et al. [30]
CsA	N/A	Animal study	200 mg/kg	CsA stimulate the production of NO. Seizure is induced by the interaction between the GABA and NO	Fujisaki et al. [31]

Abbreviations: CsA: cyclosporine A; GABA: gamma aminobutyric acid; HSCT: hematopoietic stem cell transplantation; FK506: tacrolimus; N/A: not applicable: NO: Nitric oxide; RAD: everolimus; SRL: sirolimus.

5.2. Metabolic disorders

In recipients of transplantation, seizures may also be induced by electrolyte disorders (such as hyponatremia, hypomagnesemia, hypokalemia, etc.) or changes in blood glucose levels. Hyponatremia may cause seizures by causing brain edema, and the pathogenesis of seizures in patients with hypoglycemia may be related to hypoxia of the brain [34,35]. Studies have found that the type of metabolic disorders that can induce seizures may be different for different patients [16,36]. Drake et al. [37] and Wells et al. [38] found that seizures may be related to low blood glucose or to a drop in blood osmotic pressure and serum sodium but that hypomagnesemia or hypocalcemia may not increase the risk of developing seizures in renal transplant recipients. In addition, the literature reported that the etiology for most seizures involves hyponatremia combined with hypokalemia in recipients of hematopoietic stem cell transplantation [39].

5.3. Infection

Listeria aspergillus, Cryptococcus neoformans and aspergillus fumigatus are the main pathogens causing central nervous system infections [40]. Central nervous system infections, particularly viral or fungal infections, can cause brain damage and induce seizures [39,41–43]. In addition, seizures may also be related to the inflammatory response, and there is literature reported that IL-1beta can break the balance between glutamate and GABA [44]. Zhang et al. [39] found that 17% of seizures are associated with infection in recipients of bone marrow transplantation and that the most common pathogen is fungi, followed by viruses, bacteria and toxoplasma. The risk of bacterial meningitis is higher in recipients of solid organ transplantations [43]. Meanwhile, recipients of bone marrow transplantation are prone to opportunistic pathogen infection because the recovery of postoperative hematopoietic function and immune function take some time [42].

5.4. Cerebrovascular disease

Cerebrovascular accidents, such as stroke, cerebral hemorrhage, subdural hematoma, etc., are common neurological complications, in the early stage of post-operation (usually referring to 30 days after transplantation) and may induce seizures [45]. In the early stage of stroke, seizures are associated with the release of massive glutamate and focal metabolic imbalance, whereas, in the late stage of stroke, seizures may be caused by scar formation and gliosis [46]. And it is reported that, in patients with subdural hematomas, seizures may be related with the production of hemosiderin [35].In adult recipients of heart transplantation, cerebrovascular accidents are the major cause of seizures. Because, if these patients have diseases such as diabetes, hypertension and atherosclerosis, their risk of stroke may be increased [47]. Zhang et al. [48] found that intracranial hemorrhage is the most common neurological complication in recipients of allogeneic hematopoietic stem cell transplantation and that seizure may be the first symptom in most of these patients.

6. Seizures after different types of transplantations

6.1. Seizures after liver transplantation

6.1.1. Etiology and risk factors

Seizures after liver transplantation may mostly be related to neurotoxicity caused by CsA or FK506, especially in the early stages [36]. Intracranial hemorrhage is relatively rare, but considering that recipients of liver transplantation may have a risk of bleeding when they show recurrent GTCSs, the possibility of intracranial hemorrhage should be taken into account [49].

6.1.2. Clinical manifestations

6.1.2.1. Incidence. The incidence of seizures after liver transplantation varies from each study and is generally observed to be 1–42% [45,50,51]. Compared with the recipients of cadaveric donor liver transplantation, the incidence of seizures is significantly lower in recipients of living donor liver transplantation [18,52]. Saner et al. [18] found that, of 170 patients who had been transferred to an intensive care unit after liver transplantation, about a quarter of the recipients of cadaveric donor transplantation showed postoperative seizures, while only one fifth of the recipients of living donor transplantation exhibited seizures after the survey, which may be related to the fact that organs of living donors experience short times of ischemia and are of good quality. In recent years, there has been a decreasing trend in the incidence of this type of seizure, which may be due to timely postoperative managements that include correcting metabolic disorders, dealing with poisoning and using immunosuppressive agents with fewer side effects [52].

6.1.2.2. Seizure type. Generalized seizures are common, particularly GTCSs [51,53,54]. Derle et al. [53] conducted a survey of 176 patients who had received liver transplants between 1955 and 2013 and found that approximately 6% of the adult patients had seizures. Only two of the patients showed SE or focal awareness impaired seizure, and the others were characterized as GTCSs. Xie et al. [54] conducted a single-center retrospective study and found that of 27 pediatric recipients of liver transplantation, four patients showed seizures in the first two weeks after transplantation, and the seizures were all characterized as GTCSs. However, Kılıç et al. [55] collected statistics from 28 pediatric patients and found that focal seizures were more common than generalized seizures.

6.1.2.3. Onset time and course of disease. Wszolek et al. [51] found that there are two peaks of seizure occurrence after transplantation, namely, the first week and the fifth to sixteenth weeks after surgery. Adult patients usually experience seizures in the early postoperative period [51,53–56]. Xie et al. [54] found that pediatric patients often show seizures within the first two weeks after liver transplantation; this idea was supported by Kılıç et al. [55]. Moreover, Ghosh et al. [56] analyzed the data of 65 pediatric recipients of liver transplantation and found that most seizures occur within three months after transplantation. These seizures in the recipients of liver transplantation are usually self-limited, and very few of these patients will develop intractable epilepsy [56].

6.1.3. Antiepileptic treatment

In patients who experience seizures after liver transplantation, antiepileptic drugs (AEDs), which have lower hepatotoxicity and fewer drug interactions, are the most ideal treatment. AEDs such as phenobarbital or carbamazepine, which are metabolized through hepatic enzymes, should be avoided because they may reduce both the blood concentration and function of immunosuppressive agents [57]. Currently, levetiracetam, which is metabolized through the kidneys, is probably the more suitable drug [55,58,59]. Lin et al. [58] reported that levetiracetam was used to control seizures at a starting dose of 250–2000 mg in 15 patients who experienced seizures after liver transplantation, and during the period of maintenance, the dosage was 500–2500 mg/day. None of the patients had a seizure during the treatment. In following these patients, it was discovered that two of them had died, though their deaths had nothing to do with the drug, and that the rest of the patients remained seizure-free. In pediatric patients, levetiracetam (15–60 mg/kg/day) may also be effective, and a study found that 89% of children reached a seizure-free state after using this drug [59].

Lennox–Gastaut syndrome, which is a type of epileptic encephalopathy, may occur in recipients of liver transplantation. Velizarova et al. [60] reported of a patient that experienced epilepsy after liver

transplantation that was characterized by increasingly frequent GTCSs, atypical absences and tonic seizures. Approximately 20 years later, tonic seizures appeared, and an electroencephalogram showed slow background activity, multiple slow spike waves, and poly-spike waves. Therefore, this patient was diagnosed with Lennox–Gastaut syndrome. Valproic acid was used at an initial dosage of 100 mg/week through venous titration. During the treatment, the valproic acid was gradually increased to 1000 mg/day, and applications of topiramate (175 mg/day), lamotrigine (125 mg/day), and phenobarbital (100 mg/day) were started. Consequently, the seizures were partly controlled in this patient. In addition, after reducing the phenobarbital to 50 mg/day and increasing the valproic acid to 1500 mg/day, the GTCSs finally stopped, and the patient only experienced a small number of tonic seizures. Valproic acid is the first-line drug for the treatment of Lennox–Gastaut syndrome, and this study suggested that valproic acid could be safely used in patients who experience seizures after liver transplantations if we monitor liver function strictly, although it may have potential hepatotoxicity [60].

6.2. Seizures after kidney transplantation

6.2.1. Etiology and risk factors

In pediatric recipients of living donor kidney transplantation, polyuria may appear, leading to hyponatremia and induced seizures [37,61]. Other than the common risk factors, Bezinover et al. [62] reported a relatively rare case in which a recipient of kidney transplantation experienced hyperammonemia and seizures due to a deficiency in the urea cycle. Tumors can also induce seizures. There is literature reporting that four years after kidney transplantation, a patient showed postoperative seizures, which may have been related to primary brain T-cell lymphoma [63]. Currently, some scholars think that a preoperative history of seizures is also a risk factor for postoperative seizures, but there is also a study suggesting that a preoperative history of seizures may not increase the risk of seizures after kidney transplantation [64,65].

6.2.2. Clinical manifestations

6.2.2.1. Incidence. Yardimci et al. [66] analyzed approximately 130 adult recipients of kidney transplantation and found that there were three recipients who experienced postoperative seizures, resulting in the incidence of seizures being approximately 2.2%. However, in children, the highest incidence was 20.1% [67]. Also, there is literature that has reported no pediatric patient presenting with seizure after kidney transplantation, which may have been related to preoperative and postoperative management [65].

6.2.2.2. Seizure type. The type of seizure experienced after kidney transplantation may be either generalized seizure or focal seizure. The most reported type is generalized seizure, especially GTCS [37,68–71], while the focal seizure type is relatively rare [63]. Drake et al. [37] reported that three recipients of kidney transplantation experienced post-operative generalized seizures, and two of the them being classified as well-defined GTCS. In addition, Ertilav et al. [69] reported that a 25-year-old male patient, who began to show nausea, vomiting, muscle pain and GTCSs after renal transplantation, was considered to have developed an infection of West Nile virus. Additionally, the literature of Da Costa et al. [68] described a patient who had received cadaveric donor kidney transplantation due to end-stage renal disease, and 15 years after the surgery, this patient was admitted to the hospital because of a GTCS.

6.2.2.3. Onset time and course of disease. There is literature that has reported that seizures can appear in the first 24 h after renal transplantation and that they may be related to changes in plasma osmotic pressure and to the decline of serum sodium (more than 15 mmol/l) [14,37]. After transplantation, seizures are common between the first day and the 30th day [66,69,71]. Also, there are some patients who experienced seizures many years after transplantation [68,72].

6.2.3. Antiepileptic treatment

Hillebrand et al. [73] supported that valproic acid is the first-line drug for treating patients who show seizures after kidney transplantation, but more relevant clinical evidence is needed. Now, there are rarely any studies that have investigated what kind of antiepileptic therapy is optimal. A case report mentioned that a drug combination of lamotrigine, clonazepam and levetiracetam can effectively control seizures in a recipient of kidney transplantation [71].

6.3. Seizures after heart transplantation

6.3.1. Etiology and risk factors

In recipients of heart transplantation, early post-transplant seizures are the most relevant to cortex stroke and reversible posterior encephalopathy(PRES) caused by immunosuppressants. Other than the common factors, tumor, a history of preoperative seizures, diabetes, kidney dysfunction, etc. can also induce seizures [8,11,74–76]. The interaction of non-immunosuppressant drugs is a relatively rare etiology of seizures after heart transplantation. Urbanowicz et al. [77] reported that after using metoclopramide and overdosed theophylline, two recipients of heart transplantation experienced seizures on the seventh and 15th post-operative days, respectively. After transplantation, hypoxic encephalopathy caused by cardiac arrest can also induce seizures, which is characterized by generalized myoclonic seizures in pediatric patients and by SE in adult patients [47].

6.3.2. Clinical manifestations

6.3.2.1. Incidence. The incidence of seizures after heart transplantation is approximately 2–20% [11,47,75,77]. Van et al. [74] conducted a survey of over 313 patients who had received heart transplant surgeries at the Mayo Clinic between 1988 and 2006 and found that approximately 2.5% of patients experienced postoperative seizures. In a retrospective study by Ocal et al. [47], the incidence of seizures after heart transplantation was approximately 11.9%.

6.3.2.2. Seizure type. The type that has been reported the most is GTCS [11,47,64]. Navarro et al. [11] performed a study of 166 patients who had received heart transplantation and found that 5% of the patients experienced post-operative seizures (there were three patients who had a history of preoperative epilepsy), except for one patient who had experienced visual hallucinations and disturbance of consciousness; the others were characterized by GTCSs. Ocal et al. [47] analyzed recipients of heart transplantation between 2004 and 2016 at their institute, and it was found that the seizures appeared in five pediatric patients and eight adult patients. In this study, GTCS and generalized myoclonic seizure were the most common in the pediatric patients, while in the adult patients, the GTCS was the most common and the generalized myoclonic seizure was second.

6.3.2.3. Onset time and course of disease. Most seizures appear during the first month after surgery [11]. SE and generalized myoclonic seizures are usually the early manifestations post operation (approximately two months after transplantation), and GTCSs and focal motor seizures are common in the advanced stages (approximately six months after transplantation) [47].

6.3.3. Antiepileptic treatment

There is no unified view regarding the first-line drugs for treating seizures after heart transplantation. In a study by Ocal et al. [47], levetiracetam was found to be able to control 80% of seizures in pediatric patients and parts of seizures in adult patients, and levetiracetam combined with phenytoin sodium was able to control SE. Moreover,

Urbanowicz et al. [77] reported that using gabapentin and valproic acid can control seizures after heart transplantation. In addition, there was a retrospective study that found that 1–3 mg/day of clonazepam can also control seizures in recipients of heart transplantation [11]. Patients with a history of epilepsy can consider the prophylactic use of AEDs [64].

6.4. Seizures after hematopoietic stem cell transplantation

6.4.1. Etiology and risk factors

Zhang et al. [39] conducted a retrospective study of over 1400 recipients of hematopoietic stem cell transplantation and found that 7% of the patients experienced postoperative seizures, while 40% of the seizures were associated with drug application (such as the imipenem, immunosuppressants, etc.); moreover, if the dose of these drugs was increased or stopped, the risk of seizures would increase. In addition, preoperative chemotherapy or radiotherapy, metabolic encephalopathy, etc. are also the reasons why patients show seizures after hematopoietic stem cell transplantation [39].

6.4.2. Clinical manifestations

6.4.2.1. Incidence. The incidence of seizures in recipients of hematopoietic stem cell transplantation is approximately 1.6–15.4% [39,41,78,79]. Of the patients who are infected with human herpes virus 6 after transplantation, 40–70% experience seizures [80–82], and half of patients who suffer from CNI poisoning have post-operative seizures [83]. Zhong et al. [41] found that recipients of unrelated hematopoietic stem cell transplantation have a higher incidence of seizures than recipients of related hematopoietic stem cell transplantation.

6.4.2.2. Seizure type. In a study by Zhang et al. [39], generalized seizures were found to be the most common (approximately 65%), followed by focal impaired awareness seizures and focal aware seizures. Gaggero et al. [79] conducted an investigation of more than 180 pediatric patients who used CsA after transplantation and found that there were 15 children who had experienced seizures. In this study, generalized seizures and focal seizures each accounted for 46%. The first seizure after transplantation is usually characterized by focal non-convulsive seizure, such as visual hallucination, strabismus, etc., especially in seizures secondary to the PRES [9].

6.4.2.3. Onset time and course of disease. Zhong et al. [41] found in 159 recipients of hematopoietic stem cell transplantation that eight of them had seizures, and these seizures appeared between 29 and 760 days after surgery. Most seizures occur within 0–100 days after transplantation, and about a quarter of them occur within 100 days–1 year; only a small number of them appear after the first year [39]. Half of the patients only experience a single seizure, and recurrent seizures usually reoccur one week after the first onset [9]. In addition, seizures secondary to PRES are often longer than the other types [9].

6.4.3. Anti-epileptic treatment

Masetti et al. [84] recommended that benzodiazepines (such as diazepam) or midazolam as first-line AEDs in patients who show seizures after hematopoietic stem cell transplantation, and phenobarbital, phenytoin sodium or anesthetics that have anticonvulsive effects can be used in patients who experience intractable epilepsy after transplantation. Similarly, Cordelli et al. [9] recommended the use of benzodiazepines as the first line of therapy in children, and using propofol in patients with refractory SE. A study reported that patients experience secondary transplantation failure after using levetiracetam, and this failure may be related to myelodysplastic syndrome induced by levetiracetam [85]. In the future, there should be more studies that aim to confirm the safety of recipients of hematopoietic stem cell transplantation using levetiracetam, and we should use AEDs that have fewer effects on bone marrow.

Some studies have found that patients who use busulfan as a pretreatment before transplantation are prone to have seizures, especially in pediatric patients. Therefore, in these patients, prophylactic use of AEDs is recommended [15].

7. Auxiliary examinations

7.1. Laboratory examinations

When seizures occur in recipients of transplantation, blood glucose levels, electrolytes, drug concentration of immunosuppressive agents, etc. should be tested to find the causes of the seizure. When a patient has signs of infection or meningism, cerebrospinal fluid examination, as well as blood and urine cultures, should be done to determine whether there is a central nervous system infection [16]. In the early stages of infection, changes in cerebrospinal fluid may not be obvious, so cerebrospinal fluid should be examined many times in the course of the disease, and PCR technology can be used to find the pathogen of infection [78].

7.2. Imaging examinations

The computed tomography and magnetic resonance imaging (MRI) techniques can be used to analyze abnormal clinical manifestations and to determine etiology [11,86]. In general, MRI is the preferred method [86]. It has been suggested that, during MRI examinations, if a white matter enhancement appears on both sides of the brain on T2 scans, especially in parietal-occipital regions, it may indicate neurotoxicity by CsA [30]; if the peripheral system has a high signal, this may be related to human herpes virus type 6 infection [78]. Navarro et al. [11] found that, in patients who experience seizures after heart transplantation, approximately 50% of their MRI scans indicate lesions on both sides of the brain. These lesions are seen in high densities on FLAIR imaging and keep the same intensity in diffusion weighted imaging.

7.3. Electroencephalogram

The electroencephalogram (EEG) can help to define the characteristics of seizures and to exclude non-epileptic seizures (such as myoclonus). When a patient is in a coma, EEG can help to identify whether the coma is caused by encephalopathy or non-convulsive SE [14,16]. Preoperative EEG is hardly effective in predicting postoperative seizures, but postoperative EEG monitoring is helpful for diagnosis and treatment [9,65]. In patients with SE, if the epileptiform activity is concentrated in the posterior part of the brain, it is necessary to consider PRES [87].

8. Diagnosis

First, we should be clear about whether there is a seizure by analyzing the clinical manifestations of patients and the results of EEG. Second, the corresponding neurological, laboratory and imaging examinations should be done as soon as possible to find the causes and risk factors of the seizure [9,16]. Finally, the relationship between the seizure and the potential causes should be determined according to the incidence, onset time, the type of seizure, the effect of treatment and so on. When a patient is in a coma, it is necessary to consider the possibility of non-convulsive SE; in this case, EEG can help to make a clear diagnosis [14].

9. Treatment

9.1. Treatment according the etiology or inducement

If patients experience seizures after transplantation, therapies

Table 2
Possible treatment strategy of CNIs-induced seizure.

Treatment strategy	The type of study	Outcome	Reference
Replace of lower dosage of the FK506	Retrospective study	Reach seizure-free	Xie et al. [54]
Supply 20% soybean oil (0.1–0.2 ml/kg/h for 2–3days)	Prospective study	Neurological symptoms alleviated	Ide et al. [91]
Convert FK506 to everolimus	Retrospective study	Neurological symptoms alleviated or resolved	Bilbao et al. [90]
Combine CsA with N-(3', 4'-dimethoxycinnamoyl)anthranilic acid	Animal study	Lower side effect of CsA	Yong et al. [92]

Abbreviations: CsA: cyclosporine A; FK506: tacrolimus.

should be implemented according to the corresponding etiologies or inducements, such as maintaining the balance of electrolytes and fluids, anti-infection, and etc. [9,39]. According to the experience of Schnuelle et al. [88], a crystalloid solution is preferred. If a patient's post-transplant seizure is considered to be associated with immunosuppressive drugs, replacing the drug or lowering its dosage can help to terminate the seizure [9,89,90]. A study put forward that when seizures appear after the use of FK506, we should replace FK506 with CsA because CsA has fewer side effects on the nervous system [10]. In addition, for immunosuppressant-induced seizures, lipids can also be added to prevent lipophilic CNIs crossing the blood-brain barrier [91]. Dialysis and combined therapy may also be considered [64,92]. There are more relevant details in Table 2.

9.2. Control seizures

AEDs are needed for patients with recurrent seizures or patients who have a single seizure along with an obvious abnormity in auxiliary examinations. Most patients can stop using AEDs after a period of time, but the long-term use of AEDs is essential if the patients have metabolic disorders that are difficult to control, unbearable recurrent seizures or brain damage caused by epilepsy [57,93]. When deciding on the anti-epileptic therapy, AEDs that merely combine with protein, interact with immunosuppressive agents, induce enzyme and metabolized by liver is preferred [16]. Regarding the selection of drugs, more details have been previously described——"***5. Seizures after different types of transplantations***".

10. Prognosis

Most patients no longer have seizures after using AEDs. If seizures are related to some reversible risks, the prognosis is good. If postanoxic myoclonic SE occurs or if seizures are related to sepsis, rejection of the transplanted organ or cerebrovascular disease, the prognosis is poor [8,14,16,39,94]. Seizures related to CsA may develop into intractable epilepsy [79].

11. Results

Significant details of each study are shown in Table 3.

12. Discussions

Li et al. [95] analyzed the data of American inpatients and found that patients with preoperative seizures were more prone to have surgical complications after kidney transplantation, and thus led to worse clinical outcomes. However, more studies are needed to support this idea.

Some retrospective studies found that, in patients who showed seizures after transplantation, the duration of hospitalization was prolonged and the survival rate was significantly reduced [9,39,96]. Cordelli et al. [9] conducted a statistical study on patients with hematopoietic stem cell transplantation and found that in patients with postoperative seizures, their 5-year survival rate was lower than it in patients without postoperative seizures. In study of Zhang et al. [39], the 5-year survival rate was 71.4% in patients without postoperative seizures, but in patients who show seizures after transplantation it was only 31.1% (21.5% of these patients died because of seizures). However, Lee et al. [97] believed that the postoperative seizures could not directly affect the survival rate of these patients and induce graft failure that related to the factors such as liver or kidney dysfunction, sepsis, and severe metabolic disorder. The potential reasons behind this phenomenon need further investigations.

13. Conculsions

After transplantation, seizures may occur, which is usually characterized as generalized onset [3]. But the underlying pathogenesis of this postoperative seizure is still not so clear, the risk factors include application of drugs, metabolic disorders, infection, cerebrovascular diseases, tumors and some other factors [19,37,39,45,63]. The incidence of seizures is different in each type of transplantation, and a prospective study is needed to reveal a more reliable statistic about seizures in recipients of transplantation. After transplantation, the appearance of epilepsy is relatively rare [9,54,56,67]. In relevant articles, when authors counted the quantity of patients who showed epilepsy after transplantation, those who have a history of preoperative epilepsy were not strictly excluded [9,54,56,67]. So, a precise data about the incidence of new-onset epilepsy after transplantation is urgently needed.

Treatment include the elimination of related risk factors and anti-epileptic treatment. However, a unified AEDs regimen is lacking. There is a consensus that AEDS metabolized mainly by liver, interact with other drugs, induce enzyme and bind significant protein should be avoided [16]. Most of patients can be seizure-free after treatment. But there are still a group of patients who may develop to epilepsy, so a long-term AEDs therapy is necessary in these patients [57].

According to some studies, the prognosis is poor in patients who show postanoxic myoclonic SE or who have preoperative or postoperative seizures or who's seizures are related to rejection of the transplanted organ, sepsis or cerebrovascular diseases [8,14,16,39,94,95]. However, more researches are needed to support these finds.

Funds

Study Funded by National Natural Science Foundation of China (Nos. 81471319, 81671301).

Conflict of interest

We declare that we have no conflict of interest.

Acknowledgements

PL analyzed the material, designed and wrote the article; XT helped to submit this article; XW designed the article and provided supervision and guidance for the writing process. All authors read and approved the final manuscript.

Table 3
Significant details of each study.

Transplantation type	Diagnose	Time from transplantation to first seizure	Seizure type	Seizure or epilepsy history prior to transplantation	How many developed to epilepsy	Seizure outcome	Study
LT	N/A	In first month	GTCS	N/A	N/A	Seizures stopped in all patients	Sevmis et al. [10]
LT	N/A	Two weeks	GTCS	None	None	Achieved seizure-free without AEDS	Xie et al. [54]
LT	Acute liver failure (39.3%), cholestatic liver disease (17.8%), CC (17.8%), WD (10.7%), metabolic liver disease (7.1%), CHF (3.5%), AIH (3.5%)	Two weeks	FS (75%) and GS (25%)	N/A	N/A	Seizure completed ended in 88.9% of patients	Kilic et al. [55]
LT	N/A	Most of the patients show seizures within 3 months of transplantation	The majority are GTCS	N/A	N/A	Seizure control achieved in 83.3% of patients, and other patients need long-term AEDS	Ghosh et al. [56]
KT	Nephronophthisis and obstructive uropathy are most common	N/A	None patients show seizures	17% of the patients have preoperative seizure	N/A	N/A	Hamiwka et al. [65]
KT	congenial renal anomaly (61.3%) and glomerular nephritis (38.7%)	N/A	GS is the most common	52% of the patients have preoperative seizure,2% of the patients have the history of epilepsy	8.33% of the patients	N/A	McEnery et al. [67]
HT	Severe DCM (75%), severe dilated valvular cardiopathy (12.5%) and ischemic cardiopathy (12.5%)	A median period of 29.2 days	GS and FS	12.5% of the patient has preoperative epilepsy	N/A	Seizures stopped in all patients	Navarro et.al [11]
HT	N/A	N/A	Include GTCS (46.15 %), generalized myo-clonic seizure (30.77 %), SE (7.7%) focal impaired awareness seizure (15.38%)	N/A	N/A	Seizure control achieved in all patients	Ocal et al. [47]
HSCT	AL (40%), CML (20%), HLH (13.3%), MDS (6.67%), CDG (6.67%), FA (6.67%), OP (6.67%)	N/A	GS (46.7%), FS (33.3 %), focal to bilteral tonic-clonic seizure (13.3%) and absence SE (6.7%)	6.7% of patients have postoperative seizure	26.7% of patients	46.7% of patients remained seizure free within the first year	Gaggero et al. [79]
HSCT	Leukemia (73.5%), MDS (21.5%), AA (5.1%)	A median period of 56 days	GS is the most comm--on and followed by FS	1.3% of the patients have preoperative epilepsy	N/A	N/A	Zhang et al. [39]
HSCT	AL (75%), CML (25%)	29–760 days	Include GTCS, FS, absence seizure and focal to bilateral tonic-clonic seizure	None	N/A	Seizures get improved in 75% of patients	Zhong et al. [41]
HSCT	75% are oncological diseases and 25% are Non-oncological diseases	A median period of 78 days	In most of patients the first seizure was FS	14.28% of the patients have preoperative epilepsy	None	Seizures stopped in 96.43% of patients with the usage of AEDs	Cordelli et al. [9]

Abbreviations: AA: aplastic anemia; AEDs: anti-epileptic drugs; AIH: autoimmune hepatitis; AL: acute leukemia; CC: cryptogenic cirrhosis; CDG: chronic granulomatosis; CHF: congenital hepatic fibrosis; CML: chronic myelogenous leukemia; DCM: dilated cardiomyopathy; FA: Fanconi's anemia ; FS: focal seizure; GS: generalized seizure ; GTCS: generalized tonic-clonic seizure; HLH: hemophagocytic lymphohistiocytosis; HT: heart transplantation; HSCT: hematopoietic stem cell transplantation; KT: kidney transplantation; LT: liver transplantation; MDS: myelodysplastic syndrome; N/A: not applicable; OP: osteopetrosis ;SE: status epilepticus; WD: Wilson diseas.

References

[1] Organ Procurement and Transplant Network. Based on OPTN data as of 2015.
[2] Pizzi M, Ng L. Neurologic complications of solid organ transplantation. Neurol Clin 2017;35(4):809–23.
[3] Senzolo M, Ferronato C, Burra P. Neurologic complications after solid organ transplantation. Transpl Int 2009;22(3):269–78.
[4] Tyler HR. Neurological complications of dialysis, transplantation, and other forms of treatment in chronic uremia. Neurology 1965;15(12):1081–8.
[5] Gross ML, Pearson RM, Sweny P, Moorhead JF. Convulsions associated with cyclosporin A in renal transplant recipients. Br Med J (Clin Res Ed) 1985;290(6467):555.
[6] Estol CJ, Lopez O, Brenner RP, Martinez AJ. Seizures after liver transplantation: a clinicopathologic study. Neurology 1989;39(10):1297–301.
[7] Server A, Bargallo N, Floisand Y, Sponheim J, Graus F, Hald JK. Imaging spectrum of central nervous system complications of hematopoietic stem cell and solid organ transplantation. Neuroradiology 2017;59(2):105–26.
[8] Zivkovic SA, Abdel-Hamid H. Neurologic manifestations of transplant complications. Neurol Clin 2010;28(1):235–51.
[9] Cordelli DM, Masetti R, Zama D, Gueraldi D, Rondelli R, Cottone C, et al. Etiology, characteristics and outcome of seizures after pediatric hematopoietic stem cell transplantation. Seizure 2014;23(2):140–5.
[10] Sevmis S, Karakayali H, Emiroglu R, Akkoc H, Haberal M. Tacrolimus-related seizure in the early postoperative period after liver transplantation. Transplant Proc 2007;39(4):1211–3.
[11] Navarro V, Varnous S, Galanaud D, Vaissier E, Granger B, Gandjbakhch I, et al. Incidence and risk factors for seizures after heart transplantation. J Neurol 2010;257(4):563–8.
[12] Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58(4):522–30.
[13] Scheffer IE, French J, Hirsch E, Jain S, Mathern GW, Moshé SL, et al. Classification of the epilepsies: New concepts for discussion and debate-Special report of the ILAE Classification Task Force of the Commission for Classification and Terminology. Epilepsia Open 2016;1(1–2):37–44.
[14] Dhar R. Neurologic complications of transplantation. Handb Clin Neurol 2017;141:545–72.
[15] Caselli D, Rosati A, Faraci M, Podda M, Ripaldi M, Longoni D, et al. Risk of seizures in children receiving busulphan-containing regimens for stem cell transplantation. Biol Blood Marrow Transplant 2014;20(2):282–5.
[16] Shepard PW, St Louis EK. Seizure treatment in transplant patients. Curr Treat Options Neurol 2012;14(4):332–47.
[17] Loar RW, Patterson MC, O'Leary PW, Driscoll DJ, Johnson JN. Posterior reversible encephalopathy syndrome and hemorrhage associated with tacrolimus in a pediatric heart transplantation recipient. Pediatr Transpl 2013;17(2):E67–70.
[18] Saner F, Gu Y, Minouchehr S, Ilker K, Fruhauf NR, Paul A, et al. Neurological complications after cadaveric and living donor liver transplantation. J Neurol 2006;253(5):612–7.
[19] Forgacs B, Merhav HJ, Lappin J, Mieles L. Successful conversion to rapamycin for calcineurin inhibitor-related neurotoxicity following liver transplantation. Transpl Proc 2005;37(4):1912–4.
[20] McDiarmid SV, Busuttil RW, Ascher NL, et al. FK506 (tacrolimus) compared with cyclosporine for primary immunosuppression after pediatric liver transplantation. Results from the U.S. Multicenter Trial. Transplantation 1995;59(4):530–6.
[21] Freise CE, Rowley H, Lake J, Hebert M, Ascher NL, Roberts JP. Similar clinical presentation of neurotoxicity following FK 506 and cyclosporine in a liver transplant recipient. Transpl Proc 1991;23(6):3173–4.
[22] Lewis MB, Howdle PD. Neurologic complications of liver transplantation in adults. Neurology 2003;61(9):1174–8.
[23] Klawitter J, Gottschalk S, Hainz C, Leibfritz D, Christians U, Serkova NJ. Immunosuppressant neurotoxicity in rat brain models: oxidative stress and cellular metabolism. Chem Res Toxicol 2010;23(3):608–19.
[24] Shuto H, Kataoka Y, Fujisaki K, Nakao T, Sueyasu M, Miura I, et al. Inhibition of GABA system involved in cyclosporine-induced convulsions. Life Sci 1999;65(9):879–87.
[25] Katsarou AM, Moshe SL, Galanopoulou AS. Interneuronopathies and their role in early life epilepsies and neurodevelopmental disorders. Epilepsia Open 2017;2(3):284–306.
[26] Garcia PA, Laxer KD, van der Grond J, Hugg JW, Matson GB, Weiner MW. Correlation of seizure frequency with N-acetyl-aspartate levels determined by 1H magnetic resonance spectroscopic imaging. Magn Reson Imaging 1997;15(4):475–8.
[27] Yanagimachi M, Naruto T, Tanoshima R, Kato H, Yokosuka T, Kajiwara R, et al. Influence of CYP3A5 and ABCB1 gene polymorphisms on calcineurin inhibitor-related neurotoxicity after hematopoietic stem cell transplantation. Clin Transpl 2010;24(6):855–61.
[28] Daoud D, Scheld HH, Speckmann EJ, Gorji A. Rapamycin: brain excitability studied in vitro. Epilepsia 2007;48(4):834–6.
[29] Wong M, Yamada KA. Cyclosporine induces epileptiform activity in an in vitro seizure model. Epilepsia 2000;41(3):271–6.
[30] Trullemans F, Grignard F, Van Camp B, Schots R. Clinical findings and magnetic resonance imaging in severe cyclosporine-related neurotoxicity after allogeneic bone marrow transplantation. Eur J Haematol 2001;67(2):94–9.
[31] Fujisaki Y, Yamauchi A, Dohgu S, Sunada K, Yamaguchi C, Oishi R, et al. Cyclosporine A-increased nitric oxide production in the rat dorsal hippocampus mediates convulsions. Life Sci 2002;72(4–5):549–56.
[32] Jung S, Yang H, Kim BS, Chu K, Lee SK, Jeon D. The immunosuppressant cyclosporin A inhibits recurrent seizures in an experimental model of temporal lobe epilepsy. Neurosci Lett 2012;529(2):133–8.
[33] Setkowicz Z, Ciarach M, Guzik R, Janeczko K. Different effects of neuroprotectants FK-506 and cyclosporin A on susceptibility to pilocarpine-induced seizures in rats with brain injured at different developmental stages. Epilepsy Res 2004;61(1–3):63–72.
[34] Nardone R, Brigo F, Trinka E. Acute symptomatic seizures caused by electrolyte disturbances. J Clin Neurol 2016;12(1):21–33.
[35] Beleza P. Acute symptomatic seizures: a clinically oriented review. Neurologist 2012;18(3):109–19.
[36] Wijdicks EF, Hocker SE. Neurologic complications of liver transplantation. Handb Clin Neurol 2014;121:1257–66.
[37] Drake K, Nehus E, Goebel J. Hyponatremia, hypo-osmolality, and seizures in children early post-kidney transplant. Pediatr Transpl 2015;19(7):698–703.
[38] Wells TG, Ulstrom RA, Nevins TE. Hypoglycemia in pediatric renal allograft recipients. J Pediatr 1988;113(6):1002–7.
[39] Zhang XH, Xu LP, Liu DH, Chen H, Han W, Chen YH, et al. Epileptic seizures in patients following allogeneic hematopoietic stem cell transplantation: a retrospective analysis of incidence, risk factors, and survival rates. Clin Transpl 2013;27(1):80–9.
[40] Hooper DC, Pruitt AA, Rubin RH. Central nervous system infection in the chronically immunosuppressed. Medicine (Baltim) 1982;61(3):166–88.
[41] Zhong ZD, Li L, Wu YH, You Y, Li WM, Zou P. Analysis of seizure risk factors after allogeneic hematopoietic stem cell transplantation: a 8 case report and literature review. J Huazhong Univ Sci Technol Med Sci 2013;33(5):656–60.
[42] Reddy SM, Winston DJ, Territo MC, Schiller GJ. CMV central nervous system disease in stem-cell transplant recipients: an increasing complication of drug-resistant CMV infection and protracted immunodeficiency. Bone Marrow Transpl 2010;45(6):979–84.
[43] van Veen KE, Brouwer MC, van der Ende A, van de Beek D. Bacterial meningitis in solid organ transplant recipients: a population-based prospective study. Transpl Infect Dis 2016;18(5):674–80.
[44] Zhu G, Okada M, Yoshida S, Mori F, Ueno S, Wakabayashi K, et al. Effects of interleukin-1beta on hippocampal glutamate and GABA releases associated with Ca2+-induced Ca2+ releasing systems. Epilepsy Res 2006;71(2–3):107–16.
[45] Vizzini G, Asaro M, Miraglia R, Gruttadauria S, Filì D, D'Antoni A, et al. Changing picture of central nervous system complications in liver transplant recipients. Liver Transpl 2011;17(11):1279–85.
[46] Bladin CF, Alexandrov AV, Bellavance A, Bornstein N, Chambers B, Coté R, et al. Seizures after stroke: a prospective multicenter study. Arch Neurol 2000;57(11):1617–22.
[47] Ocal R, Sezer T, Kibaroglu S, Derle E, Benli S, Sezgin A, et al. Epilepsy After Heart Transplant: A Single Center Experience. Exp Clin Transpl 2016.
[48] Zhang XH, Wang QM, Chen H, Chen YH, Han W, Wang FR, et al. Clinical characteristics and risk factors of Intracranial hemorrhage in patients following allogeneic hematopoietic stem cell transplantation. Ann Hematol 2016;95(10):1637–43.
[49] Oh SY, Lee H, Park YH, Ryu HG. Intracranial hemorrhage induced uncontrolled seizure in a deceased donor liver transplant patient: a case report. Korean J Anesthesiol 2016;69(5):527–31.
[50] Stein DP, Lederman RJ, Vogt DP, Carey WD, Broughan TA. Neurological complications following liver transplantation. Ann Neurol 1992;31(6):644–9.
[51] Wszolek ZK, Steg RE. Seizures after orthotopic liver transplantation. Seizure 1997;6(1):31–9.
[52] Saner FH, Sotiropoulos GC, Gu Y, Paul A, Radtke A, Gensicke J, et al. Severe neurological events following liver transplantation. Arch Med Res 2007;38(1):75–9.
[53] Derle E, Kibaroglu S, Ocal R, Kırnap M, Can U, Benli S, et al. Neurologic complications after liver transplant: experience at a single center. Exp Clin Transpl 2015;13(Suppl 1):327–30.
[54] Xie M, Rao W, Sun LY, Zhu ZJ, Deng YL, Shen ZY, et al. Tacrolimus-related seizure after pediatric liver transplantation–a single-center experience. Pediatr Transpl 2014;18(1):58–63.
[55] Kilic B, Gungor S, Arslan M, Selimoglu MA, Yilmaz S. Seizures in pediatric patients with liver transplant and efficacy of Levetiracetam. J Child Neurol 2017;32(8):740–5.
[56] Ghosh PS, Hupertz V, Ghosh D. Neurological complications following pediatric liver transplant. J Pediatr Gastroenterol Nutr 2012;54(4):540–6.
[57] Chabolla DR, Wszolek ZK. Pharmacologic management of seizures in organ transplant. Neurology 2006;67(Suppl. (4)):S34–8.
[58] Lin CH, Chen CL, Lin TK, Chen NC, Tsai MH, Chuang YC. Levetiracetam in the treatment of epileptic seizures after liver transplantation. Medicine (Baltim) 2015;94(38):e1350.
[59] Patsalos PN. Clinical pharmacokinetics of levetiracetam. Clin Pharmacokinet 2004;43(11):707–24.
[60] Velizarova R, Gelisse P, Pageaux GP, Genton P, Crespel A. Valproate treatment after liver transplant in a patient with Lennox-Gastaut syndrome. Seizure 2011;20(6):500–1.
[61] Cansick J, Rees L, Koffman G, Van't Hoff W, Bockenhauer D. A fatal case of cerebral oedema with hyponatraemia and massive polyuria after renal transplantation. Pediatr Nephrol 2009;24(6):1231–4.
[62] Bezinover D, Douthitt L, McQuillan PM, Khan A, Dalal P, Stene J, et al. Fatal hyperammonemia after renal transplant due to late-onset urea cycle deficiency: a case report. Transpl Proc 2010;42(5):1982–5.

[63] Su IC, Lien HC, Chen CM. Primary brain T-cell lymphoma after kidney transplantation: a case report. Surg Neurol 2006;66(Suppl. (2)):S60–3.
[64] Heroux A, Pamboukian SV. Neurologic aspects of heart transplantation. Handb Clin Neurol 2014;121:1229–36.
[65] Hamiwka LD, Midgley JP, Hamiwka LA. Seizures in children after kidney transplantation: has the risk changed and can we predict who is at greatest risk? Pediatr Transpl 2008;12(5):527–30.
[66] Yardimci N, Colak T, Sevmis S, Benli S, Zileli T, Haberal M. Neurologic complications after renal transplant. Exp Clin Transpl 2008;6(3):224–8.
[67] McEnery PT, Nathan J, Bates SR, Daniels SR. Convulsions in children undergoing renal transplantation. J Pediatr. 1989;115(4):532–6.
[68] da Costa BM, Verdelho M, Cotovio P, Nolasco F. New-onset seizures 15 years after renal transplant. Am J Transpl 2016;16(7):2232–4.
[69] Ertilav M, Ozkul A, Zeytinoglu A, Sen S, Sipahi S, Töz H, et al. [Meningoencephalitis caused by West Nile virus in a renal transplant recipient]. Mikrobiyol Bul 2014;48(4):674–82.
[70] Haughey D, Narsipur SS. Posterior reversible encephalopathy syndrome after renal transplant: a simple solution for a complicated patient. Case Rep Nephrol Dial 2015;5(1):20–5.
[71] Vernon HJ, Sperati CJ, King JD, Poretti A, Miller NR, Sloan JL, et al. A detailed analysis of methylmalonic acid kinetics during hemodialysis and after combined liver/kidney transplantation in a patient with mut (0) methylmalonic acidemia. J Inherit Metab Dis 2014;37(6):899–907.
[72] Moris D, Vernadakis S, Lionaki S, Daikos G, Zavos G. An uncommon cause of acutely altered mental status in a renal transplant recipient. Ups J Med Sci 2014;119(1):50–4.
[73] Hillebrand G, Castro LA, van Scheidt W, Beukelmann D, Land W, Schmidt D. Valproate for epilepsy in renal transplant recipients receiving cyclosporine. Transplantation 1987;43(6):915–6.
[74] van de Beek D, Kremers W, Daly RC, Edwards BS, Clavell AL, McGregor CG, et al. Effect of neurologic complications on outcome after heart transplant. Arch Neurol 2008;65(2):226–31.
[75] Perez-Miralles F, Sanchez-Manso JC, Almenar-Bonet L, Sevilla-Mantecon T, Martinez-Dolz L, Vilchez-Padilla JJ. Incidence of and risk factors for neurologic complications after heart transplantation. Transpl Proc 2005;37(9):4067–70.
[76] Zierer A, Melby SJ, Voeller RK, Guthrie TJ, Al-Dadah AS, Meyers BF, et al. Significance of neurologic complications in the modern era of cardiac transplantation. Ann Thorac Surg 2007;83(5):1684–90.
[77] Urbanowicz T, Pawlowska M, Buczkowski P, Perek B, Baszyńska-Wachowiak H, Straburzyńska-Migaj E, et al. Seizures after heart transplantation–two cases of non-immunosuppressant drug interactions in young patients. Ann Transpl 2014;19:417–20.
[78] Bhanushali MJ, Kranick SM, Freeman AF, Cuellar-Rodriguez JM, Battiwalla M, Gea-Banacloche JC, et al. Human herpes 6 virus encephalitis complicating allogeneic hematopoietic stem cell transplantation. Neurology 2013;80(16):1494–500.
[79] Gaggero R, Haupt R, Paola Fondelli M, De Vescovi R, Marino A, Lanino E, et al. Intractable epilepsy secondary to cyclosporine toxicity in children undergoing allogeneic hematopoietic bone marrow transplantation. J Child Neurol 2006;21(10):861–6.
[80] Zerr DM. Human herpesvirus 6 and central nervous system disease in hematopoietic cell transplantation. J Clin Virol 2006;37(Suppl. (1)):S52–6.
[81] Muta T, Fukuda T, Harada M. Human herpesvirus-6 encephalitis in hematopoietic SCT recipients in Japan: a retrospective multicenter study. Bone Marrow Transpl 2009;43(7):583–5.
[82] Seeley WW, Marty FM, Holmes TM, Upchurch K, Soiffer RJ, Antin JH, et al. Post-transplant acute limbic encephalitis: clinical features and relationship to HHV6. Neurology 2007;69(2):156–65.
[83] Rodriguez TE. Neurologic complications of bone marrow transplantation. Handb Clin Neurol 2014;121:1295–304.
[84] Masetti R, Cordelli DM, Zama D, Vendemini F, Biagi C, Franzoni E, et al. PRES in Children Undergoing Hematopoietic Stem Cell or Solid Organ Transplantation. Pediatrics 2015;135(5):890–901.
[85] Peyrl A, Weichert N, Kuhl JS, Ebell W, Hernaiz Driever P. Levetiracetam as a possible cause of secondary graft failure after allogenic hematopoietic stem cell transplantation. Eur J Paediatr Neurol 2015;19(1):75–7.
[86] Donmez FY, Guvenc Z, Emiroglu FK, Coskun M, Haberal M. Evaluation of neurological complications in pediatric liver transplant recipients: MRI versus CT. J Child Neurol 2009;24(6):656–63.
[87] Cordelli DM, Masetti R, Bernardi B, Barcia G, Gentile V, Biagi C, et al. Status epilepticus as a main manifestation of posterior reversible encephalopathy syndrome after pediatric hematopoietic stem cell transplantation. Pediatr Blood Cancer 2012;58(5):785–90.
[88] Schnuelle P, Johannes van der Woude F. Perioperative fluid management in renal transplantation: a narrative review of the literature. Transpl Int 2006;19(12):947–59.
[89] Graus F, Saiz A, Sierra J, Arbaiza D, Rovira M, Carreras E, et al. Neurologic complications of autologous and allogeneic bone marrow transplantation in patients with leukemia: a comparative study. Neurology 1996;46(4):1004–9.
[90] Bilbao I, Dopazo C, Castells L, Lazaro J, Caralt M, Sapisochin G, et al. Immunosuppression based on everolimus in liver transplant recipients with severe early post-transplantation neurotoxicity. Transpl Proc 2014;46(9):3104–7.
[91] Ide K, Ohdan H, Tahara H, Ishiyama K, Shishida M, Irei T, et al. Possible therapeutic effect of lipid supplementation on neurological complications in liver transplant recipients. Transpl Int 2007;20(7):632–5.
[92] Yong-Gang X, Ming-Zhe W, Jin-Yan Z, Zhi-Hai P, Jun-Ming X. Combination of N-(3'4'-dimethoxycinnamoyl) anthranilic acid with cyclosporin A treatment preserves immunosuppressive effect and reduces the side effect of cyclosporin A in rat. Eur J Pharmacol 2014;728:16–23.
[93] Grigg MM, Costanzo-Nordin MR, Celesia GG, Kelly MA, Silver MA, Sobotka PA, et al. The etiology of seizures after cardiac transplantation. Transpl Proc 1988;20(3 Suppl 3):937–44.
[94] Choi EJ, Kang JK, Lee SA, Kim KH, Lee SG, Andermann F. New-onset seizures after liver transplantation: clinical implications and prognosis in survivors. Eur Neurol 2004;52(4):230–6.
[95] Li N, Jean R, Tooley JE, Mulligan DC, Yoo PS. Partners in crime: kidney transplantation and seizure disorder. Transpl Proc 2016;48(8):2700–8.
[96] Otan E, Aydin C, Yonder H, Kayaalp C, Kaplan Y, Yilmaz S. Evaluation of early postoperative neurological complications following living donor liver transplantation. Noro Psikiyatr Ars 2015;52(1):15–8.
[97] Lee YJ, Yum MS, Kim EH, Choi HW, Oh SH, Kim DY, et al. Risk factors for neurological complications and their correlation with survival following pediatric liver transplantation. Pediatr Transpl 2014;18(2):177–84.