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Case Report

Drug resistant epilepsy with mesial temporal sclerosis as possible late neurological complication in two AML survivors after stem cell transplantation

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1. Introduction

Drug resistant epilepsy with mesial temporal sclerosis (MTS) has previously been reported as a late complication of hematological malignancies, mainly acute lymphoblastic leukaemia (ALL) and lymphoma with or without stem cell transplantation (SCT) [1,2]. Most cases had no prior central nervous system inflammation or infection. It has been suggested that brain irradiation or intrathecal use of cytosine or methotrexate were possible causes [1]. Here we report two cases of MTS in survivors of childhood acute myeloid leukaemia (AML) who had also received SCT, and review the literature of the reported cases of late onset drug resistant epilepsy with MTS in childhood haematological malignancies.

2. Material and methods

We reviewed two patients with history of AML having received SCT who developed medically resistant epilepsies several years after completing treatment. Both developed MTS and required epilepsy surgery to become seizure-free. Literature review was performed through OVID/EMBASE using the keywords Leukemia, hematological cancers, mesial temporal sclerosis, childhood, epilepsy and seizure. Articles published in English from 1990 to 2016 with MTS as a late complication for hematological cancers were identified and reviewed.

3. Results

3.1. Case summaries

3.1.1. Patient 1

A 24-year-old lady initially presented to our hospital with pallor at age six in 1997. She was diagnosed with AML and was treated with Hong Kong Pediatric Hematology and Oncology Study Group (HKPHOSG) 1996 protocol. Three courses of chemotherapy were given. Intravenous chemotherapy included daunorubicin, cytarabine, etoposide and amsacrine. Three doses of triple intrathecal chemotherapy (methotrexate, cytarabine and hydrocortisone) were given during the treatment course. Cerebrospinal fluid did not show abnormal cells and no craniospinal irradiation was prescribed. She received one antigen mismatch peripheral blood SCT in 1998. Conditioning agents included busulfan and cyclophosphamide. There was good engraftment and subsequent recovery. Another six doses of triple intrathecal chemotherapy were given during the post-transplantation period as central nervous system prophylaxis. She suffered from grade II graft-versus-host disease and was treated with steroids and cyclosporine. There was no central nervous system infection or inflammation during intensive chemotherapy and SCT.

She was first noted to have seizures in 2005 at age 14 (8 years after initial diagnosis and 7 years after transplantation). She developed recurrent focal seizures with impaired awareness associated with temporal lobe epilepsy. She had daily brief attacks of incoherent speech, forced head turning to left side with eye staring or tonic limb posturing. There was no prior history of febrile convulsion or family history of epilepsy. Physical examination did not reveal any focal neurological signs. First magnetic resonance imaging (MRI) of the brain was performed in 2006 which did not reveal any abnormalities. Interictal electroencephalogram (EEG) in 2006 showed isolated right temporal sharp waves. She was managed as temporal lobe epilepsy with anti-seizure medication. She failed multiple medication including sodium valproate, carbamazepine, oxcarbazepine, levetiracetam and clobazam. She still had approximately 10 seizures per month and her schooling was severely affected. Repeated MRI

Abbreviations: MTS, Mesial temporal sclerosis; ALL, Acute lymphoblastic leukaemia; AML, Acute myeloid leukaemia; SCT, Stem cell transplantation; MRI, Magnetic resonance imaging; EEG, Electroencephalogram; PET, Positron emission tomography; CNS, Central nervous system; FIAS, Focal impaired awareness seizure; IPI, Initial precipitant injury; PRES, Posterior reversible encephalopathy syndrome.

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brain in 2008 showed subtle decrease in volume in right hippocampus. Positron emission tomography (PET) showed a right hypometabolic temporal lobe. Ictal EEG was concordant with right side seizure onset (Fig. A.1). Surgery was performed in 2009 at age 18 with right anterior temporal lobectomy and amygdalahippocampectomy. Pathology showed mild loss of neurons and gliosis involving the right hippocampus. After the surgery, she was seizure-free and all medications was weaned. She made good neurological recovery, finished her education and now enjoys gainful employment.

3.1.2. Patient 2

A 16-year-old boy was diagnosed with AML at eight months of age in year 2002. He had favourable cytogenetics inversion 16. He was treated according to the HKPHOSG 1996 protocol with four courses of chemotherapy including intravenous daunorubicin, cytarabine, etoposide, amsacrine and mitoxantrone. Intrathecal chemotherapy during the induction course was withheld due to fever. He developed a brief seizure manifest as lip smacking and staring during the induction course. Cerebrospinal fluids were normal with no atypical cells, bacteria or viruses identified. EEG was unremarkable. CT brain at that time showed small hyperdense foci in the posterior limb of the internal capsule extending to left corona radiata which could represent small bleed or leukemic infiltration. He was begun on phenobarbital for six months and there was no further seizure recurrence. Subsequent MRI brain showed resolution of the suspicious lesions. Two doses of triple intrathecal chemotherapy (methotrexate, cytarabine and hydrocortisone) were subsequently given. He completed treatment in November 2002.

He had relapse of AML in July 2003. He was given intravenous fludarabine, cytarabine, daunoxome and one dose of triple intrathecal chemotherapy. He received two antigen mismatched unrelated cord blood transplantation in Oct 2003 at 22 months of age. Conditioning agents included busulfan, cyclophosphamide, melphalan and lymphoglobulin. The transplant was uneventful. Six doses of triple intrathecal chemotherapy were given as CNS prophylaxis during postransplant period. He had grade II graft versus-host disease which was improved with prednisolone and cyclosporin.

He developed focal seizures with impaired awareness at seven years of age (six years after initial AML diagnosis and five years after SCT). He had daily seizures which presented with tonic upper limb posturing with staring and/or irrelevant speech with purposeless movements preceded with aura. Initial interictal EEG showed no focal abnormalities or epileptiform discharges. His seizures were not well controlled with sodium valproate and levetiracetam. He also had comorbid attention deficit/hyperactivity and mood disorders.

Repeated MRI brain showed bilateral mesial temporal sclerosis with right sided hippocampal atrophy (Fig. B.1) [Fig. B1 legend: Left is FLAIR, Right is T2]. Ictal EEG showed right side onset seizures (Fig. B.2). Right anterior lobectomy and amygdalohippocampectomy was performed in July 2013 at age 11. Pathology showed atrophy and sclerosis of right hippocampus. After the surgery, he was seizure-free in the subsequent four years and is in the process of weaning off anti-seizure medications.

3.2. Literature review

There were six articles with twelve patients reported. All patients suffered from epilepsy as a late complication of acute leukemia in childhood. They suffered from leukemia before 18 years of age. The onset of epilepsy was at least two years after chemotherapy. Of the twelve patients, eight patients had MTS or corresponding MRI findings. Table C.1 summarises the demographics, diagnosis, use of intrathecal chemotherapy and application of cranial irradiation in the patients. Table C.2 summarises the features of epilepsy including seizure types, use of anti-seizure medications and neurological outcomes [2–7].

Among the twelve reported cases, patients were diagnosed childhood leukemia from eight months to 13 years of age with a median age of four and a mean age of five. Among all, four of them were females and eight of them were males. 11 patients had the primary diagnosis of ALL and one patient was diagnosed to have non-Hodgkin lymphoma. CNS leukemia was not identified in most cases. Only one patient had an infiltrative lesion in the brain, which subsequently resolved with courses of chemotherapy. Intrathecal chemotherapy with methotrexate were given in all cases except one case with no treatment details regarding intrathecal chemotherapy. Five of them received craniospinal irradiation. None had received SCT.

Eight patients had documented brain insults during treatment period including methotrexate induced encephalopathy, intracranial bleeding or acute symptomatic seizure. They remained well for an average of 6.7 years from the initial diagnosis. The other four had no documented CNS infection or inflammation at all. Focal impaired awareness seizure (FIAS) (91%) was the predominant seizure type. MRI findings or EEG findings were suggestive of MTS in eight patients (67%). Among these patients, Leng et al. described presence of temporal-plus epilepsy rather than the conventional temporal lobe epilepsy [6]. But in common, seizures were mostly drug resistant and four out of eight patients (50%) received epilepsy surgery and subsequently achieved seizure freedom.

In our two reported patients, both of them had diagnosis of AML. They had received intrathecal chemotherapy with no brain irradiation. No overt CNS infection or inflammation has been documented. They developed FIAS six to eight years later which were resistant to medical treatment. Epilepsy surgery was performed and had rendered them seizure free.

4. Discussion

Seizures are seen in 8–13% of patients in ALL [8]. Most seizures occur during the induction and consolidation phases. For AML, there is no data on seizure incidence in the current literature. However, it is believed to be much lower than in ALL. These seizures are usually precipitated by intracranial infections, electrolyte disturbances and immediate side effects from chemotherapy. Seizures are relatively easy to control when the culprit drug has been withheld or the underlying causes have been managed [9]. Few cases had persistent seizures since then and developed MTS [10]. Late onset seizures were relatively uncommon.

With the advancement of various chemotherapy and supportive treatment, the curative rate of childhood leukemia has improved. According to the data from American Cancer Society, overall 5-year survival rate increased to more than 85% in childhood ALL and 60%–70% in childhood AML, disregarding the different subtypes. Since 2003, there were several articles describing survivors from childhood lymphoblastic leukemias and lymphomas developing drug resistant epilepsies years after remission from their hematological malignancies.

4.1. Mesial temporal sclerosis as late complication in AML survivors

Prince of Wales Hospital is a tertiary hospital that has a specialised Children's Cancer Center. We receive referrals from the territory for management of oncology patients. We are one of the two centers equipped with bone marrow transplantation unit in Hong Kong. From August 2006 till July 2017, there were 160 new cases of ALL and 74 new cases of AML. During the period, we have performed SCTs for 37 ALL patients and 41 AML patients. The current two cases accounts for 4.9% of the 41 AML patients.

Our report adds two cases of MTS as a late complication of AML survivors who had received SCT to the literature. Previous cases reported by Goyal et al. in 2003 had early epilepsy soon after SCT [3]. An 18-year-old gentleman was diagnosed to have AML at age 12 with no CNS involvement. He developed early FIAS two months after bone marrow transplantation associated with high serum cyclosporin level (three times the upper limit). Initial MRI brain was normal. He had second seizure five months later and gradually became more frequent with seizures up to two to three times per month. Repeated MRI brain (Two and a half year after initial study) showed left MTS.

4.2. Initial precipitant injury for mesial temporal sclerosis

MTS develops several years after an initial precipitant injury (IPI), leading to hippocampal lesions associated with the epileptogenic zone. Common IPIs identified are perinatal hypoxia, febrile seizures, CNS infection, and trauma etc. Suggested IPIs in oncology patients were hypertensive encephalopathy, posterior reversible encephalopathy syndrome (PRES) [10], recurrent seizures, limbic encephalitis, chemotherapy toxicities, intrathecal cytosine, intrathecal methotrexate and brain irradiation [1].

Our two AML patients developed drug resistant seizures six to eight years after the initial diagnosis, which was comparable to the average latent period of 6.7 years in reported cases in development of MTS. For all 14 patients (twelve reported cases in the literature and our two patients), five out of 14 patients (35.7%) had no prior seizures or encephalopathy during the treatment period, nine out of 14 patients (64.2%) had not received any intracranial radiation and 12 patients (85.7%) had not had SCT. Six out of 14 patients (42.8%) have received intrathecal cytosine. Among all, it had to be noted that intrathecal methotrexate was administered in all patients except one patient with no data on intrathecal chemotherapy. Epileptogenesis is complex and multifactorial but intrathecal methotrexate is believed to be one of the key factors leading to the development of MTS and late onset drug resistant seizures. Methotrexate is a dihydrofolate reductase inhibitor. Several mechanisms had been postulated to be the cause of MTS. Methotrexate leads to folate deficiency and elevated levels of homocysteine [11]. Homocysteine has been described in pathogenesis of methotrexate neurotoxicity with damage to vascular endothelial injury [12]. Homocysteine is also an endogenous NMDA receptor agonists, causing enhancement of glutamate release which is one of the excitatory neurotransmitters in the brain [13]. Excess glutamate is believed to be involved as one of the epileptogenic mechanisms.

Similar speculation for postulation was also described by Fasano et al. in 2008 [1] and Yoshida et al. in 2013 [7]. Yet there is no data available regarding the association of dose of intrathecal medication use and seizure activity.

4.3. Early surgical evaluation

Most seizures in the reported cases were resistant to medical treatment. Together with the two cases that we reported, ten out of fourteen (71.4%) had temporal lobe epilepsy and MTS as suggested on subsequent MRIs and interictal/ictal EEGs. Six out of ten (60%) had epilepsy surgery performed and all achieved seizure freedom. Therefore, early referral for epilepsy surgery workup would be beneficial. Early epilepsy surgery should be considered when the seizures are drug resistant.

5. Conclusion

MTS is a potential late complication of childhood leukemia, for both ALL and AML. Increased vigilance for epilepsy in survivors of childhood leukemia is required. Exact mechanisms are to be further investigated. These seizures are usually drug resistant and when seizures are disabling early surgical evaluation is warranted.

Declaration

No author has disclosed any conflicts of interest.

The study was conducted in accordance with good clinical practice guidelines and the Declaration of Helsinki.

Appendix A

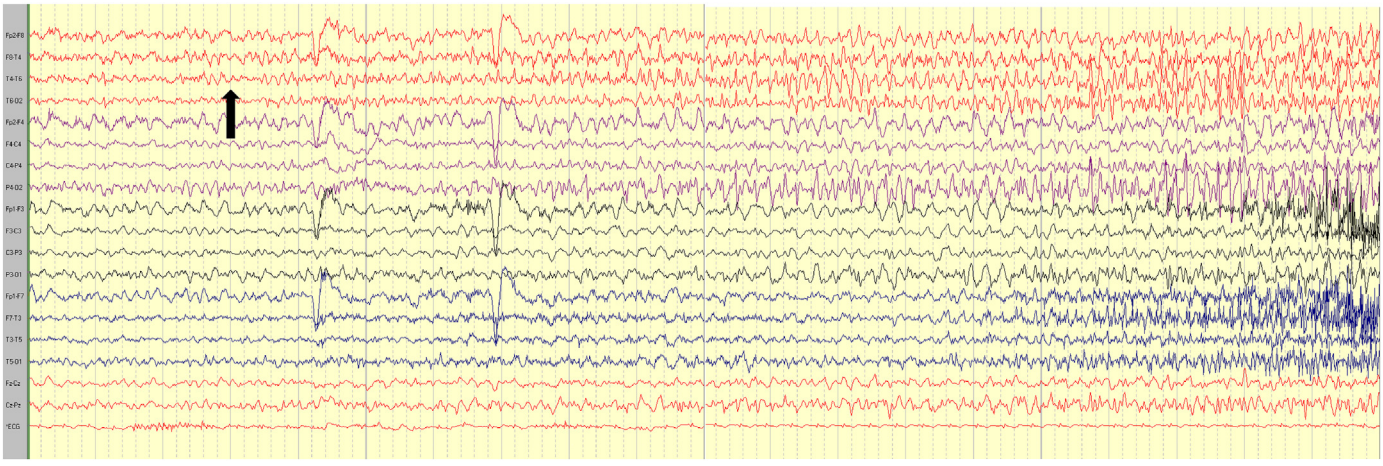

Fig. A.1. Ictal EEG of patient 1 EEG is shown in bipolar montage (Top: leads on right side; Bottom: leads on left side) The arrow indicates right temporal onset of seizure.

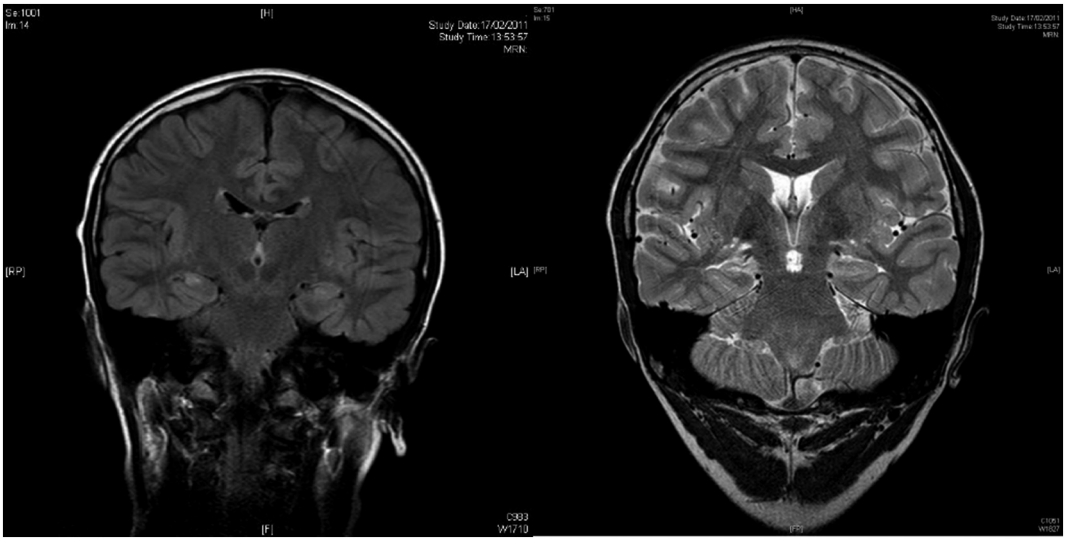

Fig. B.1. MRI brain of patient 2 (Left: T2 coronal view; Right: FLAIR coronal view) It shows bilateral mesial temporal sclerosis with rights sided hippocampal atrophy.

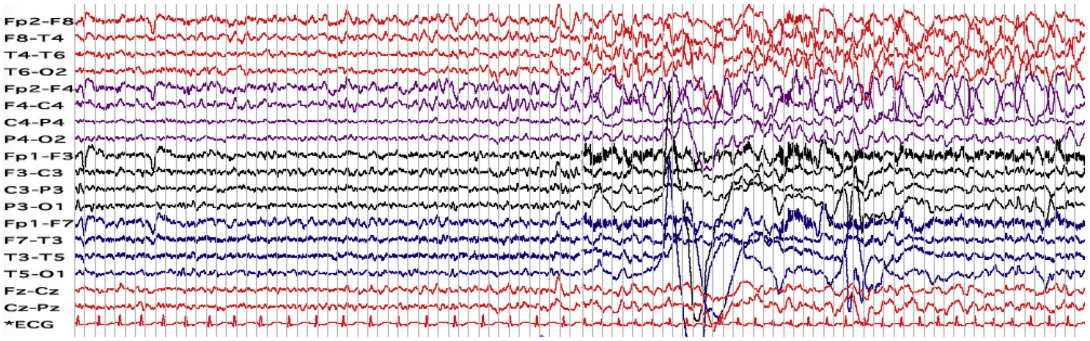

Fig. B.2.

Table C1
Summary of demographics, diagnosis and treatment of leukaemia in patients.

Article	Patient demographics				Disease status			Treatment for leukaemia			
	Patient	Age at diagnosis (years)	Sex	Comorbidity	Type of leukaemia	CNS disease	History of encephalitis/ encephalopathy during treatment	Chemotherapy (intravenous and oral)	IT chemotherapy	Brain irradiation	SCT
1	1a	2	M	–	ALL	–	GTC after given L-asparaginase during induction	VCR, Prednisone, L-asparaginase, Daunorubicin, Ara-c, Cyclophosphamide, Doxorubicin, 6MP, MTx	MTx	–	–
2	2a	5	M	–	ALL	–	Methotrexate induced encephalopathy	VCR, Prednisone, L-asparaginase, arabinosykytosine, cyclophosphamide, 6MP	MTx, hydrocortisone	–	–
3	3a	2.5	M	–	ALL	–	One Febrile seizure	VCR, Prednisone, Daunorubicin, Doxorubicin	MTx, Ara-C	18 Grey	–
	3b	2.5	F	–	ALL	–	–	VCR, Prednisone, L-asparaginase, methotrexate	MTx	18 Grey	–

Table C1 (*continued*)

Article	Patient demographics				Disease status			Treatment for leukaemia			
	Patient	Age at diagnosis (years)	Sex	Comorbidity	Type of leukaemia	CNS disease	History of encephalitis/ encephalopathy during treatment	Chemotherapy (intravenous and oral)	IT chemotherapy	Brain irradiation	SCT
	3c	7	M	–	ALL	–	Status epilepticus during induction	VCR, Prednisone, L-asparaginase, Daunomycin	MTx, Ara-C	18 Grey	–
	3d	3	F	–	ALL	–	–	VCR, Prednisone, L-asparaginase, Daunorubicin	MTx	18 Grey	–
	3e	0.67	M	–	ALL	–	Symptomatic seizure due to hyponatraemia	VCR, Prednisone, Daunorubicin	MTx	18 Grey	–
4	4a	13	F	–	NHL	–	–	VCR, Prednisone, L-asparaginase, Daunorubicin, cyclophosphamide	MTx, Ara-C, hydrocortisone	–	–
5	5a	10	M	–	ALL	–	Left parietal-occiptal lobe intracranial haemorrhage, left occiptal epidural haemorrhage	VCR, Prednisone, L-asparaginase, Daunomycin, cyclphosphamide, VM26, Ara-C, methotrexate	MTx, Ara-C	–	–
	5b	3	M	–	ALL	Infiltrative lesion	Infiltrative brain lesion	VCR, Prednisone, L-asparaginase, Daunomycin, VM26, Ara-C, methotrexate	N/A	N/A	–
6	6a	6	F	–	ALL	–	Methotrexate encephalopathy with seizure	VCR, Prednisone, L-asparaginase, Adriamycin, Ara-C, cyclphosphamide, 6MP, MTx	MTx, Ara-C, hydrocortisone	–	–
	6b	5	M	–	ALL	–	–	VCR, Prednisone, L-asparaginase, Adriamycin, Ara-C, cyclphosphamide, 6MP, MTx	MTx, Ara-C, hydrocortisone	–	–
Our patients	Patient 1	6	F	–	AML	–	–	Daunorubicin, Ara-c, etoposide, amsacrine	MTx, Ara-C, hydrocortisone	–	Yes
	Patient 2	0.67	M	–	AML	CT: small hyperdense foci, resolved subsequenly	One episode of afebrile seizure during chemotherapy	Daunorubicin, Ara-c, etoposide, amsacrine, mitoxantrone, fludarabine, daunoxome	MTx, Ara-C, hydrocortisone	–	Yes

Key: ALL: Acute lymphoblastic leukaemia; AML: Acute myeloid leukaemia; APL: Acute promyelocytic leukaemia; NHL: Non-Hogkin lymphoblastic lymphoma
IT chemotherapy: intrathecal chemotherapy; BMT: Bone marrow transplantation.
PRES: Posterior reversible encephalopathy syndrome.
VCR: Vincristine, MTx: methotrexate; Ara-C: cytarabine; VM26: teniposide.
Article 1: Monisha Goyal, Barbara A Bangert, Max Wiznitzer. Mesial Temporal sclerosis in Acute Childhood Leukaemias. Epilepsia 2003; 44: 131–134.
Article 2: Kouhei Hamamoto, Noboru Oriuchi, Takashi Kanazawa, Tetsuya Higuchi, Keigo Endo. Mesial temporal sclerosis associated with methotrexate induced leukoencephalopathy. Paediatr Neurol 2009; 40: 306–309.
Article 3: Rebecca E. Fasano, Donna C. Bergen. Intractable epilepsy in patients treated for childhood acute lymphocytic leukaemia. Seizure 2009; 18: 298–302. [DOI: https://doi.org/10.1016/j.seizure.2008.10.008]
Article 4: Rafael Sivera, Luis Bataller, Jesus Martinez, Vicente Villanueva. Mesial Temporal sclerosis as a complication of hematologic cancer. J Neurol 2009; 256: 1759–1761 [DOI: https://doi.org/10.1007/s00415-009-5168-5]
Article 5: Yun Leng, Tao Yu, Yongjie Li, Wenming Chen. Surgical treatment of refractory epilepsy after chemotherapy in two children with leukaemia. Epilepsy and Behavior Case Reports 1 2013: 32–34.
Article 6: Emi Kasai-Yoshida, Masaaki Ogihara, Miwa Ozawa, Taiki Nozaki, Michiharu Horino, Atsushi Manabe, Ryota Hosoya. Temporal Lobe Epilepsy With Hippocampal Sclerosis in Acute Lymphoblastic Leukaemia. Paediatrics 2013; 132; 252–256.

Table C2
Features of features of epilepsy and respective treatment in patients.

Article	Patient	Epilepsy					Investigation		Treatment		Neurological outcome	
		Age of onset	Time from diagnosis (years)	Time from SCT (years)	Seizure type	Frequency	MRI findings	EEG findings	No of anticonvulsants tried	Non-drug trial/epileptic surgery	Seizure control	Cognitive impairment
1	1a	11	9	–	FIAS	Frequent (N/A)	Right MTS	N/A	2	–	Fair (poor compliance)	N/A
2	2a	12	7	–	FIAS +/− GTC	1×/week	Left MTS	No significant abnormality	1	–	Seizure free	N/A
3	3a	15	12.5	–	Absence, FIAS	6×/day	Unremarkable	Multifocal epileptiform discharges, 3 Hz spike-and-wave discharges	4	–	Good (6×/year) with valproate and lamotrigine	Impaired
	3b	14	11.5	–	FIAS +/− GTC	1×/day	Multiple areas of high T2 and FLAIR signal in bilateral cerebral white matter	Left temporal epileptiform discharge	9	VNS	Refractory (1–2 seizure per month) with VNS, topiramate and carbamazepine	Impaired
	3c	10	3	–	FIAS	3×/week	Unremarkable	Bilateral frontotemporal epileptiform discharges	9	–	Refractory (2 seizures/month) with phenytoin and leveciracetam	Impaired
	3d	9	6	–	Absence, GTC, Atonic	≥ 1×/day	Increased signal over left mesial temporal lobe	Multifocal epileptifom discharges/genrealized spike-and-wave	8	VNS	Refractory (daily seizures)	Impaired
	3e	9	8.33	–	FIAS, GTC, Atonic	≥ 1×/day	High T2 and FLAIR signal in white matter	Bifrontal epileptiform discharges	10	Ketogenic diet	Refractory (daily seizures)	Impaired
4	4a	14	1; * refractory in 6 years	–	FIAS	Frequent	Right MTS	Ictal: right temporal theta activity	Several (not specified)	Right hippocampectomy	Seizure free	N/A
5	5a	N/A	>4 (4 years after stopping treatment)	–	FIAS	Several times/week	Slight atrophy of cortex of left temporal occipital lobe	Left temporal occiptal discharges	6	Surgical excision of epileptogenic tissue in left temporal parietal region, followed by left anterior temporal lobe excision	Seizure free (on carbamaezepine and lamotrigine after operation)	N/A
	5b	5	2	–	FIAS	20×/day	Right MTS and Right temporal–parietal lesion	Right temporal parietal discharges	4	Resection of right hippocapmus and posterior temporal lesion	Seizure free (still on oxycarbamazepine after operation)	N/A
6	6a	11	5	–	FIAS	≥ 1×/day	Left MTS	Ictal: left temporal spikes	6	Subpial transections of left mesial temporal lobe	Seizure free	N/A
	6b	11	6	–	FIAS	1× per 2 months	Left MTS	High voltage slow waves in left hemisphere	1	–	Seizure free	N/A
Our patients	Patient 1	14	8	7	FIAS	10×/month	Subtle decrease in volume in right hippocampus	Right temporal sharp waves	5	Right anterior temporal lobectomy and right amygdalahippocampectomy	Seizure free	Not impaired
	Patient 2	7	6	5	FIAS	2×/day	Bilateral mesial temporal sclerosis with right hippocampal atrophy	Ictal: Right side onset	2	Right anterior lobectomy and amygdalohippocampectomy	Seizure free (still on leveciracetam)	Not impaired

Key: GTC: generalised tonic–clonic seizure; FIAS: focal impaired awareness seizure
MTS: mesial temporal sclerosis.
VNS: vagal nerve stimulator.
Refractory seizure defined as ≥ 1 seizure per month.
Article 1: Monisha Goyal, Barbara A Bangert, Max Wiznitzer. Mesial Temporal sclerosis in Acute Childhood Leukaemias. Epilepsia 2003; 44: 131–134.
Article 2: Kouhei Hamamoto, Noboru Oriuchi, Takashi Kanazawa, Tetsuya Higuchi, Keigo Endo. Mesial temporal sclerosis associated with methotrexate induced leukoencephalopathy. Paediatr Neurol 2009; 40: 306–309.
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Article 6: Emi Kasai-Yoshida, Masaaki Ogihara, Miwa Ozawa, Taiki Nozaki, Michiharu Horino, Atsushi Manabe, Ryota Hosoya. Temporal Lobe Epilepsy With Hippocampal Sclerosis in Acute Lymphoblastic Leukaemia. Paediatrics 2013; 132; 252–256.

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