Indian Journal of
Neurology

Open Science Publications

Volume 2, Issue 1 - 2021

www.opensciencepublications.com

Cyclosporine Induced Mesial Temporal Sclerosis - A Case Report

Case Report

Sachin SJ[1]*, Shalaka S[2], Goutham KJ[2], Smruthy AM[2], Anjali M[1], Priyank T[2], Hrishi V[2], Amey CP[1], Nishit[1] and Shivakumar S[3]

[1]*Deparment of Haematology and Stem cell transplant, HCG Cancer Hospital, India*

[2]*Deparment of Clinical Pharmacology, HCG Cancer Hospital, India*

[3]*Deparment of Radiology, HCG Cancer Hospital, India*

***Corresponding author:** Dr. Sachin SJ, Group Head, Haematology and Stem Cell Transplant, HCG Cancer Hospital, Bangalore India, Tel: 9741351357; Email: drsachin.jadhav@hcgel.com

Article Information: **Submission:** 13/10/2021; **Accepted:** 18/11/2021; **Published:** 20/11/2021

Abstract

Cyclosporine is an imperative part of GvHD prophylaxis post-transplant. It acts as an immunosuppressive agent by targeting T-cells and inhibiting the activation cascade for lymphokine production. Among much toxicity, Cyclosporine induced neurotoxicity remains slightly daunting owing to inadequate number of studies elucidating the mechanism and implication behind it. The toxicities present with varying symptoms such as visual disturbances, ataxia, seizure episodes and signs of encephalopathy. Herein We report a case of AML, FLT3-ITD mutated with low allelic ratio, C-KIT mutated and AML 1-ETO positive, Post Allogenic stem cell transplant on cyclosporine for immunosuppression which induced Mesial temporal sclerosis. Cyclosporine induced Mesial Temporal Sclerosis is inadequately reported and therefore briefly understood. The availability of case reports with similar clinical picture encourages further study to understand the risk factors and consequent management of the toxicity.

Keywords: Cyclosporine; Mesial Temporal Sclerosis

Introduction

Cyclosporine (CSA)is an imperative part of Graft vs Host Disease (GvHD) prophylaxis post-transplant. It acts as an immunosuppressive agent by targeting T-cells and inhibiting the activation cascade for lymphokine production. Among many toxicities, CSA induced neurotoxicity remains slightly daunting owing to inadequate number of studies elucidating the mechanism and implication behind it. The toxicities present with varying symptoms such as visual disturbances, ataxia, seizure episodes and signs of encephalopathy [1-3].

Among the several manifestations of neurotoxicity, Mesial Temporal Sclerosis (MTS) also known as hippocampal sclerosis is very rare and scarcely reported. It is considered to be one of the causes of drug resistant epilepsy among adults. It is characterized by structural and functional alterations and brain lesions in the hippocampus. It is also considered to be a secondary consequence of seizure activity as it is vulnerable to prolonged seizures, traumatic brain injuries and other inflammation [4].

This case report describes a patient a known case of Acute Myeloid Leukemia, treated as per guidelines, post haploidentical stem cell transplant who developed prominent hippocampal and Para hippocampal changes in MRI indicating Mesial Temporal Sclerosis, after the use of CSA. Due consent was taken before writing the report.

Case Details

Herein reported is the case of a 39-year-old female. An evaluation following complaints of generalized weakness, bleeding per vaginal and passing clots, revealed 52% blasts in peripheral smear.

Consequently, bone marrow aspiration biopsy with flow cytometry and Fluorescence in situ hybridization (FISH) reports led to the diagnosis of Acute Myeloid Leukaemia (AML), FLT3-ITD mutated with low allelic ratio, C-KIT mutated and AML 1-ETO positive. Her induction therapy included 7+3 regimen with Daunorubicin and Cytarabine, during which she developed an episode of hyponatremia induced seizures(Na+: 116 mg/dL). She was prescribed Levetiracetam thereafter for appropriate epilepsy control.

Her bone marrow post one cycle of consolidation with intermediate dose Cytarabine, showed remission and FLT3-ITD was negative. She was counselled and initiated on conditioning therapy for Haploidentical Stem Cell Transplant in CR1. Conditioning regimen comprised of Fludarabine, Treosulfan, Anti-thymocyte globulin (ATG) and Total Body Irradiation (TBI). Post stem cell transplant she had one fever spike and XCyton revealed Aspergillus in the blood. She was treated with Voriconazole for the same. She presented with Grade 2 mucositis and radiation induced dermatitis which resolved eventually. Patient was on CSA for GvHD prophylaxis.On D+35 she was admitted for Cytomegalovirus (CMV) colitis and CMV pneumonitis (Viral load: 1,69,100 cp/mL). She was treated with Ganciclovir (28 days) and IV-Ig for the same. Subsequent CMV-PCRs were negative.

OnD +104, she was admitted to the hospital with complaints of febrile episodes, with a recorded temperature of 100.4 °F. Her vitals were stable and an unhealthy mucosa in the oral cavity was noted, indicating resolving acute oral GvHD. Her initial blood biochemistry revealed low potassium and magnesium levels (K+: 2.63 mg/dL; Mg2+: 0.8 mg/dL) and CSA trough levels were 27.85 ng/mL. Required microbiology profiles were sent for evaluation and she was treated with appropriate antibiotics and electrolyte corrections.

On D+106, the patient complained of generalized weakness which worsened on standing. The following day, the patient complained of blurring of vision and loss in the center of field of vision. There was no history of falls, blackouts or seizures. On examination she presented right sided ataxia and scotoma of the left eye. There was non-specific imbalance in gait. Her motor score was 4/5 for both upper limbs and lower limbs. An MRI done, revealed Prominent right choroid fissure with volume loss of right hippocampus, Para hippocampal gyrus and bilateral mamillary bodies. These findings raised a concern for and indicated Mesial Temporal Sclerosis (Figure 1). Repeated Cyclosporin trough levels were 152.29 ng/mL. Given there was no history of trauma or recent episodes of seizures, drug toxicity were suspected. CSA in known to cause neurological adverse reactions such as PRES, visual disturbances and cerebellar ataxia. Using the WHO-UMC Adverse Drug Reaction (ADR) causality assessment scale, the reaction was graded as Certain [5].

Based on the literature available and the patient's condition, a decision was taken to discontinue CSA and replace it with Mycophenolate Mofetil. Following the change in medication, the patient's vision improved and her gait stabilized. There were no episodes of seizures or falls in the coming days. She recovered from the adverse effect with no residual symptoms.

Discussion

Cyclosporin, a lipophilic cyclic oligopeptide, is a potent immunosuppressant which is widely used in transplant setting. CSA exerts its immunosuppressant action via reversibly inhibiting the activation of primary T-helper cells and the consequent release of lymphokines such as interleukine-2 (IL-2). CSA binds to various blood components such as lipoproteins, erythrocytes and leukocytes, leaving less than 5% free drug concentration. Thus, lipoprotein structures serve as drug reservoir. It is extensively metabolized in the liver by the CYP450 family, its metabolites having inferior immunosuppressive action. However, the metabolites tend to be more toxic [1, 6].

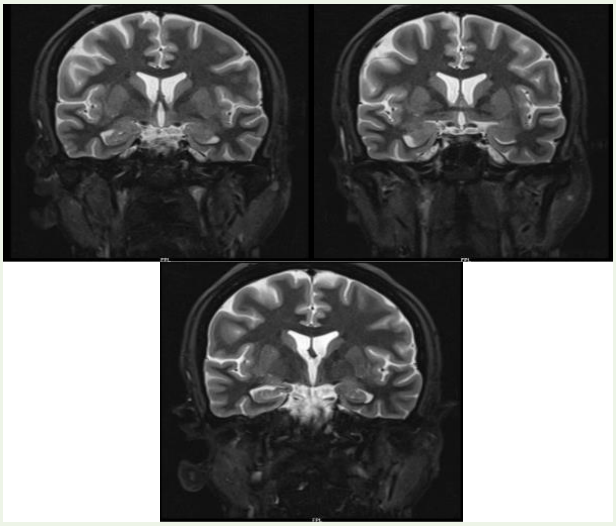

Figure 1: T2 coronol MRI Images showing Prominent right choroid fissure with volume loss of right hippocampus (A, B), Para hippocampal gyrus (C) and bilateral mamillary bodies, indicating Mesial Temporal Sclerosis.

CSA requires stringent therapeutic drug monitoring owing to its narrow therapeutic index and variable absorption. While there is a risk of subclinical dose, there is also a risk of adverse events if the plasma concentrations are above the desired range [6]. Hypertension and renal damage have been established toxicities among others. Despite a fair incidence of neurotoxicity induced by CSA, it remains an inadequately studied adverse effect of the drug [7].

CSA induced neurotoxicity presents with a spectrum of symptoms ranging from mild visual disturbance and ataxia to severe encephalopathy, seizures and related changes in Magnetic Resonance Image. Many of the lower grade symptoms and damages appear to be reversible. However, the risk of irreversible changes induced by the symptoms of neurotoxicity such as seizures and encephalopathy also remain [7, 8].

The mechanism of CSA induced neurotoxicity is poorly understood however a few experimental studies point towards interference in mitochondrial function and induction of neuronal apoptosis. Studies also suggest the neurotoxicity to be a result of direct neuronal synaptic hyperexcitability, or indirect damage to brain vasculopathy by the release of vasoconstrictors such as endothelin or thromboxane which cause vaso spasm. Additionally, studies suggest, lower plasma levels of cholesterol may contribute to

Citation: Sachin SJ, Shalaka S, Goutham KJ, Smruthy AM, Anjali M, et al. Cyclosporine Induced Mesial Temporal Sclerosis - A Case Report. Indian J Neurol. 2021;2(1): 104.

higher toxicity rates, given the drug is highly lipoprotein bound. In situations where, blood levels of CSA are higher than the therapeutic range, neurotoxicity symptoms can be expected, however, studies suggest that the milder symptoms can occur at concentrations well within the therapeutic range as well [1, 8-10].

A case series by Anna Noè et al, presented the clinical picture of six patients who developed varied symptoms of neurotoxicity due to CSA such as seizures, signs of endocranial hypertension and MRI images implying reversible leukoencephalopathy. The drug levels were within the desired therapeutic range, indicating higher blood levels are not necessarily a risk factor for neurotoxicity. Interestingly, the occurrence of evident neurotoxicity in these patients was preceded by symptoms of arterial hypertension, headache, visual disturbances and vomiting. These patients were then prescribed Tacrolimus following which the patients remained symptom-free at median survival of 882 days [11]. Our patient experienced a similar pattern, where she presented with visual disturbance and gait imbalance, before the MRI investigation. Three days following the withdrawal of CSA, the patient symptoms improved.

While Mesial Temporal sclerosis, a highly epileptogenic lesion marked by changes in hippocampus, and amygdala, can be considered as a manifestation of neurotoxicity, reports of CSA induced MTS are scarce. A case serious published by M Faraci et al, elucidated similar findings as our patient in pediatric patients post BMT. Three out of four of the patients developed seizures induced by toxic levels of CSA. The symptoms recurred even on rechallenging the drug making it certain the neurotoxicity was caused by CSA. The authors theorized that factors such as neurotoxic therapy in first line and conditioning regimens along with history of febrile seizures and other CNS injuries may have induced irreversible vascular damage causing hippocampal shrinkage and subsequent MTS. [10]. Some recent studies done, have shed light on the possible risk factors for CSA induced neurotoxicity. A retrospective observational study done by Alberto Lue et al, among patients who underwent liver transplant elucidated the risk factors of CSA induced neurotoxicity. Although, the transplant setting is different from our patient, some non-specific risk factors such as previous history of encephalopathy, and pre-transplant Sodium levels can be recognized. A retrospective case series study by Yong Wang et al, among children who underwent haploidentical stem cell transplant, reported hypertension to be higher among the group with CSA induced neurotoxicity than the non-neurotoxicity group. Transient headache was another common prodrome among these patients [12, 13].

CSA induced mesial temporal sclerosis although rare, needs to be studied elaborately to understand its occurrence and implications. Contrary to previous reports we observed that MTS is not always preceded by elevated plasma CSA levels or seizure episodes. Therefore, it is advisable to monitor symptoms of neurotoxicity among patients receiving CSA.

Conclusion

CSA induced Mesial Temporal Sclerosis is inadequately reported and therefore briefly understood. The availability of case reports with similar clinical picture encourages further study to understand the risk factors and consequent management of the toxicity. Studies have indirectly pointed towards certain predictors such as changes in blood pressure and occurrence of headaches; however, dedicated studies will help us understand the event in more detail.

References

1. Kahan BD (1989) Cyclosporine. New England Journal of Medicine 321: 1725-1738.
2. Reece DE, Frei-Lahr DA, Shepherd JD, Dorovini-Zis K, Gascoyne RD (1991) Neurologic complications in allogeneic bone marrow transplant patients receiving cyclosporin. Bone marrow transplantation 8: 393-340
3. Gleeson JG, duPlessis AJ, Barnes PD, Riviello Jr JJ (1998) Cyclosporin A acute encephalopathy and seizure syndrome in childhood: clinical features and risk of seizure recurrence. J Child Neurol 13: 336-44.
4. Walker MC (2015) Hippocampal sclerosis: causes and prevention. Semin Neurol 35: 193-200.
5. Who causality assessment? (2021) world health organization [Internet]. WHO UMC Causality Assessment Scale.
6. Jorga A, Holt DW, Johnston A (2004) Therapeutic drug monitoring of cyclosporine. InTransplantation proceedings 36: 396-403.
7. Gijtenbeek JM, Van den Bent MJ, Vecht CJ (1999) Cyclosporine neurotoxicity: a review. J Neurol 246: 339-346.
8. Faraci M, Lanino E, Dallorso S, Morreale G, Cappelli B (2003) Mesial temporal sclerosis–a late complication in four allogeneic pediatric recipients with persistent seizures after an acute episode of cyclosporine-A neurotoxicity. Bone marrow transplantation 31: 919-922.
9. McDonald JW, Goldberg MP, Gwag BJ, Chi SI, Choi DW (1996) Cyclosporine induces neuronal apoptosis and selective oligodendrocyte death in cortical cultures. Annals of Neurology: Official Ann Neurol 40: 750-758.
10. Serkova NJ, Christians U, Benet LZ (2004) Biochemical mechanisms of cyclosporine neurotoxicity. Molecular interventions. 4: 97.
11. Noè A, Cappelli B, Biffi A, Chiesa R, Frugnoli I, et al. (2010) High incidence of severe cyclosporine neurotoxicity in children affected by haemoglobinopaties undergoing myeloablative haematopoietic stem cell transplantation: early diagnosis and prompt intervention ameliorates neurological outcome. Italian journal of pediatrics. 36: 1-6.
12. Lué A, Martinez E, Navarro M, Laredo V, Lorente S, et al. (2019) Donor age predicts calcineurin inhibitor induced neurotoxicity after liver transplantation. Transplantation 103: 211-215.
13. Wang Y, Zheng Y, Wen J, Ren J, Yuan X, et al. (2021) Cyclosporine A-related neurotoxicity after haploidentical hematopoietic stem cell transplantation in children with hematopathy. Ital J Pediatr 47: 83.

Citation: Sachin SJ, Shalaka S, Goutham KJ, Smruthy AM, Anjali M, et al. Cyclosporine Induced Mesial Temporal Sclerosis - A Case Report. Indian J Neurol. 2021;2(1): 104.