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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 antiepileptic 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