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Characterizing the phenotype of drug-resistant childhood epilepsy associated with leukemia: A case series

Elham Abushanab *, Elia Pestana Knight, Ahsan N. Moosa

Cleveland Clinic, Epilepsy Center, Neurological Institute – Desk S50, Cleveland Clinic, 9500 Euclid Ave, Cleveland, OH 44195, United States

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ABSTRACT

Children with leukemia are at risk for epilepsy due to primary disease or neurotoxic therapies. We describe the phenotypes of drug-resistant epilepsy in 10 children with history of leukemia.

Of 10 cases, 6 had features of Lennox-Gastaut syndrome, and 4 had focal epilepsy. Mean age of epilepsy onset was 5 years in Lennox-Gastaut cases and 6.5 years in focal epilepsy cases. Mean latency between leukemia diagnosis and seizure onset was about 3 years. Brain MRI of 2 patients with epileptic encephalopathy had structural abnormalities – unclear if causative for epilepsy, and 4 had no overt structural abnormalities. In focal epilepsy group, 3 had temporal lobe epilepsy and one had fronto-temporal localization. All 10 patients had received intrathecal chemotherapy; 2 also had received whole brain irradiation. Seizures were poorly controlled in the epileptic encephalopathy group. Three underwent corpus callosotomy with variable response. Two patients with temporal lobe epilepsy had temporal lobectomy with Engel 1 outcome at 2 year follow-up in both.

Two phenotypes of refractory epilepsy were observed in children with previous history of leukemia, focal epilepsy and epileptic encephalopathy. Children with temporal lobe epilepsy had good response to temporal lobectomy; response to palliative surgery was variable.

1. Introduction

Children with leukemia are at risk for neurological injury due to the primary disease or its treatment. Seizures are a common presentation of CNS involvement [1,2]. About 10–13% of children with leukemia had acute seizures that usually occurred at the time of induction chemotherapy [1]. The development of chronic epilepsy is less common, especially in the setting of no obvious CNS injury or lesion [2]. In this case series, we describe the phenotype of 10 cases with drug-resistant epilepsy in the setting of prior childhood leukemia including the surgical management in 6 children.

2. Methods

We identified 226 children with a history of malignancy and seizures from the Cleveland Clinic electronic medical records, January 2003 through September 2019. We identified 26 children with hematological malignancy and history of seizures; 18 had seizures after leukemia. Five had acute symptomatic seizures, three chronic controlled epilepsy, and ten drug-resistant epilepsy. Drug-resistant epilepsy was defined as failure to achieve seizure freedom despite adequate trials of two tolerated, appropriately chosen anti-seizure medications. We reviewed medical records for clinical history of leukemia and epilepsy, diagnostic work up, treatment, and outcome. The Cleveland Clinic Institutional Review Board approved this study.

3. Results

Of ten children with childhood leukemia and drug-resistant epilepsy, six presented as an epileptic encephalopathy and four as focal epilepsy.

3.1. Phenotype 1: epileptic encephalopathy

Details regarding cases with epileptic encephalopathy are outlined in Table 1. Mean age at leukemia diagnosis was 2 years. Of the six, three had CNS involvement at diagnosis. One had ocular involvement at diagnosis with cerebellar and base of spine spread on relapse. Two had leptomeningeal involvement detected on CSF analysis. All received systemic and intrathecal chemotherapy, including intrathecal methotrexate. Case 2 also received intrathecal steroids and cytarabine. Case 3 underwent brain and spine irradiation and later bone marrow transplant. All cases achieved remission.

* Corresponding author.
E-mail addresses: eeabushanab2391@gmail.com, abushae@ccf.org (E. Abushanab).

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Table 1
Phenotype; LGS = Lennox-Gastaut, TLE = Temporal lobe epilepsy, FTE = frontotemporal epilepsy; Cancer Dx = Cancer Diagnosis; ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia. CNS+ = positive CNS involvement by leukemia. Therapy; Sys = systemic chemotherapy, IT = intrathecal chemotherapy, RT = radiation therapy, SCT = stem cell transplant. Seizure types; T = tonic, A = absence/atypical absence, M = myoclonic, FIA = focal seizure with impaired awareness, GTC = generalized tonic-clonic, At = atonic seizures, ES = epileptic spasms. EEG; R = right, L = left. MRI; MTS = mesial temporal sclerosis. TTX = other treatments; CC = corpus callosotomy, VNS = vagus nerve stimulation, KD = ketogenic diet, TL = temporal lobectomy. Outcome; GDD = global developmental disability.

Case (Gender) Phenotype	Age at: Cancer Dx First Seizure	Cancer Diagnosis	CNS+	Therapy	Seizure Type	EEG	MRI	TTX	Outcome
1 (M) LGS	2 y 4 y	ALL	No	Sys, IT	T, A, M, FIA,GTC	Slow spike-and-waves, Polyspikes, Continuous slowing	Normal	CC VNS	Engel; IVB GDD
2 (F) LGS	3 y 4 y	AML	+ (CSF)	Sys, IT	T, At, M	Spikes, Polyspikes, Continuous background slowing	Diffuse atrophy, ventriculomegaly, several foci on SWI	KD	Uncontrolled seizures; GDD
3 (M) LGS	10 m 4 y	AML	+ (Orbit)	Sys, IT, RT, SCT	T, ES, At	Slow Spike-and-Wave, Polyspike, Continuous Slow (G)	Multifocal white matter hyperintensities	VNS	Engel; IVB GDD
4 (F) LGS	3 y 8 y	ALL	+ (CSF)	Sys, IT	T, At, A	Slow Spike-and-Wave, Polyspike, Background Slowing	Normal	CC VNS	Weekly/monthly seizures; No falls after CC; Engel IIIA
5 (M) LGS	2 y 6.5 y	ALL	No	Sys, IT	T, At, A, M	Slow spike-and-wave, Polyspike (G)	Normal	VNS CC	Lost to follow up
6 (M) LGS	2.5 y 5 y	ALL	No	Sys, IT	T, ES, At, FIA, A	Slow spike-and-Waves, Polyspikes, Background Slowing	Normal	–	Uncontrolled seizures; GDD
7 (M) TLE	3.5 y 7 y	ALL	Relapse	Sys, IT, RT, SCT	FIA, GTC	Sharp Wave, R Temporal	R MTS	TL	Engel IA
8 (F) TLE	5 y 6 y	ALL	No	Sys, IT	FIA, GTC	Sharp waves, L Temporal	L MTS	TL	Engel IC; Mild cognitive impairment
9 (F) TLE	3 y 3.5 y	ALL	No	Sys, IT	FIA, GTC	Sharp waves, L Temporal	Hyperintensity inL Hippocampus	–	Weekly seizures; Mild cognitive impairment
10 (F) FTE	14 m 10 y	ALL	No	Sys, IT	FIA, GTC	Sharp Wave, Frontal-Temporal	Normal	–	Monthly Seizures Mild cognitive impairment

Mean age at first seizure was 5 years. Mean latency between leukemia diagnosis and first seizure was 3 years; range of 1–5 years. Four of the six developed seizures after remission and two (case 1 and 6) had their first seizure before remission. Case 1 had initial seizures in the setting of presumed acute methotrexate neurotoxicity; events were unclear in case 6. Risk factors to seizures, outside of oncological histories, were limited to distant family history of epilepsy in two, HHV6 infection (CSF positive) in one, and VP shunt placement in another.

Only one (case 6) had signs of developmental delay prior to leukemia diagnosis. The remaining had evidence of delay following leukemia diagnosis, with further regression after onset of epilepsy. All six developed daily seizures with poor response to treatment. All had multiple seizure types (Table 1) including generalized tonic seizures. EEG showed slowing of the background rhythms and abundant generalized or multifocal epileptiform discharges consistent with epileptic encephalopathy. Generalized slow spike-and-wave complexes and generalized polyspikes were seen in all, consistent with Lennox-Gastaut syndrome. Brain MRI was normal in four. Two, with AML and CNS involvement at diagnosis, had subcortical MRI abnormalities without overt cortical lesions.

All were on multiple anti-seizure medications. One failed the ketogenic diet. Four had a vagus nerve stimulation device placed with a modest change in seizure burden. Three underwent corpus callosotomy with resolution of atonic seizures in one and no change in another; third patient was lost to follow up.

3.2. Phenotype 2: Focal epilepsy

Of the four with focal epilepsy, three had temporal lobe epilepsy and one frontotemporal epilepsy, as shown in Table 1. Mean age at leukemia diagnosis was 3 years. All had CNS-negative ALL at diagnosis. All had exposure to systemic and intrathecal chemotherapy, including intrathecal methotrexate. One had CNS relapse, subsequently receiving neuroaxis irradiation and bone marrow transplant. All cases achieved remission.

Mean age at seizure onset was 6.5 years. Mean latency between leukemia diagnosis and first seizure was 3.5 years; range of 6 months to 9 years. All three with temporal epilepsy had epilepsy onset prior to remission of leukemia. Case 6 with frontotemporal epilepsy had seizure onset 9 years after leukemia diagnosis. All four had focal impaired awareness with or without progression to bilateral tonic-clonic seizures. Seizures occurred weekly to monthly and were resistant to medications. EEG showed focal epileptiform discharges in the temporal regions in three and frontotemporal region in one. MRI showed features of mesial temporal sclerosis in all three temporal epilepsy cases but was normal in the frontotemporal localization case.

All had mild developmental disability primarily involving cognitive domain, presenting after diagnosis and treatment of leukemia. Two cases with mesial temporal lobe sclerosis had temporal lobectomy; both were seizure free at 2-year follow-up. The other two had persistent seizures despite medical therapy. Mesial temporal epilepsy in these children with leukemia appeared to have good surgical outcome, similar to other causes of temporal lobe epilepsy.

4. Discussion

Children with leukemia may develop seizures during the acute phase of the disease or less commonly later. In this series of 10 children with history of leukemia who developed drug-resistant epilepsy, we found 2 distinct phenotypes: Lennox-Gastaut syndrome and focal epilepsy. Latent period from onset of leukemia to development of epilepsy was variable, ranging from months to a few years; one child developed epilepsy 9 years after the initial

leukemia diagnosis. Phenotypic resemblance between our cases and prior published cases, as shown in Table 2, suggests a strong association to underlying leukemia and or its treatment.

LGS in a patient with prior diagnosis of leukemia was first reported in English literature in 1996 [3]. Since then, 11 cases have been reported [4–6]. In one case series of 7 children with epileptic encephalopathy and leukemia, patients had features of LGS except for generalized tonic seizures [4]. In many of these reports, prior CNS involvement was not noted. This suggested that brain injury due to CNS prophylaxis including IT methotrexate and radiation were the possible cause for epileptogenesis. Brain irradiation, in addition to its direct neurotoxic effects, is thought to compromise the blood–brain-barrier with potentiation of chemotherapy [3]. Contradictory to this, some cases have demonstrated that drug-resistant epilepsy including LGS can occur without brain irradiation [4,6]. This was seen in our patients, with only 2 of 10 having prior brain irradiation.

In addition to neurotoxic injury by chemotherapy and radiation, young age was proposed as a risk factor, potentially due to incomplete brain myelination [4–6]. In our series, children with LGS were relatively younger. Mean age was 2 years in LGS group vs 3 years in focal epilepsy. The immature brain's susceptibility to epileptogenesis by formation of "hyperconnected cortex" and maldevelopment of thalamocortical connections has been hypothesized in pathogenesis of LGS, making this age pattern noteworthy [7].

Previously described cases had evidence of abnormality on MRI either supportive of a leukoencephalopathy or consistent with prior radiation or chemotherapy such as brain calcifications [3–6]. However, in our series, 4 of the 6 children with LGS had no abnormalities on brain MRI. This may suggest that MRI is not a sensitive test to identify neuronal injury in this setting. Occurrence of LGS without overt structural abnormalities is not infrequent in many genetic causes of LGS.

Focal epilepsy following childhood leukemia has been described, most commonly in the form of mesial temporal sclerosis [5,6,8–10]. Some of these patients have been found to have good control on anti-seizure medications [8], however drug-resistant epilepsy has also been reported.

In those with drug-resistant epilepsy due to MTS, temporal lobectomy has led to favorable seizure outcome [6,10], similar to our two patients. Extratemporal epilepsy or "temporal plus" epilepsy has been described with seizure resolution following surgery [9]. Use of palliative surgery including vagus nerve stimulation and corpus callosotomy has not been reported widely in this setting. In our cases, a modest response after VNS placement, and variable response to corpus callosotomy was seen. One prior report described the use of anterior callosotomy in a patient with LGS, with poor response [6].

Chemotherapeutic agents, specifically methotrexate, have been heavily implicated [5,8,10], especially given known repertoire of neurotoxicity for the latter [11]. Clinical observations and animal studies suggest that methotrexate may have a direct role in causation of hippocampal injury and mesial temporal sclerosis [12,13]. Theories have included interruption of biochemical pathways including folate and homocysteine, increasing excitatory neurotransmitters (such as glutamate), as well as direct neurotoxicity, implicated in both acute and chronic effects [11]. Leukemic involvement on a microscopic level is also possible, which may not be reflected on testing or imaging.

It is unknown why certain children with leukemia with similar treatment regimens go on to develop drug-resistant epilepsy. Polymorphisms in genes related to neurodevelopment in patients with methotrexate-related neurotoxicity have been found [14]. This supports possible underlying genetic predisposition to the development of epilepsy in certain patients, ignited by a neurotoxic event. Although it would have been optimal if we had performed

Table 2
Cancer Dx = Cancer Diagnosis; ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia. CNS+ = positive CNS involvement by leukemia. TX = therapy; Sys = systemic chemotherapy, IT = intrathecal chemotherapy, RT = radiation therapy, SCT = stem cell transplant. MRI; BL = bilateral, L = left, R = right, LGS = Lennox-Gastaut, TLE = Temporal lobe epilepsy, FTE = frontotemporal epilepsy, MFE = multifocal epilepsy.

Study Author (Year) n- number of cases	Type	Cancer Diagnosis	CNS +	TX	MRI
Yam et al. (2018) n-2	Temporal Lobe Epilepsy	AML	1 of 2	Sys, IT, SCT	R Mesial temporal sclerosis (1) BL Mesial temporal sclerosis with hippocampal atrophy (1)
Gonzalez-Otarula et al. (2016) n-4	Lennox-Gastaut Syndrome (2) Temporal Lobe Epilepsy (1) Multifocal Epilepsy (1)	ALL	No	Sys, IT (4) RT (2)	Cortical and subcortical calcifications (2) L Temporal cavernous hemangioma (1) Normal (1)
Leng et al. (2013) n-2	Temporal Lobe Epilepsy	ALL	1 of 2	Sys, IT	L Temporal-Parietal-Occipital cerebral hemorrhage → Cortical atrophy (1) Lesion R Temporal-Parietal + hippocampal atrophy (1)
Fasano et al. (2009) n-5	Lennox-Gastaut Syndrome (2) Temporal Lobe Epilepsy (1) Frontal-Temporal Epilepsy (1) Multifocal Epilepsy (1)	ALL	No	Sys, IT, RT	↑ T2 signal L mesial Temporal Lobe (LGS) BL white matter abnormality (LGS + TLE) Normal (FTE) Normal (MF)
Khan et al. (2003) n-7	Lennox-Gastaut Syndrome	ALL (6) AML (1)	No	Sys, IT, RT	Atrophy (4) Diffuse/Focal leukoencephalopathy (7)
Goyal et al. (2003) n-2	Temporal Lobe Epilepsy	ALL	1 of 2	Sys, IT (2) RT (1)	R Mesial temporal sclerosis (2) R Hemispheric atrophy (1)
Mitsufuji et al. (1996) n-1	Lennox-Gastaut Syndrome	ALL	No	Sys, IT, RT	Multifocal increased signal and calcification in white matter
Sawayanagi et al. (1989) n-1	Lennox-Gastaut Syndrome	ALL	1 of 1	Sys, IT, RT	–
Akiyama et al. (1983) n-1	Lennox-Gastaut Syndrome	LL	No	Sys, IT, RT	–

genetic testing on our cases as a next step to explore this possibility, this was not feasible given lack of funding. Further studies on the mechanism are needed to understand the epileptogenesis in this cohort.

5. Conclusions

Children with childhood leukemia are at risk for developing epilepsy, even after remission of leukemia. In drug resistant patients, two phenotypes – focal epilepsy and epileptic encephalopathy with LGS phenotype were observed. Four of 6 children with epileptic encephalopathy had no structural abnormalities on brain MRI. Children with temporal lobe epilepsy had good response to temporal lobectomy while response to palliative surgery was variable in the epileptic encephalopathy group.

Ethical Statement

This paper does not involve any experimentation of humans or animals given descriptive nature.

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CRediT authorship contribution statement

Elham Abushanab: Conceptualization, Methodology, Investigation, Data curation, Writing - original draft, Visualization, Project administration. **Elia Pestana Knight:** Conceptualization, Methodology, Supervision, Project administration. **Ahsan N. Moosa:** Conceptualization, Methodology, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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