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Case Report
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Lennox-Gastaut Syndrome after Hematopoietic Stem Cell Transplantation: A Case Report and Review of the Literature

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Abstract

Hematopoietic Stem Cell Transplantation (HSCT) is one of the most important methods for treating hematopoietic diseases. Herein, we report a pediatric case developing epileptic encephalopathy after HSCT. We reviewed the literature and summarized the possible mechanism. In the future work of hematopoietic stem cell transplantation, we need to avoid possible risk factors as much as possible.

Keywords: Lennox-gastaut syndrome; Hematopoietic stem cell transplantation; Epilepsy

Abbreviations

HSCT: Hematopoietic Stem Cell Transplantation; LGS: Lennox Gastaut Syndrome; HLA: Human Leukocyte Antigen; EEG: Electroencephalogram; MRI: Magnetic Resonance Imaging; PRES: Posterior Reversible Encephalopathy Syndrome; CsA: Cyclosporine

Introduction

Hematopoietic Stem Cell Transplantation (HSCT) is one of the most important methods for treating hematopoietic diseases. With the application of HSCT, reports of post-transplant complications have also been increased, including reports of postoperative epilepsy, but there are few reports of postoperative epilepsy encephalopathy. Herein, we describe a 6 year old patient with Lennox-Gastaut Syndrome (LGS) after hematopoietic stem cell transplantation.

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Case Presentation

Our patient had been diagnosed with beta-thalassemia at the age of 6 months. She was the first child of healthy parents, and was born at 39 weeks of gestation. Birth weight was 2,670 g; length 49 cm. Apgar scores were both 10 at 1 and 5 min. The patient began repeated transfusion treatment at the age of half a year, about once a month. She is growing normally. She underwent "hematopoietic stem cell transplantation" in another hospital for "beta thalassemia" On January 2, 2014, at the age of 2 years and 6 months. The pretreatment of transplantation from 23rd December 2013, included cyclophosphamide, busulfan, fludarabine, thiotepa and antithymocyte globulin. The medication during the transplant period was shown in Figure 1. The donor was from the patient's mother and the Human Leukocyte Antigen (HLA) did not match perfectly (8/10, DQ, DR sites did not match). At 34 months of life, four months after surgery, sudden atonic falls were observed. At 41 months, she developed tonic seizures that became drug resistant. At the same time, atypical absences were also observed. After the seizure, the patient showed a progressive decline in intelligence, manifested as gradually unable to know her family, unable to eat by herself, unable to communicate, and incontinence. The clinical presentation of seizures, intellectual disability and Electroencephalogram (EEG) features (Figure 2) were all consistent with the diagnosis of the criteria of LGS. Different multiple antiepileptic drugs (levetiracetam, topiramate, clonazepam, valproate, lamotrigine, lacosamide and ketogenic-diet) were tried but failed to achieve a completely seizure-free period. Cerebral Magnetic Resonance Imaging (MRI) performed at 3 and 4 years revealed no cortical or white matter abnormalities (Figure 3,4).

Discussion

In previous reports, the incidence of epilepsy after hematopoietic stem cell transplantation is low, about 1.6% to 20% [1-9]. There are various types of seizures reported, most of which are Posterior Reversible Encephalopathy Syndrome (PRES) and temporal lobe epilepsy. Reports of

Name:					EF	62%	Patient F	HBsAg-, HBsAb+, HCV-Ab-, CMV IgM-IgG+, EBV-IgG+												
Age:2y5m,girl					BNP	Pg/ml	DonarF,28y	HBsAg-, HBsAb+, HCV-Ab-, CMV IgM-IgG+, EBV-IgG+												
BW:12.5kg					Ferritin	3162.8ng/ml	HLA	A		B		DRB1		DQB1		ABO				
Square:0.555m^2					L/S	3.5/0cm	Patient	2402	3303	4601	5801	0301	0901	0201	0303	O+				
							Mother	2402	3303	4601	5801	1301	0901	0603	0303	O+				
Deferrioxamine 0.5g(40mg/kg/d) hydroxyguanidine 0.25 bid (30mg/kg/d) Azathiopurine25mg bid(3mg/kg/d),to keep Hb more than 120g/L																				
Cy :608mg/Kg/d iv×2 (116mg/kg) Busulfan :3.8mg/kd/d×3 Fludarabine 40mg/m^2×5 Thiotepa(TT):5 mg/kd/d×1 ATG-F: 5mg/kd/d×3																				
Ursodeoxycholic acid 0.15g(12mg/kg/d) until +3month																				
Hepatin 1500u (100u/kg/d) 20hr continuing iv until + 20d if no VOD																				
CSA 20mg (1.5mg/kg/d iv)										CSA 38mg (3mg/kg/d iv) to keep 200±50ng/ml, to change as soon as po (7.5mg/kg/d)										
Cy:750mg×2					Flu:22.2mg×2							MMF 200mg bid(30mg/kg/d)beginning at 6hs post infusion→ d30 if no GVHD								
↓	↓				↓	↓	↓	↓	↓											
22/12	23	24	25	26	27	28	29	30	31	1	2/1	3	4	5	6	7	8	9	10	11
d-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2	3	4	5	6	7	8	9
T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W
			↑	↑	↑	65mg		↑	↑	↑	PBS									
			Bu:12.35mgq6h IV			TTbid		ATG(65mg×3d)			CT	MTX	CF	MTX	CT		MTX	CF		
							↑	↑	↑	↑		10mg/m^2		7mg/m^2			7mg/m^2			
							Donar: G-CSF 10ug/kg/d, qd×5													
12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	1/2
d+10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
T	F	S	S	M	T	W	T	F	S	S	M	T	W	T	F	S	S	M	T	W
CSA 38mg (3mg/kg/d iv) to keep 200±50ng/ml, to change as soon as po (7.5mg/kg/d) (2.5times of iv)																				
MMF 200mg bid (30mg/kg/d) beginning at 6hs post infusion→ d30 if no GVHD																				

Figure 1: Medication during transplantation.

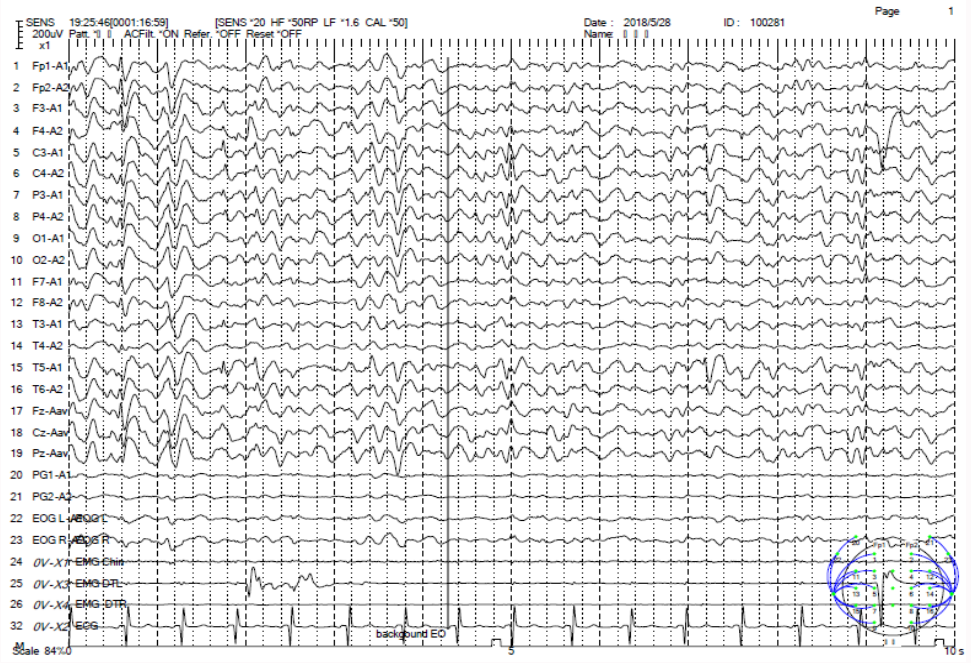

Figure 2a: Interictal EEG showed abnormal background activity associated with slow waves predominant in the posterior area.

epileptic encephalopathy are lacking. LGS is a severe childhood epileptic encephalopathy characterized by multiple and drug resistant seizure types, specific EEG patterns, and cognitive disability. Approximately 70% to 80% of patients show a known structural brain disorder such as cerebral malformation, hypoxic ischemic encephalopathy, or neurocutaneous syndromes, whereas, in 20% to 30% of cases, the etiology is unknown or remains unexplained. The patient had a normal growth and development curve before the bone marrow transplant and had a seizure four months after the transplant. We hypothesized that epileptic seizures are closely related to bone marrow transplantation. Combined with the clinical data of this patient and literature analysis, the possible factors of epilepsy after transplantation were analyzed:

Thalassemia

Although bone marrow transplantation for non-neoplastic diseases is also considered as an independent risk factor for post

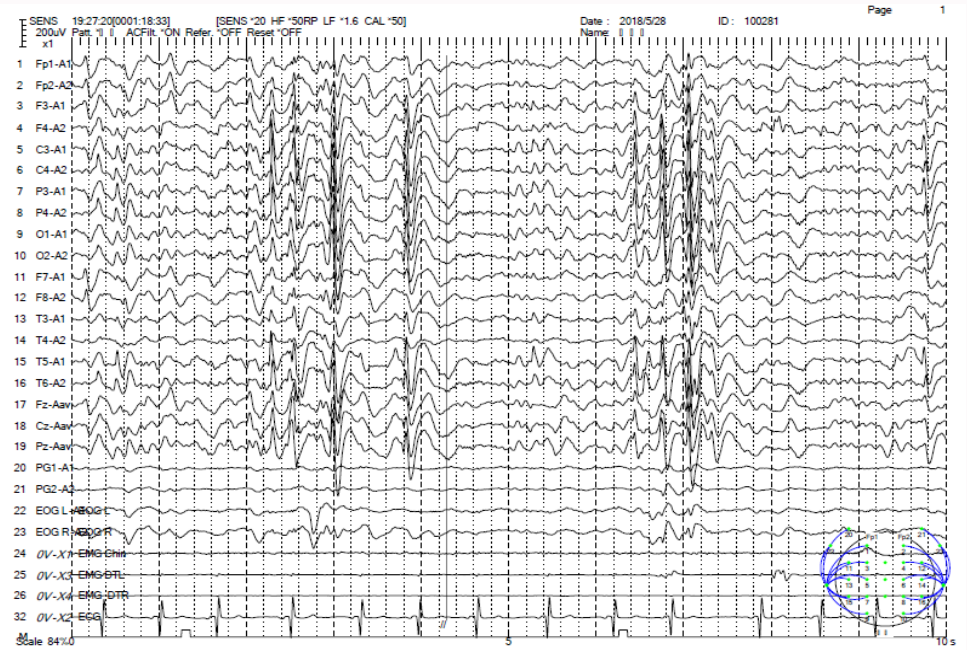

Figure 2b: Interictal EEG showed slow spike-and-slow-waves of 1 to 2.5 Hz.

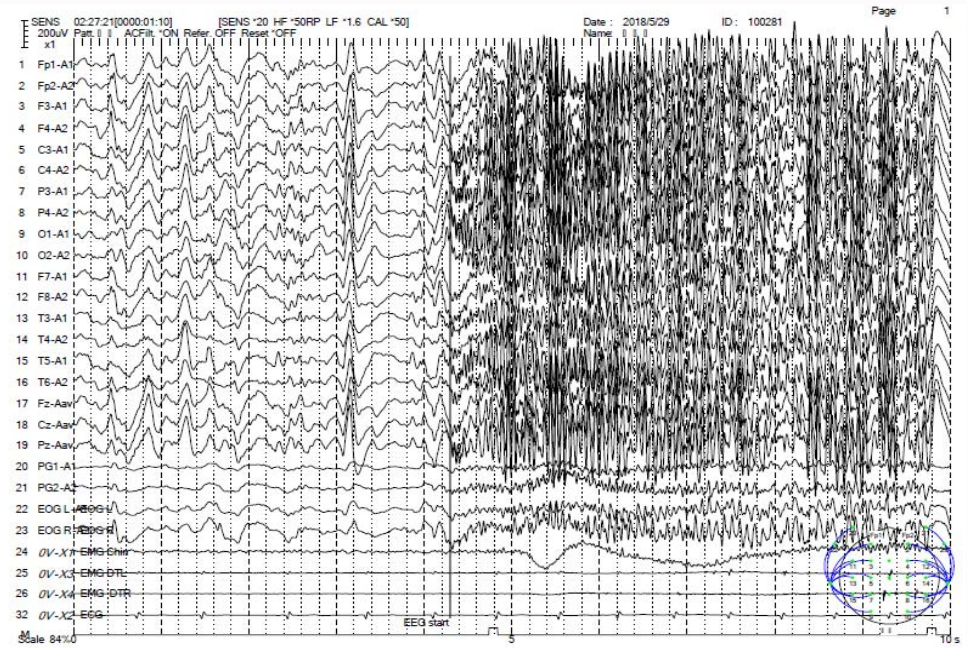

Figure 2c: Ictal EEG of the tonic seizure showed short term burst of 14 to 20 Hz.

transplant seizures, there is no data suggesting that thalassemia can cause epilepsy [10]. Our patient had normal growth and development curve before transplantation and no seizure, so it was speculated that seizure was not associated with thalassemia.

Drug

Many studies have shown that drug is an important cause of seizures after allogeneic hematopoietic stem cell transplantation. Occipital white matter appears to be uniquely susceptible to the neurotoxic effects of cyclosporine (CsA); injury to both the major and minor vasculature may cause hypo perfusion or ischemia and local secondary toxicity in the white matter. This may be the mechanism of epileptic seizures in patients receiving the immunosuppressant CsA [11]. Cyclosporine also interferes with the brain's blood supply, causing abnormal electrical discharges in the cerebral cortex that can lead to seizures. CsA elicited spontaneous or stimulation induced epileptiform activity in the DG or CA3 region of approximately 40% of combined hippocampus entorhinal cortex slices [12]. Cyclosporin induced brain imaging is usually reversible after withdrawal, supporting the idea of angio edema. Methylprednisolone, bupropion and methotrexate may also induce seizures in post transplant patients, which are more likely to occur when combined with cyclosporine [13]. Zhong Z et al. analyzed 8 patients with epilepsy after transplantation. All patients were treated with short term methylprednisolone and

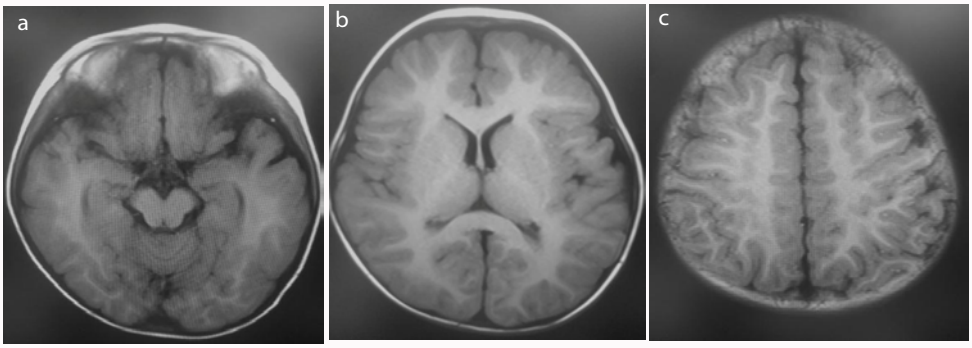

Figure 3(a-c): The Magnetic Resonance Imaging (MRI) of the patient at May 5, 2015: There is no obvious abnormality without cortical or white matter abnormalities.

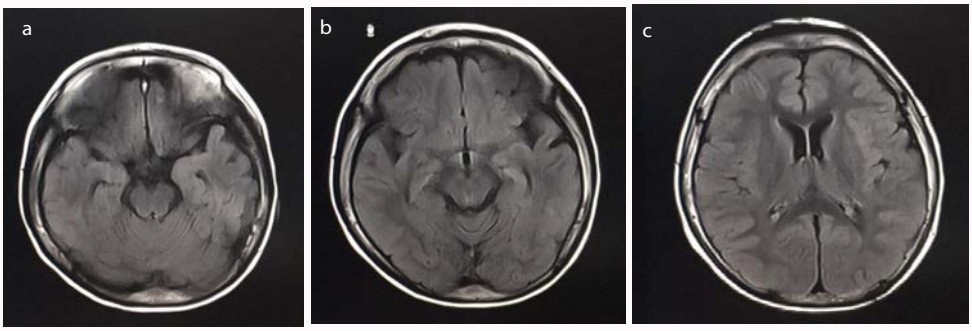

Figure 4(a-c): There is no obvious abnormality without cortical or white matter abnormalities.

methotrexate, and 6 patients received the dose of busulfan [14]. It has long been found that the incidence of seizures in patients using high dose benzodiazepine is 10% in adults and 7.5% in children, which is speculated to be related to the good blood brain barrier penetration of the drug [15-17]. The pretreatment regimen was classical and the dose was not conventional, in the pretreatment, the steady state blood concentration (external standard method) for monitoring busulfan was 614.31, which did not exceed the predicted range. The immunosuppressant was completely metabolized within 3 months, and the patient had seizures until 4 months after transplantation. Therefore, it is speculated that immunosuppressive agents are unlikely to directly cause epilepsy, but secondary damage cannot be excluded to cause seizures, which still requires further clinical observation and research.

Iron overload

Our patients had a high level of serum ferritin before transplantation. Ikeda M and colleagues found mean transferrin saturation was significantly higher in the epilepsy group (39.9 ± SD; 19.6%) than in the control group (29.1 ± SD; 14.9%) and iron overload other than the C282Y mutation underlies epilepsy [18]. The classic epilepsy rat model was established by a single injection of 5 ml or 10 ml of ferrous or ferric chloride into rat or sensorimotor cortex (Recurrent seizures induced by cortical iron injection: a model of posttraumatic epilepsy) [19,20].

PRES

PRES is a complication of post transplant immunotherapy. The incidence of epilepsy in PRES patients was up to 76% [21,22]. No seizures were noted beyond the first day. After discontinuation of antiepileptic medication, no patients experienced seizure recurrence during a 6 month follow up [23]. There is a triggering role of PRES in the development of hippocampus sclerosis [24]. Our patient did not have PRES, and her epilepsy was not associated with PRES.

We summarized the possible causes of epileptic encephalopathy in this patient, and perhaps some rare factors were not explored. In addition, the reexamination of head MRI 4 years after the seizure of this patient showed no obvious brain atrophy, hippocampus sclerosis and other imaging changes, which is also worthy of further discussion. Epilepsy after transplantation often seriously affects the quality of life and prognosis of patients and is increasingly valued by clinicians. We hope that with the progress of research, we can clarify the risk factors of epileptic seizures and fully improve the quality of life of patients after hematopoietic stem cell transplantation.

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