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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

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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

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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

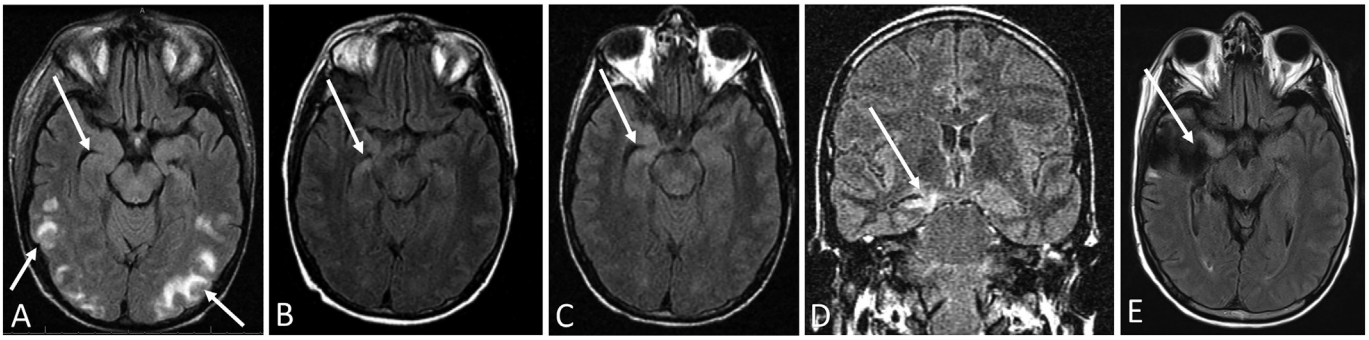

Fig. 1. Axial T2 MRI of MTS progression and post-operative outcome. A) Axial FLAIR MRI following cyclosporine-induced seizure showing diffuse occipital and parietal signal intensity increase consistent with posterior reversible encephalopathy syndrome (PRES). No preexisting mesial temporal sclerosis present. B) Axial FLAIR MRI after first seizure recurrence showing subtle signal intensity increase in right insular cortex and hippocampus with volume loss. C) Axial FLAIR MRI 10 months post-seizure recurrence showing slight right hippocampal signal intensity and volume loss indicative of right mesial temporal sclerosis (MTS). D) Coronal FLAIR MRI 2 years post-seizure recurrence showing marked right hippocampal signal intensity and volume loss. E) Axial FLAIR MRI showing post-operative resection of hippocampus and amygdala.

with a mean age of 5.5 years at transplant (range: 2.3–15 years). All but three patients had no history of prior seizures (three patients had history of febrile seizures). Nine of fifteen patients (60%) had a hematopoietic stem cell transplant (HSCT), and the remaining (40%) had solid organ transplants. Initial CSA-induced seizures occurred an average of 1.6 ± 1.1 months after transplant and seizure recurrence 9.2 ± 8.0 months after transplant (recurrence time N/A for 9 patients). All reported CSA routes of administration (n = 6) were intravenous and 7 of 9 (78%) reported CSA blood levels above the therapeutic range. MTS on neuroimaging was observed in 40% (n = 6) with one confirmed by pathology. Only 13% (n = 2) underwent a temporal lobectomy and amygdalohippocampectomy. Latest follow-ups of an average 6.9 years' post-transplant reveal that 80% (n = 12) continued to have seizures while the two patients with anterior temporal lobectomies were seizure-free. One patient died five months' post-transplant due to deteriorating neurological status.

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, developmental delay, motor or mental deficiencies, and traumatic brain injury [11,18–20]. These risks factors are increased if the patient has had more than 10 seizures before receiving antiseizure treatment or has a seizure frequency of greater than one per month [18,21]. Intrathecal chemotherapy, intensive pre-transplant chemotherapy or total body irradiation may contribute to these risk factors [2,22]. If the patient presents with these significant pre-transplant risk factors, pursuing an alternative to cyclosporine for GvHD prevention could be considered. In addition to these pre-transplant risk factors, post-transplant risk factors for intractable epilepsy development include CSA neurotoxicity, young age, GvHD, herpes simplex 1 infection, 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]. Additionally, most adults that go on to develop DRE have had medically-controlled epilepsy since age 12 or younger (about 80%) [18]. Although drug-resistance etiology in epilepsy is multifactorial and not well

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

	Type	Characteristics	Frequency
Seizure semiology	Focal aware seizures	Numbness/tingles of LUE, odd smell/taste	Several/day
	Focal impaired awareness seizures	Numbness/tingles of LUE, odd smell/taste, left eye blink, giggle, left hand claw, unaware, unresponsive	4–5/week
	GTCS	Numbness/tingles of LUE, odd smell/taste, generalized convulsions, LOC	3 lifetime

	Time of surgery	Failed
Antiseizure drugs	Levetiracetam, lamotrigine	Phenytoin, levetiracetam, oxcarbazepine
	Ictal	Interictal
EEG	Localized to right anterior temporal lobe	Right temporal slowing, occasional right anterior temporal sharp waves
	MRI	PET
Neuroimaging	Right mesiotemporal sclerosis	Right temporal hypometabolism
Neuropsychology cognitive assessment	Bilateral mesial temporal lobe dysfunction, moderate anterograde memory impairments	

	Visual memory	Verbal memory	Language
Wada testing	Left lateralizing	Left lateralizing	Left lateralizing

GTCS = generalized tonic–clonic seizure; LUE = left upper extremity; LOC = loss of consciousness; MRI = magnetic resonance imaging; PET = positron emission tomography.

Table 2
Literature review of a CSA-induced seizure followed by development of drug-resistant epilepsy — transplant and first seizure.

Patient #	Author	Year	Patient transplant					First CSA-induced seizure			
			Age at transplant/ Gender	Underlying disease	Transplant type	Prophylactic GvHD regimen	CSA dose (mg/kg/day), administration	Time (months) PT	Seizure type/neurological events	CSA blood levels (ng/ml)[b]	Long-term CSA discontinuation?
1	Gleeson et al.	1998	15/M	Polymyositis	Heart	CSA	NA	0 (1 day)	FIAS, clonic jerks	342	NA
2	Gleeson et al.	1998	6/M	GN	Renal	CSA	NA	0.7	GTCS, visual disturbance, occipital HA	350	NA
3	Gleeson et al.	1998	4/M	Biliary atresia	Liver	CSA	NA	3.0	SE, listless	550	NA
4	Faraci et al.[a]	2003	2.9/M	HLH	HSCT	CSA, ATG, MTX	3, i.v.	3.0	GS, visual disturbance, HBP	WNL	N, discontinued after 4.3 years
5	Faraci et al.[a]	2003	3.9/M	Osteopetrosis	HSCT	CSA	1, i.v.	1.7	GS, cortical blindness	2410	Y, substituted other ISPs
6	Faraci et al.[a]	2003	3.3/M	HLH	HSCT	CSA, Campath 1G,MTX	3, i.v.	2.0	GS, coma (grade 2), HBP	375	N, reduced dose, discontinued after 1.8 years
7	Gaggero et al.[c]	2006	6/M	ALL	HSCT	CSA	1, i.v.	2.5	GS, visual disturbance, HBP	377	N, discontinued for 2 days, low dose reintroduced
8	Ayas et al.	2008	11/F	ALL	HSCT	CSA,MTX	NA	0.4	GS	WNL	Y, switched to tacrolimus
9	Endo et al.	2012	6/F	Aplastic anemia	HSCT	CSA	3, i.v.	0.7	GS, LOC, HBP	NA	Y, later switched to tacrolimus
10	Chen et al.	2015	3.2/NA	Nephrotic syndrome	Renal	CSA	NA	1.0	SE, altered mental status	NA	NA
11	Chen et al.	2015	2.3/NA	Nephrotic syndrome	Renal	CSA	NA	1.0	SE, altered mental status, aggressive behavior	NA	NA
12	Chen et al.	2015	5.2/NA	Acute leukemia	HSCT	CSA	NA	2.8	Cluster sz, cortical blindness, altered mental status	NA	NA
13	Chen et al.	2015	5.4/NA	Acute leukemia	HSCT	CSA	NA	0.6	SE, altered mental status	NA	NA
14	Chen et al.	2015	5.5/NA	Thalassemia	HSCT	CSA	NA	2.7	SE, altered mental status	NA	NA
15	Dilena et al.	2016	3/F	Cirrhosis	Liver	CSA	1.5, i.v.	0.1	FIAS, clonic jerks, HBP	479	Y, switched to tacrolimus

ALL = acute lymphatic leukemia; ATG = anti-thymocyte globulin; FIAS = focal impaired awareness seizure; CSA = cyclosporine A; F = female; F/U = follow-up; GN = glomerulonephritis; GS = generalized seizure; GTCS = generalized tonic–clonic seizure; HA = headache; HLH = hemophagocytic lymphohistiocytosis; HBP = high blood pressure; HSCT = hematopoietic stem cell transplant; ISP = immunosuppressants; LOC = loss of consciousness; M = male; MTS = mesial temporal sclerosis; MTX = methotrexate; N = no; NA = data not available; PT = post-transplant; SE = status epilepticus; sz = seizures; WNL = within normal limits; Y = yes.

[a] History of febrile seizures prior to transplant.

[b] Therapeutic range: 100–200 ng/ml.

[c] Patient originally described in Faraci et al., 2003 and since updated in Gaggero et al., 2006.

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 adult with CSA-induced seizures due to his complex immunological history and degree of CSA neurotoxicity (second highest CSA blood level out of all patients in literature review).

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 with no difference in acute rejection occurrence [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 followed by readministration at a reduced dose. Often this is effective in reversing neurological symptoms, although ineffective in patients that may have experienced irreversible brain damage due to their initial CSA-induced seizure. The long-term neurotoxic effects of continuing CSA or tacrolimus beyond the early posttransplant period (one month) are unclear [33]. Potential alternatives to high dose calcineurin inhibitors, shown to exhibit lower permanent neurological side effects, are mycophenolate mofetil (either as a monotherapy or in combination with low dose CSA/tacrolimus) and mTOR inhibitors, such as everolimus [34]. However, these therapies may not achieve adequate immunosuppression for GvHD prevention in comparison to CSA and tacrolimus [35].

Table 3
Literature review of a CSA-induced seizure followed by development of drug-resistant epilepsy — epilepsy and outcomes.

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

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