Case report

Intractable epilepsy in patients treated for childhood acute lymphocytic leukemia

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ABSTRACT

Purpose: In the 1970s and 80s, standard treatment for childhood acute lymphocytic leukemia (ALL) included both intrathecal methotrexate and whole-brain irradiation. During acute treatment, seizures were not uncommon. The development of intractable epilepsy years after treatment, however, has not been well described in the literature. We describe five patients who were treated for acute lymphocytic leukemia as children, who later developed intractable epilepsy.
Results: All of the patients were diagnosed with leukemia before age seven. Treatment included both whole-brain irradiation and intrathecal chemotherapy. All five received intrathecal methotrexate; in addition, two also received intrathecal cytosine arabinoside. The first seizure occurred at a mean of 7.5 years after diagnosis. Four patients have multiple seizure types, and all patients have been on multiple antiepileptic drugs. All five patients are cognitively impaired.
Conclusions: Successful treatment for childhood leukemia may be followed by signs of late cerebral injury including intractable epilepsy. We propose that neurotoxicity resulting from exposure to intrathecal methotrexate and cranial irradiation may have contributed to the intractable epilepsy seen in our five patients.

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1. Introduction

Seizures are seen in 8–13% of patients with acute lymphocytic leukemia (ALL).[1] Most seizures occur during the acute treatment phases of induction and central nervous system consolidation, which comprise the first 6 weeks of remission-inducing treatment. In a study of 17 patients with ALL who had seizures, all but one of the patients had the initial seizure during acute treatment; seizure recurrences were infrequent, and only two of the patients, who were neurologically abnormal at baseline, developed epilepsy.[1] Another study reported that 4 of 30 children with ALL who had had a seizure would develop epilepsy; however, etiologies such as disseminated intravascular coagulopathy, hyponatremia, and stroke were identified in three of the four children with epilepsy.[2]

The development of intractable epilepsy after treatment for leukemia is less well described, and therefore, the incidence is unknown. Khan et al. reported six cases of children with atonic seizures who were survivors of childhood ALL. Two of these children developed intractable epilepsy at least a year after diagnosis with leukemia, and the other patients developed epilepsy that was either partly controlled or well-controlled.[3] We describe five adults who developed intractable epilepsy years after being treated for childhood acute lymphocytic leukemia; we propose that our patients' intractable seizures may be related to their exposure to both intrathecal methotrexate and cranial irradiation.

2. Methods

Children with a history of acute lymphocytic leukemia were identified from the Rush University Epilepsy Center. Institutional review board permission and written informed consent from parents were obtained prior to chart review. Charts were reviewed for age at diagnosis of leukemia; leukemia treatment received, including chemotherapeutic drugs and radiation; age at first seizure; seizure type(s) and frequency; anti-epileptic treatment history; electroencephalogram (EEG) findings; MRI brain findings; and cognitive status. Intractable epilepsy was defined as a seizure frequency of at least once per month.

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3. Cases

3.1. Patient 1

A 25-year-old man was diagnosed with acute lymphocytic leukemia at age $2\frac{1}{2}$. He did not have central nervous system disease. Remission was achieved after induction with vincristine, prednisone, adriamycin, and daunorubicin. As CNS prophylaxis, he received intrathecal methotrexate, intrathecal cytosine arabinoside, and 18 Gray (Gy) cranial irradiation. During the induction phase, he had a febrile seizure and was subsequently treated with phenobarbital for 1 year. He was seizure-free until age 15, when he had a staring spell. One week later, he had a generalized tonic-clonic seizure. Within weeks, he was having six seizures a day. An EEG showed generalized spike-wave discharges and focal spikes in the left and right temporal regions. Two MRIs of the brain were unremarkable. He was treated with numerous antiepileptic medications (both as monotherapy and in combination), including phenytoin, valproate, gabapentin, and lamotrigine. Seizure control was eventually obtained with valproate/lamotrigine combination therapy. Before diagnosis, he was a gifted student; afterward, he required placement in a behavior disorder classroom. Neuropsychological testing revealed moderately impaired verbal abilities. He graduated from high school, but has had difficulty retaining employment.

3.2. Patient 2

A 29-year-old female was diagnosed with acute lymphocytic leukemia at age $2\frac{1}{2}$. There was no CNS disease. She achieved remission after induction with prednisone, vincristine, L-asparaginase, and methotrexate. She received cranial irradiation and intrathecal methotrexate as CNS prophylaxis. She had no seizures during antileukemic treatment. At age 14, she began having daily complex partial seizures. She had secondarily generalized seizures several times per year. An EEG showed left temporal epileptiform discharges. An MRI of the brain revealed multiple areas of high T2 and FLAIR signal in the bilateral cerebral white matter. Seizure control was poor, despite trials of multiple medications, including carbamazepine, phenytoin, phenobarbital, lamotrigine, gabapentin, zonisamide, valproate, topiramate, and levetiracetam. After placement of a vagus nerve stimulator, her seizure frequency decreased from several seizures per week to 1–2 per month. She continues to take topiramate and carbamazepine. She required special education classes in high school. Though she graduated, she has remained at home with her parents.

3.3. Patient 3

A 27-year-old male was diagnosed with acute lymphocytic leukemia at age 7. There was no CNS disease. He achieved remission after induction with vincristine, L-asparaginase, prednisone, and daunomycin. As CNS prophylaxis, he received intrathecal methotrexate and cytosine arabinoside; he also received 18 Gy cranial irradiation. One month after induction, he went into status epilepticus and was put into a phenobarbital coma for 5 days. He recovered after a prolonged ICU stay and was seizure-free for 3 years. At age 10, he began having complex partial seizures three times a week. An EEG showed epileptiform discharges in the left and right temporal regions. An MRI of the brain was unremarkable. He was treated with multiple anti-epileptic drugs, including phenytoin, valproate, phenobarbital, tiagabine, oxcarbazepine, zonisamide, topiramate, gabapentin, and levetiracetam. Seizures continue at a frequency of 1–2 per month on phenytoin and levetiracetam. Before he developed epilepsy, he

was an average student; however, he subsequently required special tutoring in high school. Neuropsychological testing showed borderline intellectual ability with diffuse cognitive impairment.

3.4. Patient 4

A 27-year-old female was diagnosed with acute lymphocytic leukemia at age 3. There was no CNS disease. Remission was achieved after induction with vincristine, L-asparaginase, prednisone, and daunorubicin. She received intrathecal methotrexate and 18 Gy cranial irradiation as CNS prophylaxis. She had no seizures during treatment. Six years after diagnosis, and three years after she finished chemotherapy, she began having seizures. She had several different types, including staring spells, atonic seizures, and generalized tonic-clonic seizures. Her EEG showed multifocal epileptiform activity and generalized spike-wave discharges. An MRI of the brain showed increased T2 signal in the left mesial temporal lobe. Despite therapy with multiple antiepileptic drugs, including phenobarbital, phenytoin, ethosuximide, valproate, zonisamide, carbamazepine, felbamate, and gabapentin, she has continued to have daily seizures. A vagus nerve stimulator did not improve her seizure frequency. She was unable to attend regular school due to severe cognitive impairment, and ultimately required placement in a long-term care facility.

3.5. Patient 5

A 26-year-old male was diagnosed with acute lymphocytic leukemia at age 8 months. There was no CNS disease. Remission was achieved after induction with vincristine, prednisone, and daunorubicin. He received intrathecal methotrexate as CNS prophylaxis. Initially, he did not receive cranial irradiation due to his young age. At age $2\frac{1}{2}$, he was found to have a testicular mass; biopsy showed sheets of leukemia cells. He was treated with high-dose cyclophosphamide, thioguanine, cytosine arabinoside, and adriamycin; he received intrathecal methotrexate and cranial irradiation. At age 3, he had a generalized seizure 12 h after cyclophosphamide administration; he was hyponatremic at the time. He was treated with phenobarbital for 1 week. He was seizure free until age 9, when he began having daily seizures. He had multiple types, including complex partial seizures, atonic seizures, and generalized tonic-clonic seizures. At times he had up to 100 seizures per day. His EEG showed bifrontal epileptiform discharges. A brain MRI showed subtle areas of high signal in the periventricular white matter on T2 and FLAIR. He was tried on multiple medications, including phenytoin, valproate, carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, felbamate, tiagabine, topiramate, and zonisamide. The ketogenic diet did not improve seizure frequency. He required special education in school due to severe cognitive deficits, and requires full-time care in an assisted living facility.

4. Results

Clinical and demographic data are summarized in Table 1. In our clinic, a tertiary care referral center, five patients with intractable epilepsy and a history of childhood leukemia were identified. The mean age at diagnosis of leukemia was $2\frac{1}{2}$ years old. None of the children had or developed central nervous system disease. As CNS prophylaxis, all of the children received both cranial irradiation and intrathecal chemotherapy; all received intrathecal methotrexate, and two received intrathecal cytosine arabinoside as well. All of the children achieved remission from leukemia; one child (patient 5) had a testicular relapse 22 months

Table 1
Patient data.

Patient/age/age at ALL Dx:	CNS prophylaxis received	Interval to development of epilepsy	Seizure type(s)	EEG	MRI	Number of AEDs tried; non-pharmacologic tx tried	Follow-up
1/25 y/2.5 y	Intrathecal methotrexate	12.5 y	CPS	Multifocal epileptiform discharges	Unremarkable	4	Good control (6 sz/year) with valproic acid/lamotrigine
	Intrathecal ara-C		Absence	3 Hz spike-and-wave discharges			
	18 Gy cranial irradiation		GTC				
2/29 y/2.5 y	Intrathecal methotrexate	11.5 y	CPS	Left temporal epileptiform discharges	High T2 and FLAIR signal in white matter diffusely and at the gray-white junction	9	Fair control (1–2 sz/mth) with VNS, topiramate, and carbamazepine
	18 Gy cranial irradiation		2′ GTC				
						Vagus nerve stimulator	
3/27 y/7 y	Intrathecal methotrexate	3 y	CPS	Bilateral frontotemporal epileptiform discharges	Unremarkable	9	Fair control (1–2 sz/mth) on phenytoin and levetiracetam
	Intrathecal ara-C 18 Gy cranial irradiation						
4/27 y/3 y	Intrathecal methotrexate	6 y	CPS	Multifocal epileptiform discharges	Increased signal L mesial temporal lobe	8	Poor control; daily seizures
	18 Gy cranial irradiation		Atonic GTC	Generalized spike-and-wave			
						Vagus nerve stimulator	
5/26 y/2.5 y	Intrathecal methotrexate	6.5 y	CPS	Bifrontal discharges	High T2 and FLAIR signal in white matter	10	Poor control; daily seizures
	18 Gy cranial irradiation		Absence Atonic GTC	Generalized spike-and-wave		Ketogenic diet	

after diagnosis and was treated with a second round of chemotherapy, including intrathecal methotrexate.

The mean age at first seizure was ten years old. Four patients have multiple seizure types, and all have been treated with multiple anti-epileptic drugs. Two patients had vagus nerve stimulators placed (one of which experienced a benefit), and one patient unsuccessfully tried the ketogenic diet. Seizure control has been poor in these patients; all but one have seizures at least once a month, and two patients have daily seizures. All of the patients are cognitively impaired; two required placement in long-term care facilities, and the other three are unable to live independently.

5. Discussion

Until the 1980s, conventional treatment for childhood leukemia involved prophylaxis against central nervous system disease using both cranial irradiation and intrathecal methotrexate.[4] Though this treatment regimen greatly increased survival among leukemia patients, reports of neuropsychological late effects eventually led to a search for prophylaxis protocols with lower neurotoxic potential. In 1982, the combination of cranial irradiation and intrathecal methotrexate was abandoned in favor of intrathecal methotrexate alone.[4] Our patients all received both intrathecal methotrexate and cranial irradiation; two patients received intrathecal cytosine arabinoside as well. We hypothesize that our patients' intractable seizures may be related to their exposure to these neurotoxic agents.

Methotrexate has been used as a chemotherapeutic agent for many years. A dihydrofolate reductase inhibitor, its use leads to depletion of folate.[5] This affects several biochemical pathways, resulting in decreased synthesis of nucleic acids. This mechanism is responsible for both the therapeutic and toxic effects of the drug. When given intrathecally, methotrexate is associated with a wide range of neurotoxic effects, including acute seizures, encephalopathy, stroke-like episodes with focal neurologic deficits, and chronic cognitive impairment.[6] Imaging studies have shown white matter changes in patients who have received intrathecal methotrexate, and diffusion-weighted MRI abnormalities have also been described.[2]

The neurotoxic effects of methotrexate are not fully understood, and are likely multifactorial. Methotrexate administration causes folate deficiency and elevated levels of homocysteine.[5] This hyperhomocysteinemia has been implicated in the pathogenesis of methotrexate neurotoxicity, as homocysteine is known to cause vascular endothelial injury.[7,8] This may explain the stroke-like episodes and focal neurologic deficits that have been described with methotrexate use.[9]

Excess homocysteine may also be involved in the pathogenesis of seizures after treatment with methotrexate. Excess homocysteine is metabolized to sulfur-containing amino acids, such as homocysteic acid (HCA) and cysteine sulfinic acid (CSA). These substances are endogenous NMDA receptor agonists, causing enhancement of glutamate release.[10] Excess levels of glutamate, the principal excitatory neurotransmitter in the brain, have been found in epileptogenic foci.[11] One case report showed elevated levels of homocysteine, HCA, and CSA in the cerebrospinal fluid of a child with acute lymphocytic leukemia who had had a generalized tonic-clonic seizure 4 days after receiving intrathecal methotrexate.[12] Another recent study showed that glutamate uptake and clearance by astrocytes was decreased by 20–30% in cortical slices of mice who had had seizures after receiving intrathecal methotrexate.[13] Thus, glutamate excess, the end result of homocysteine metabolites, may be the cause of seizures after methotrexate administration.

The patients we describe developed intractable epilepsy several years after receiving intrathecal methotrexate. Glutamate excess is known to cause excitotoxicity and eventual neuronal death through calcium influx, which is triggered by glutamate receptor activation.[14] This is thought to be a mechanism of some epilepsies and of various neurodegenerative disorders, and may be a mechanism of our patients' epilepsy.

Two of our patients also received intrathecal cytosine arabinoside. A nucleoside analog, its mechanism involves inhibition of DNA and RNA synthesis. Neurotoxic signs include ataxia, encephalopathy, myelopathy, and seizures; the mechanism of neurotoxicity is not well understood.[15] Patients who experience seizures usually do so acutely; one case report described two patients who had seizures within 24 h of intrathecal cytosine arabinoside administration. Within 24 h the seizures had resolved, and neither patient had permanent neurological deficits.[16]

Using intrathecal cytosine arabinoside in conjunction with intrathecal methotrexate and radiation may be more neurotoxic than using cytosine arabinoside alone.[17] One case series described five children with acute lymphocytic leukemia or Burkitt's lymphoma who received intrathecal methotrexate, intrathecal cytosine arabinoside, and radiation; all of the children developed necrotizing leukoencephalopathy. Three had progressive encephalopathy, seizures, and death; at autopsy, necrosis, demyelination, and axonal damage atypical of radionecrosis were seen.[17] The authors suggested that the combination of intrathecal chemotherapeutic agents and radiation intensified neurotoxicity; however, the role of cytosine arabinoside in this process is not well understood.[17]

All of our patients also received whole-brain irradiation. Radiation exerts its effects by causing breakage of DNA strands in rapidly dividing cells; because they do not replicate, most neurons are not radiation sensitive. However, the neurons in the hippocampal area, where neurogenesis continues throughout life, are exquisitely sensitive to radiation damage.[18] Glial and vascular endothelial cells, which continue to proliferate throughout life, are also sensitive to the effects of radiation.[19]

Radiation toxicity can present clinically at many stages of treatment. Acute, early-delayed, and late-onset encephalopathy are characterized by headache, focal neurologic deficits, and transient or severe cognitive impairment; areas of contrast enhancement, white matter changes, and atrophy (in late-onset encephalopathy) are seen on CT and MRI images. Histologically, diffuse demyelination, axonal loss, necrosis, and spongiosis are seen.[20]

All of our patients received whole-brain irradiation in conjunction with intrathecal methotrexate. Though a rare cause of seizures when given alone, radiation likely potentiates the neurotoxic effects of methotrexate and other chemotherapeutic agents. Damage to vascular endothelial cells leads to increased permeability of the blood–brain barrier (BBB) with resulting higher concentrations of intravenous chemotherapeutic agents in the CNS.[21,22] The mechanism for such potentiation is less clear when the chemotherapeutic agents are given intrathecally.

Four of our patients had evidence of temporal lobe irritability on EEG; it is possible that these vulnerable areas were damaged by radiation. Studies of animal models have shown that radiation causes increased apoptosis, a decrease in cell proliferation, and a decrease in stem cell differentiation into neurons within the neurogenic region of the hippocampus[18,23–25]; this damage may be the cause of the cognitive deficits that are the hallmark of late-onset radiation encephalopathy. Such radiation-induced temporal lobe damage, followed by methotrexate-induced glutamate excess and excitotoxicity, may explain our patients' intractable epilepsy.

6. Conclusions

Successful treatment for childhood leukemia may be followed by late signs of neurotoxicity, including intractable epilepsy. Methotrexate damages the central nervous system by several mechanisms, including homocysteine-induced vascular endothelial injury and the buildup of sulfur-containing amino acids. Cranial irradiation damages neurons in the hippocampus, where neurogenesis continues throughout life. The neurotoxic damage caused by intrathecal chemotherapy and cranial irradiation likely contributed to the development of intractable epilepsy in our five patients.

References

1. Maytal J, Grossman R, Yusuf FH, Shende AC, Karayalycin G, Lanzkowsky P, et al. Prognosis and treatment of seizures in children with acute lymphocytic leukemia. _Epilepsia_ 1995;**36**:831–6.
2. DiMario FJ, Packer RJ. Acute mental status changes in children with systemic cancer. _Pediatrics_ 1990;**85**:353–60.
3. Khan RB, Marshman KC, Mulhern RK. Atonic seizures in survivors of childhood cancer. _J Child Neurol_ 2003 Jun;**18**(6):397–400.
4. Muriel FS, Svarch E, Pavlovsky S, Eppinger-Helft M, Braier J, Vergara B, et al. Comparison of central nervous system prophylaxis with cranial radiation and intrathecal methotrexate versus intrathecal methotrexate alone in acute lymphoblastic leukemia. _Blood_ 1983 Aug;**62**(2):241–50.
5. Linnebank M, Pels H, Kleczar N, Farmand S, Fleissbach K, Urbach H, et al. Methotrexate induced white matter changes are associated with polymorphisms of methionine metabolism. _Neurology_ 2005;**64**:912–3.
6. Vezmar S, Becker A, Bode U, Jaehde U. Biochemical and clinical aspects of methotrexate neurotoxicity. _Chemotherapy_ 2003;**49**:92–104.
7. Rees NM, Rodgers GM. Homocysteinemia: association of a metabolic disorder with vascular disease and thrombosis. _Thombosis Res_ 1993;**71**:337–59.
8. Malinow MR. Homocysteine and arterial occlusive diseases. _J Int Med_ 1994;**236**:603–17.
9. Haykin ME, Gorman M, van Hoff J, Fulbright RK, Baehring JM. Diffusion-weighted MRI correlates of subacute methotrexate-related neurotoxicity. _J Neuro-oncol_ 2006;**76**:153–7.
10. Flott-Rahmel B, Schurmann M, Schluff P, Fingerhut R, Musshoff U, Fowler B, et al. Homocysteic and homocysteine sulphinic acid exhibit excitotoxicity in organotypic cultures from rat brain. _Eur J Pediatr_ 1998;**157**:S112–7.
11. Sherwin AL. Neuroactive amino acids in focally epileptic human brain: a review. _Neurochem Res_ 1999;**24**:1387–95.
12. Quinn CT, Griener JC, Bottiglieri T, Hyland K, Farrow A, Kamen BA. Methotrexate, homocysteine, and seizures. _J Clin Oncol_ 1998;**16**:393–4.
13. Leke R, Oliveira DL, Schmidt AP, Avila TT, Jorge RS, Fischer A, et al. Methotrexate induces seizure and decreases glutamate uptake in brain slices: prevention by ionotropic glutamate receptors antagonists and adenosine. _Life Sci_ 2006;**80**:1–8.
14. Choi DW. Glutamate neurotoxicity in cortical cell culture is calcium dependent. _Neurosci Lett_ 1985;**58**:293–7.
15. Baker J, Royer GL, Weiss RB. Cytarabine and neurologic toxicity. _J Clin Oncol_ 1991;**9**:679–93.
16. Eden OB, Goldie W, Wood T, Etcubanas E. Seizures following intrathecal cytosine arabinoside in young children with acute lymphoblastic leukemia. _Cancer_ 1978;**42**:53–8.
17. Rubinstein LJ, Herman MM, Long TF, Wilbur JR. Disseminated necrotizing leukoencephalopathy: a complication of treated central nervous system leukemia and lymphoma. _Cancer_ 1975 Feb;**35**(2):291–305.
18. Monje ML, Palmer T. Radiation injury and neurogenesis. _Curr Opin Neurol_ 2003;**16**:129–34.
19. Gutin PH, Leibel SA, Sheline GE. _Radiation injury to the nervous system._ New York: Raven Press; 1991.
20. Cohen ME, Duffner PK. Long-term consequences of CNS treatment for childhood cancer, Part I: Pathologic consequences and potential for oncogenesis. _Pediatr Neurol_ 1991;**7**:157–63.
21. Yuan H, Gabes MW, McColgan T, Naimark MD, Kiani MF, Merchant TE. Radiation-induced permeability and leukocyte adhesion in the rat blood–brain barrier: modulation with anti-ICAM-1 antibodies. _Brain Res_ 2003;**969**:59–69.
22. Qin D, Ma J, Xiao J, Tang Z. Effect of brain irradiation on blood–CSF barrier permeability of chemotherapeutic agents. _Am J Clin Oncol_ 1997;**20**:263–325.
23. Peissner W, Kocher M, Treuer H, Gillardon F. Ionizing radiation-induced apoptosis of proliferating stem cells in the dentate gyrus of the adult rat hippocampus. _Mol Brain Res_ 1999;**71**:61–8.
24. Tada E, Parent JM, Lowenstein DH, Fike JR. X-irradiation causes a prolonged reduction in cell proliferation in the dentate gyrus of adult rats. _Neuroscientist_ 2000;**99**:33–41.
25. Parent JM, Tada E, Fike JR, Lowenstein DH. Inhibition of dentate granule cell neurogenesis with brain irradiation does not prevent seizure-induced mossy fiber synaptic reorganization in the rat. _J Neurosci_ 1999;**19**:4508–19.