Case Report

Drug-resistant epilepsy development following stem cell transplant and cyclosporine neurotoxicity induced seizures: Case report in an adult and analysis of reported cases in the literature

Adam S. Vesole, Yasunori Nagahama, Mark A. Granre, Matthew A. Howard, Hiroto Kawasakib, Brian J. Dlouhy

Introduction: Drug-resistant epilepsy (DRE) occurs in 20–30% of all patients who develop epilepsy and can occur from diverse causes. Cyclosporine-A (CSA) is an immunosuppressive drug utilized to prevent graft-versus-host disease (GvHD) in transplant patients and is known to cause neurotoxicity, including seizures. In some cases, however, patients can develop DRE. Only a limited number of cases have been reported in which DRE has developed after CSA exposure—most in children. Here we present a rare case of an adult developing DRE after post-transplant CSA neurotoxicity. In addition, we provide a comprehensive review and analysis of all reported cases in the literature.

Case report: A 29-year-old man with Non-Hodgkin’s Lymphoma underwent an allogenic hematopoietic stem cell transplant and experienced a CSA-induced seizure at 7.5 months’ post-transplant. The patient was discontinued on CSA and began a low dose tacrolimus regimen. At 33 months’ post-transplant, he had seizure recurrence and developed DRE. Imaging revealed right mesial temporal sclerosis (MTS) and video EEG localized ictal activity to the right anterior temporal lobe. He was successfully treated with a right anterior temporal lobectomy and amygdalohippocampectomy.

Conclusions: The use of cyclosporine for GvHD prophylaxis and treatment following transplantation may cause seizures and be associated with DRE. Although discontinuation and dose decrease of CSA often reverse adverse neurological events, initial CSA-induced seizures may be associated with MTS and subsequent greater risk of DRE development. The incidence of MTS (40%) in these 15 patients was significantly higher than the incidence in the general DRE population (24%) and was most effectively treated via epilepsy surgery.
antiseizure drugs in the case of seizures [2]. However, in some cases of CSA-induced seizures, patients can develop DRE — the majority of them reported in pediatric patients.

Here we discuss a rare reported case of an adult developing DRE after transplant CSA neurotoxicity. Due to its rare occurrence, few studies have characterized the onset and course of DRE following CSA-induced seizures, including discussion and effectiveness of surgical treatment [4,5,10,11,13,14]. Therefore, we provide a comprehensive literature review and analysis of all reported cases of the development of DRE following CSA-induced seizures in transplant patients. Understanding risk factors and pathogenesis for the development of drug-resistant epilepsy after CSA-neurotoxicity will be useful in limiting and treating this complication.

2. Case report

2.1. Initial presentation and development of T-cell lymphoma (Non-Hodgkin’s lymphoma)

A 28-year-old man with a history of common variable immunodeficiency (CVID) and panhypogammaglobulinemia was found to have liver lesions and adenopathy near the aortic arch. A liver biopsy revealed T-cell lymphoma, and he was subsequently treated with four cycles of CHOP chemotherapy (cyclophosphamide, hydroxydaunorubicin, Oncovin and prednisone) and two cycles of DHAP chemotherapy (dexamethasone, high dose cytarabine and cisplatin). Chemotherapy had no significant effect on T-cell lymphoma (Non-Hodgkin’s lymphoma, NHL) progression, and therefore, the patient underwent bone marrow transplant.

2.2. Allogenic bone marrow transplant

The patient began an immunosuppressive conditioning regimen of cyclophosphamide and total body irradiation (TBI) prior to an allogenic HLA-matched related bone marrow transplant from his sister and engrafted by day 20. Post-transplant, he received monthly intravenous immunoglobulin (IVIG) infusions and 550 mg of cyclosporine daily. The patient developed graft-versus-host disease (GVHD) of the liver, immunoglobulin (IVIG) infusions and 550 mg of cyclosporine daily. The patient developed graft-versus-host disease (GVHD) of the liver, and the patient was started on prednisone and continued cyclosporine. While tapering prednisone, the patient was hospitalized for herpes simplex I of the mouth and nose and bacterial sinusitis, treated successfully with acyclovir and cefepime, respectively — both suspected to have occurred due to a weakened immune system from prednisone and cyclosporine.

2.3. Cyclosporine toxicity, neurological effects, and initial seizure

Days after his hospitalization for herpes simplex and sinusitis, at 7.5 months post-transplant, the patient was readmitted due to cyclosporine toxicity with a blood level of 1467 ng/ml (therapeutic range: 100–200 ng/ml). He experienced cortical blindness and a single focal impaired awareness seizure and MRI showed increased occipital/parietal signal intensity consistent with posterior reversible encephalopathy syndrome (PRES). There was no evidence of any pre-existing epileptogenic lesions on MRI. Symptoms improved upon immediate replacement of cyclosporine with tacrolimus and administration of phenytoin. Besides cyclosporine neurotoxicity, he did not have any preexisting risk factors for epilepsy development such as febrile seizures, family history of seizures/epilepsy or childhood seizures/epilepsy.

2.4. Seizure recurrence

The next two years following cyclosporine toxicity, the patient was seizure-free although this was complicated with acute GvHD of the liver and chronic GvHD of the skin. At 33 months post-transplant, he experienced a generalized tonic–clonic (GTC) seizure and remained in non-convulsive status epileptics until treated with phenytoin. MRI at the time of seizure recurrence (Fig. 1) showed a subtle signal intensity increase in the right insular cortex and hippocampus and atrophy in the right parietal lobe. An EEG was abnormal with frequent spike–wave discharges with occasional delta slow waves in the right temporal region. His medical history, EEG and neuroimaging were consistent of a focal seizure tendency. Lumbar puncture was clear and negative for adenovirus, herpes and varicella making an encephalitis etiology unlikely. PCR confirmed the negative herpes culture.

2.5. Development of epilepsy, epilepsy surgery and postoperative outcome

The patient continued to have drug-resistant seizures. His seizures were mostly focal with impaired awareness and progressively increased in frequency from 4–5 times per week. Antiseizure drug trials of lamotrigine, levetiracetam, phenytoin and oxcarbazepine were largely unsuccessful in controlling his seizures. No autointerbody titers were tested to rule in an autoimmune etiology. MRI (Fig. 1) and PET imaging at 2 years post-seizure recurrence revealed right mesial temporal sclerosis (MTS) and right temporal hypometabolism, respectively. Seizure semiology consisted of focal aware seizures of odd smell and taste, most consistent with medial temporal localization. Ictal EEG localized to the right anterior temporal lobe and interictal EEG showed right temporal slowing with occasional right anterior temporal sharp waves. Wada testing of visual and verbal memory and language all lateralized to the left hemisphere. A neuropsychological cognitive assessment revealed bilateral mesial temporal dysfunction and moderate anterograde memory deficits. Presurgical workup (Table 1) and discussion at our multidisciplinary epilepsy conference indicated the patient for a right anterior temporal lobectomy and amygdalohippocampectomy without intracranial electrode monitoring at eight years post-transplant. Pathology showed subpial gliosis in the right anterior temporal lobe with dentate cell dispersion and right hippocampal sclerosis. The surgery was uncomplicated, and the patient developed no cognitive deficits. A 3-month postoperative neuropsychological cognitive assessment indicated stable or improved functioning in most cognitive domains with a less severe anterograde memory deficit compared to the preoperative assessment. At the eight-year follow-up, with the exception of two episodes concerning for focal aware seizures at the two-year follow-up, the patient was seizure free since surgery (Engel Score Class Ia) and remains in NHL remission 16 years post-transplant.

3. Discussion

Seizures, the second most common adverse neurological effect in CSA toxicity, have been well documented in post-transplant patients. However, CSA-induced seizures and the development of DRE are uncommon. Here we report a rare case of an adult developing DRE after CSA neurotoxicity post-transplant. In addition, we provide a comprehensive characterization of all reported patients who have developed DRE after CSA neurotoxicity.

3.1. Incidence of CSA neurotoxicity — seizures and DRE

Stratifying CSA neurotoxicity by age, about 82% of adults (over age 18) will have a single, reversible event, while about half of children (under age 18) will experience recurrent seizures [15,16]. Of all the patients that experience a CSA-induced seizure, 32–50% will have an independent seizure recurrence, and about half of seizure recurrent patients will develop DRE [10,11,17]. Based upon work from Gaggero et al. and Gleeson et al., we calculated the incidence of DRE development after administration of post-transplant CSA at approximately 0.4–0.5%, assuming no preexisting neurological conditions [10,11]. We identified a total of 15 patients (not including ours) from the literature that developed DRE after CSA-neurotoxicity. These were all pediatric patients.
3.2. Risk factors for the development of DRE

Patients that undergo transplantation for any cause and require a post-transplant immunosuppressant regimen should be assessed for risk factors associated with the development of DRE. Significant risk factors for intractable epilepsy development include prior febrile or neonatal seizures, earlier age of seizure onset, family history of intractable epilepsy, neuroimaging abnormality such as MTS, persistent EEG abnormalities, and MTS on MRI [4,23–25]. Another significant risk factor to consider in the context of our patient is a preexisting autoimmune disease, such as CVID. Positive autoantibody titers for voltage-gated potassium channels, GAD, AMPA receptors and GABA receptors have been shown to be associated with DRE [26].

3.3. Age and CSA-induced DRE

All 15 patients reported in the literature that have developed CSA-induced DRE (Table 2) were pediatric patients (less than 18 years old) at the time of transplantation and CSA administration. Interestingly, the patient described here in our report is an adult known to have developed DRE following post-transplant CSA-induced neurotoxicity — a presentation uncommonly found in adults. In the general population, DRE in adults is much less common compared to in children [27]. Although drug-resistance etiology in epilepsy is multifactorial and not well understood, in the patient described here in our report is an adult known to have developed DRE following post-transplant CSA-induced neurotoxicity — a presentation uncommonly found in adults. In the general population, DRE in adults is much less common compared to in children [27].

Table 1
Presurgical workup for drug-resistant epilepsy patient post-bone-marrow-transplantation.

| Type                                      | Characteristics                                      | Frequency          |
|-------------------------------------------|------------------------------------------------------|--------------------|
| Seizure semiology                         | Focal aware seizures                                 | Several/day        |
|                                           | Focal impaired awareness seizures                    |                    |
|                                           | GTCS                                                 |                    |
|                                           | Numbriness/tingles of LUE, odd smell/taste           |                    |
|                                           | Numbriness/tingles of LUE, odd smell/taste, left eye blink, giggle, left hand claw, unaware, unresponsive |                    |
|                                           | Numbriness/tingles of LUE, odd smell/taste, generalized convulsions, LOC |                    |
| Time of surgery                           | Failed                                               |                    |
|                                           | Intact                                               |                    |
| Antiseizure drugs                         | Levetiracetam, lamotrigine                           |                    |
|                                           | Phenytoin, levetiracetam, oxcarbazepine              |                    |
| EEG                                       | Localized to right anterior temporal lobe            |                    |
|                                           | Right temporal slowing, occasional right anterior temporal sharp waves |                    |
| MRI                                       | PET                                                  |                    |
| Neuroimaging                              | Right mesiotemporal sclerosis                        |                    |
| Neuropsychology cognitive assessment      | Right temporal hypometabolism                        |                    |
|                                           | Bilateral mesial temporal lobe dysfunction, moderate anterograde memory impairments |                    |
|                                           | Visual memory                                        |                    |
|                                           | Verbal memory                                        |                    |
| Wada testing                              | Left lateralizing                                    |                    |

GTCS = generalized tonic–clonic seizure; LUE = left upper extremity; LOC = loss of consciousness; MRI = magnetic resonance imaging; PET = positron emission tomography.
understood, some have hypothesized that DRE pathogenesis is thought to arise from antiseizure drugs not reaching their target (predominately voltage-gated ion channels and GABA receptors), an alteration of the antiseizure drug targets, and/or antiseizure drugs binding incorrect targets [28,29]. Why children are more susceptible to these antiseizure drug resistance mechanisms and DRE development remains unclear, but this may explain why DRE development in those with CSA-induced seizures are mostly children [28]. However, our adult patient appeared to have been at a higher risk of developing DRE compared to an average patient originally described in Faraci et al., 2003 and since updated in Gaggero et al., 2006.

### 3.4. Oral vs. intravenous cyclosporine

Of the six reported cyclosporine administrations that led to DRE in our review (Table 2), all experienced CSA neurotoxicity while on intravenous CSA. Whether intravenous CSA contributes to a higher incidence of neurotoxicity than oral CSA is unclear. However, past studies have found that microemulsion oral CSA (Neoral) causes fewer neurological complications than intravenous CSA [30,31]. Although the adult patient we reported here was given oral CSA, the use of oral CSA instead of intravenous CSA may reduce the chance of CSA-induced seizures, especially in those patients presenting with existing risk factors for DRE.

### 3.5. Cyclosporine discontinuation, reduction and substitution

Four of the seven patients, in addition to the patient we presented here, were discontinued on CSA following their first CSA-induced seizure and placed on tacrolimus (or a milder immunosuppressant) (Table 2). Despite discontinuation of CSA, the time to seizure recurrence was not significantly different compared to those that remained on CSA (CSA discontinued: 11.0 ± 11.5 months vs. CSA continued: 7.5 ± 4.4 months) nor was seizure frequency following recurrence. In fact, a systematic review has shown that tacrolimus has a significantly higher relative risk ratio for neurological complications when compared to cyclosporine [32]. The standard of care for CSA or tacrolimus-induced neurotoxicity is to initially discontinue CSA or tacrolimus beyond the early posttransplant period (one month) are unclear [33]. Potential alternatives to high dose continuing CSA or tacrolimus beyond the early posttransplant period are unclear. The long-term neurotoxic effects of continuing CSA or tacrolimus beyond the early posttransplant period are unclear. The long-term neurotoxic effects of continuing CSA or tacrolimus beyond the early posttransplant period are unclear. The long-term neurotoxic effects of continuing CSA or tacrolimus beyond the early posttransplant period are unclear.
Table 3
Literature review of a CSA-induced seizure followed by development of drug-resistant epilepsy — epilepsy and outcomes.

| Patient # | Time (months) of PT of seizure recurrence | Seizure type | Seizure frequency per month | Intractable? | Neuroimaging findings | EEG results | Outcomes |
|-----------|------------------------------------------|--------------|----------------------------|--------------|-----------------------|-------------|----------|
|           |                                          |              |                            |              |                       |             | Epilepsy surgery? Pathology Time (months) of PT of last F/U F/U outcome |
| 1         | NA                                       | GS           | NA                         | Y            | Asymmetric ventricular enlargement Moderate atrophy | Focal left temporal slowing | N            | NA        | 42       | Continued GS |
| 2         | NA                                       | GS, severe   | NA                         | Y            | Normal                | Multifocal epileptiform discharges with posterior slowing | N            | NA        | 72       | Continued GS |
| 3         | NA                                       | FIAS         | NA                         | Y            | Left MTS              | NA          | N            | NA        | 72       | Continued FIAS |
| 4         | 9                                        | FIAS         | Several                    | Y            | Right MTS            | Bilateral occipital slowing, left hemisphere paroxysmal activity Mild, slow abnormalities | N            | NA        | 96       | Continued FIAS |
| 5         | 6.7                                      | Focal motor sz | N                        | Y            | Right MTS            | Multifocal epileptiform discharges, focal central occipital paroxysmal activity | N            | NA        | 108      | Continued FIAS |
| 6         | 2.5                                      | Focal motor sz, secondary generalized | Several        | Y            | Right MTS            | Bilateral central-occipital slowing, right-central-temporal paroxysmal activity | Y (120 months PT) | NA        | 126      | Continued focal motor sz |
| 7         | 11                                       | FIAS w/ left laterality | 1                      | Y            | Right MTS            | Diffuse epileptiform discharges, focal central occipital paroxysmal activity | N            | NA        | 60       | Continued focal motor sz |
| 8         | 2.2                                      | Focal seizure | Several                    | Y            | Global extensive white matter changes suggestive of CSA/tacrolimus toxicity Bilateral high-intensity in parietal | NA          | N            | NA        | ≈ 5      | Died from deteriorating neurological status Continued sz, severe cognitive impairments |
| 9         | NA                                       | NA           | NA                         | Y            | Global cerebral atrophy | NA          | N            | NA        | 60       | Continued sz, tremors Continued sz, severe cognitive impairments, autism |
| 10        | NA                                       | NA           | NA                         | Y            | Parietal-occipital cerebral atrophy, right basal ganglion gliosis | NA          | N            | NA        | 108      | Continued sz, severe cognitive impairments, autism |
| 11        | NA                                       | NA           | NA                         | Y            | Bilateral parietal cerebral atrophy | NA          | N            | NA        | 11       | Continued sz, dysmetria |
| 12        | NA                                       | NA           | NA                         | Y            | Bilateral parietal cerebral atrophy | NA          | N            | NA        | 48       | Continued sz |
| 13        | NA                                       | NA           | NA                         | Y            | Left MTS, bilateral parietal cerebral atrophy | NA          | N            | NA        | 144      | Continued sz, HA, ADHD |
| 14        | NA                                       | NA           | NA                         | Y            | Left MTS              | Focal left temporal slowing with sharp waves | Y (144 months PT) | Left MTS | 204      | Seizure-free |
| 15        | 24.0                                     | FIAS, sometimes GTCS | 30–60                 | Y            | Left MTS              | Focal left temporal slowing | Y (144 months PT) | Left MTS | 204      | Seizure-free |
3.6. Incidence of MTS in CSA-induced drug-resistant epilepsy

Following CSA neurotoxicity, six of the fifteen (40%) patients reviewed had MTS on neuroimaging while five (33%) showed parietal cerebral atrophy (Table 3). Of the six MTS patients, two (33%) underwent epilepsy surgery and one received a pathologic confirmation of MTS (the other had no pathology described). Similarly, our patient showed right MTS on MRI and confirmed by pathology after right temporal lobectomy and amygdalohippocampectomy.

Based on a 2002 Icelandic epidemiological study, a patient experiencing a single seizure has a predicted 6% chance of eventually developing temporal lobe epilepsy with MTS as indicated by MRI [25]. Furthermore, MTS appears to be a significant risk factor for developing drug-resistant epilepsy. Semah et al. found that 11% of epilepsy patients with MTS on antiseizure drugs were seizure-free compared to 31% of those with temporal lobe epilepsy without MTS and 45% of all epilepsy patients. Of the 55% of all epilepsy patients that did not respond to antiseizure drugs (DRE), 24% had MTS [36]. Comparing this to the population of CSA-induced intractable epilepsy patients, 40% had MTS. The difference found between the population incidence of MTS in intractable epilepsy and MTS in CSA-induced intractable epilepsy may be due to the increased risk for developing MTS following an initial precipitating incident such as febrile seizures, trauma, infection, hypoxia or CSA neurotoxicity.

Pathogenesis of MTS following an initial precipitating event is not well understood but potential mechanisms could be neuronal death due to mitochondrial dysfunction, glutamate neurotoxicity, excessive immune response, or genetic predisposition [25].

4. Conclusion

The use of cyclosporine following a solid organ or bone marrow transplant for GVHD prophylaxis and treatment may cause neurotoxicity and result in seizures that lead to DRE. Risk factors for CSA-induced seizures and subsequent epilepsy development should be considered before and after administration of post-transplant CSA to best avoid neurotoxicity. Although temporary discontinuation and long-term dose decrease of CSA often reverse adverse neurological events that could lead to seizure recurrence, initial CSA-induced seizures status epilepticus may be associated with MTS that and subsequent greater risk of epilepsy development via MTS pathogenesis. In these cases, epilepsy surgery is the most effective means for treating DRE.

Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper. The patient gave signed consent for the release of his health information in the context of this case study. He is a subject of our research protocol that has been reviewed and accepted by the University of Iowa’s Institutional Review Board (IRB).

References

[1] Kahan BD. Cyclosporine. N Engl J Med 1989;321(25):1725–38.
[2] Gijtenbeek JM, van den Bent MJ, Vecht CJ. Cyclosporine neurotoxicity: a review. J Neurol 1999;246(5):339–46.
[3] Sayer RH, et al. Severe neurological events following liver transplantation. Arch Med Res 2007;38(1):75–9.
[4] Faraci M, et al. Mesial temporal sclerosis—a late complication in four allogeneic pediatric recipients with persistent seizures after an acute episode of cyclosporine-A neurotoxicity. Bone Marrow Transplant 2003;31(10):919–22.
[5] Dilena R, et al. Epilepsy surgery in a liver-transplanted girl with temporal lobe epilepsy and hippocampal sclerosis following PRES with status epilepticus. Eur J Paediatr Neurol 2016;20(4):652–6.
[6] Rege DE, et al. Neuropathologic complications in allogenic bone marrow transplant patients receiving cyclosporin. Bone Marrow Transplant 1991;8(5):393–401.
[7] Trullemans F, et al. Clinical findings and magnetic resonance imaging in severe cyclosporine-related neurotoxicity after allogenic bone marrow transplantation. Eur J Paediatr Neurol 2001;67(2):94–9.
[8] Bird CL, et al. Cyclosporin-associated akinetic mutism and extrapyramidal syndrome after liver transplantation. J Neurol Neurosurg Psychiatry 1990;53(12):1068–71.
[9] Cyclosporine neurotoxicity, N Engl J Med 1991;324(24):1744–5.
[10] Gaggin R, et al. Intractable epilepsy secondary to cyclosporine toxicity in children undergoing allogenic hematopoetic bone marrow transplantation. J Child Neurol 2006;21(10):861–6.
[11] Gleeson JG, et al. Cyclosporin A acute encephalopathy and seizure syndrome in childhood: clinical features and risk of seizure recurrence. J Child Neurol 1998;13(7):336–44.
[12] O’Sullivan DP. Convulsions associated with cyclosporin A. Br Med J (Clin Res Ed) 1985;290(6471):458.
[13] Endo A, et al. Posterior reversible encephalopathy syndrome in childhood: report of four cases and review of the literature. Pediatr Emerg Care 2012;28(2):153–7.
[14] Ayas M, Al-Jefri A, Al-Serhai A. In cyclosporine induced neurotoxicity, is tacrolimus an appropriate substitute or is it out of the frying pan and into the fire? Pediatr Blood Cancer 2009;50(2):246 [author reply 427].
[15] Chen LW, et al. Age-dependent vulnerability of cyclosporine-associated encephalopathy in children. Eur J Paediatr Neurol 2015;19(4):464–71.
[16] Hauben M. Cyclosporine neurotoxicity. Pharmacotherapy 1996;16(4):576–83.
[17] Zong ZD, et al. Analysis of seizure risk factors after allogeneic hematopoetic stem cell transplantation: a 8 case report and literature review. J Huazhong Univ Sci Technol Med Sci 2013;33(5):656–60.
[18] Völz A, et al. Predicting drug resistance in adult patients with generalized epilepsy: a case–control study. Epilepsy Behav 2015;53:126–30.
[19] Wirrell E, et al. Predictors and course of medically intractable epilepsy in young children presenting before 36 months of age: a retrospective, population-based study. Epilepsia 2012;53(9):1563–9.
[20] Seker Yılmaz B, Ökçüay C, Komur M. Predictors of intractable childhood epilepsy. Pediatr Neurol 2013;48(8):145–54.
[21] Camfield C, et al. Does the number of seizures before treatment influence ease of control or remission of childhood epilepsy? Not if the number is 10 or less. Neurology 1996;46(1):41–4.
[22] Kasai-Yoshida E, et al. Temporal lobe epilepsy with hippocampal sclerosis in acute lymphoblastic leukemia. Pediatrics 2013;132(1):e252–6.
[23] Loothai G, et al. Chronic herpes simplex type-1 encephalitis with intractable epilepsy in an immunosuppressed patient. Infection 2016;44(1):121–5.
[24] Zhang XD, et al. Epileptic seizures in patients following allogeneic hematopoietic stem cell transplantation: a retrospective analysis of incidence, risk factors, and survival rates. Clin Transplant 2013;27(1):80–9.
[25] Wieser HG. ILAE commission report. Mesial temporal lobe epilepsy with hippocampal sclerosis. Epilepsia 2004;45(6):695–714.
[26] Bien CG, Scheffler IE. Autoantibodies and epilepsy. Epilepsia 2011;52(Suppl 3):18–22.
[27] Giussani G, et al. A population-based study of active and drug-resistant epilepsies in Northern Italy. Epilepsy Behav 2016;55:30–7.
[28] Kwan P, Schachter SC, Brodie MJ. Drug-resistant epilepsy. N Engl J Med 2011;365(10):919–26.
[29] Meldrum BS, Rogawski MA. Molecular targets for antiepileptic drug development. Neurotherapeutics 2007;4(1):18–61.
[30] Levy GA, et al. Neoral in de novo liver transplantation: adequate immunosuppression without intravenous cyclosporine. Liver Transpl Surg 1997;3(6):571–7.
[31] Hemming AW, et al. Microembolization of cyclosporine without intravenous cyclosporine in liver transplantation. Transplantation 1998;66(2):1798–802.
[32] Webber A, et al. Tacrolimus versus cyclosporin as primary immunosuppression for kidney transplant recipients. Cochrane Database Syst Rev 2005(4):CD003961.
[33] Behcetin WO. Neurotoxicity of calcineurin inhibitors: impact and clinical management. Transpl Int 2000;13(5):313–26.
[34] Vogelsang GB, Arai S. Mycophenolate mofetil for the prevention and treatment of graft-versus-host disease following stem cell transplantation: preliminary findings. Bone Marrow Transplant 2001;27(12):1255–62.
[35] Jimenez-Perez M, et al. Everolimus plus mycophenolate mofetil as initial immunosuppression in liver transplantation. Transpl Proc 2015;47(1):90–2.
[36] Semah F, et al. Is the underlying cause of epilepsy a major prognostic factor for recurrence? Neurology 1998;51(5):1256–62.