Cyclosporine induced neurotoxicity in a stem cell transplant recipient

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Abstract

Neurological complications are quite frequent in stem cell transplant (SCT) recipients. Major causes are conditioning regimen toxicity, metabolic and electrolyte disturbances, viral infections and cyclosporine related toxicity.

Cyclosporine induced neurotoxicity is a well documented complication in stem cell transplant recipients. These patients usually present with seizures which are easily controlled with anti-convulsants and by reducing/withholding the drug. However uncontrolled seizures requiring ventilatory support are rarely reported. Here we present a case report of cyclosporine induced uncontrolled seizures in a young female after allogeneic SCT which was unresponsive to anti-convulsive therapy but was successfully treated with mechanical ventilatory support.

Introduction

Bone Marrow transplant recipients are predisposed to generalized seizures for a variety of reasons. This predisposition starts during conditioning, and continues after transplant for as long as the patient is on immunosuppressive treatment. Total body irradiation (TBI) and drugs like busulphan, etoposide, cyclosporine (CSA) and antibiotics used during conditioning increase patients' susceptibility to seizures.[1-3] After transplant variety of other factors come into play which increase patients predisposition to fits, these include hypertension, steroids used for GvHD prophylaxis, electrolyte imbalance especially hypomagnesaemia, infections, intracerebral and subarachnoid haemorrhage.[4]

The seizures are normally shortlived and easy to

control with conventional treatment. We describe here a patient of aplastic anaemia who presented three months after allogeneic transplant with headache, blurring of vision and uncontrolled seizures, which were refractory to all conventional treatment.

Case report

A 22 years old female with aplastic anaemia underwent allogeneic stem cell transplant (allo SCT) from her sibling sister in May 2005 after conditioning with cyclophosphamide 50mg/kg daily for 04 days (total dose: 200 mg/kg) and antithymocyte globulin (Lymphoglobulin-Sang stat- Lyon- France) 15 mg/kg daily for 03 days (total dose: 45mg/kg) . She had a smooth post transplant recovery and was discharged from hospital on D+18 post SCT. She was receiving cyclosporine (5mg/kg in two divided doses daily) and methyl prednisolone (0.5mg/kg daily) as GvHD prophylaxis and was on regular follow up in out patient department. On Day +27 post SCT she was brought in emergency with complaints of severe headache, vomiting, blurring of vision in both eyes, twitching of face and eyelids. On examination, she was conscious and oriented, her BP was 160/100 mm Hg, pupils were reactive and equal and there was no neck stiffness. Fundoscopy revealed no papilloedema. Her reflexes were normal with down going plantars. Considering the possibility of CSA toxicity, the next dose of CSA was withheld and blood was sent to the laboratory for CSA level. Complete blood count and chemistry including urea, creatinine, electrolytes, liver functions, and glucose levels were also carried out.

Shortly afterwards she started having generalized tonic and clonic seizures. She was initially given intravenous diazepam (10mg), along with other supportive measures (airway maintenance, 25% dextrose 100 ml). Diazepam was repeated after 10 minutes as slight jerky movements of the limbs persisted and loading dose of phenytoin sodium (20mg/kg) was also given. However, fits recurred within few minutes and she was given another dose of diazepam 10mg intravenously. Generalized seizures were uncontrollable despite all active measures. After an hours effort during which her vital signs were carefully monitored and magnesium sulphate infusion started, it was decided to put her on mechanical ventilation under general anaesthesia to prevent further fits and to avoid any damage to vital organs. She remained on the ventilator for next two days and was then gradually weaned off. Her cyclosporine level received next day was 931ng/ml. Her blood counts and chemistry were within normal limits. Upon recovery she was restarted on lower dose of cyclosporine (3mg/kg daily) with mycofenolate mofetil (30mg/kg daily). Later on CSA was replaced by mycofenolate mofetil. Today at 20 months post SCT, she is off all immuno suppressive therapy and is leading a healthy life. It is worth mentioning here that a couple of weeks ago she gave birth to a healthy girl.

Discussion

Neurological complications and seizures are an important cause of treatment related morbidity and mortality in SCT patients. Neurological complications have been described in 11-59% SCT patients. The clinical presentation in the early post transplant period has most frequently included convulsions, cranial nerve palsies and symptoms consistent with increased intra cranial pressure.[5]

Cyclosporine metabolic encephalopathy has been described as one of the most important etiological factors for development of neurological symptoms.[6] Other causes leading to neurological complications have been reported to be systemic infection, cerebrovascular lesions, micro angiopathy, busulphan induced seizures and other factors.[2]

Even though cyclosporine is not believed to cross the intact blood brain barrier, neurological side effects occur is about 20 percent organ transplant recipients, resulting in tremors, burning paraesthesias, headache, flushing, depression, confusion and somnolence. Seizures of new onset may be triggered by hypocholesterolemia, hypertension, intravenous methyl prednisolone therapy, hypomagnesaemia, infection, haemorrhage and cerebral infarction. Visual disorders, paresis, disorientation and coma improve when CSA is discontinued but recur when reinstituted. On computerized axial tomography, the occurence of a neurotoxic effect is associated with white matter hypodensity, which suggests increased water content in the brain.[7]

A retrospective review of 239 recipients of SCT given CSA based GvHD prophylaxis revealed that 10 patients (4.2%) experienced a syndrome characterized by hypertension, severe visual disturbances, seizures and occipital lobe density changes on CT brain. Neurological findings were reversible after temporary discontinuation of CSA. This study also identified the risk factors for neurotoxicity as use of unrelated or HLA mismatched related donors, administration of etoposide or total body irradiation as part of conditioning, use of cortico-steroids for prophylaxis or treatment of acute GvHD or development of either acute GvHD or clinically significant microangiopathic haemolytic anaemia (MAHA) post SCT.[1] This reversible syndrome of headache, altered mental functioning, seizures, loss of vision associated with findings indicating predominantly posterior leukoencephalopathy on imaging studies is labeled as reversible posterior leukoencephalopathy syndrome.[8]

Recently a syndrome of irreversible leukoencephalopathy has been reported in six children after allogeneic SCT, who received CSA for GvHD prophylaxis. These children exhibited progressive and continued severe neurological deterioration lasting for more than 2 weeks and consistent with non-localizing CNS abnormalities.[8] For SCT recipients who develop-CSA induced neurotoxicity alternative GvHD prophylaxis treatment is needed. Tacrolimus (FK506) and mycofenolate mofetil have been evaluated in such patients and found effective and relatively safe.[9]

Our patient was receiving CSA along with steroids when he developed this complication. Initially CSA was restarted in low dose combined with mycofenolate mofetil. Later on CSA was totally replaced by mycofenolate mofetil due to CSA induced nephrotoxicity.

In summary CSA has multiple interactions with commonly used drugs beside its direct side effects like neurotoxicity and nephrotoxicity, which further potentiate its adverse effects. These drugs alter its metabolism leading to either dangerously high or low blood levels, which can render the drug either useless or toxic. Therefore, it is of paramount importance that when prescribing CSA with other drugs its interactions be kept in mind. We recommend that strict and regular monitoring of CSA levels is recommended in transplant recipients, particularly, when these patients are on multiple drugs during post-transplant follow up.

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