Epilepsy & Behavior Case Reports 10 (2018) 8–13

Contents lists available at ScienceDirect

Epilepsy & Behavior Case Reports

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

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 [a], Yasunori Nagahama [b], Mark A. Granner [c], Matthew A. Howard [a,b,d], Hiroto Kawasaki [b], Brian J. Dlouhy [a,b,d,*]

[a] University of Iowa Carver College of Medicine, Iowa City, IA, USA
[b] Department of Neurosurgery, University of Iowa Hospitals and Clinics, Iowa City, IA, USA
[c] Department of Neurology, University of Iowa Hospitals and Clinics, Iowa City, IA, USA
[d] Pappajohn Biomedical Institute, University of Iowa Carver College of Medicine, Iowa City, IA, USA

ARTICLE INFO

Article history:
Received 7 January 2018
Received in revised form 19 January 2018
Accepted 27 January 2018
Available online 08 February 2018

Keywords:
Drug-resistant epilepsy
Medically intractable epilepsy
Antiseizure drugs
Seizures
Cyclosporine-A
Cyclosporine neurotoxicity
Transplant
Mesial temporal sclerosis

ABSTRACT

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 — all 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.

Literature review: Seven peer-reviewed studies described 15 patients who underwent transplantation with post-transplant CSA administration and subsequently developed DRE following an initial CSA-induced seizure. All 15 patients were children suggesting that young age is a risk factor for DRE after CSA-induced seizures. Initial CSA-induced seizures occurred at an average of 1.6 ± 1.1 months after transplant and seizure recurrence 9.2 ± 8.0 months after transplant. All reported CSA routes of administration (n = 6) were intravenous and 7 of 9 (78%) reported CSA blood levels above the therapeutic range. 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.

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 that and subsequent greater risk of DRE development.

1. 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 a common immunosuppressant drug utilized to prevent graft-versus-host disease (GvHD) in patients who undergo solid organ or bone marrow transplantation. Twenty to 40% of transplant patients experience a central nervous system (CNS) complication due to CSA, most commonly in the first few months post-transplant [1,2].

Acute CSA-induced neurotoxic effects include headache, encephalopathy, mental status changes, visual disturbances, akinetic mutism, stroke and seizures [3–9]. Seizures, the second most common of CSA-induced neurotoxic events, have been reported in 2.5–8.4% of pediatric and 1.5–5.5% of adult post-transplant patients [2,10–12]. The neurotoxic effects of CSA often resolve after discontinuing CSA, switching to a different immunosuppressant drug such as tacrolimus, or administering

* Corresponding author at: Department of Neurosurgery, University of Iowa Children's Hospital, University of Iowa Hospitals and Clinics, 200 Hawkins Drive, Iowa City, IA 52242, USA.
E-mail address: brian-dlouhy@uiowa.edu (B.J. Dlouhy).

https://doi.org/10.1016/j.ebcr.2018.01.002

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, 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 epilepticus 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 to 4–5 times per week. Antiseizure drug trials of lamotrigine, levetiracetam, phenytoin and oxcarbazepine were largely unsuccessful in controlling his seizures. No autoantibody 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 Ib) 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