Of 71 acute lymphoblastic leukemia survivors at our hospital over the past 10 years, 2 children developed mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS). This is the first report to describe the clinical course of MTLE-HS observed longitudinally by EEG and MRI. Patient 1 experienced a seizure during chemotherapy involving intrathecal methotrexate. Postseizure MRI suggested methotrexate encephalopathy or leukemic invasion. Anticonvulsant therapy was initiated; subsequent EEGs and MRIs revealed normal results. Three years after chemotherapy, a diffuse, irregular spike-and-wave pattern was observed on interictal EEG. Five years after chemotherapy, the patient developed MTLE-HS comprising complex partial seizures, typical temporal spikes on EEG, and hippocampal sclerosis (HS). Patient 2 did not experience seizures during chemotherapy. Four years later, the patient started experiencing complex partial seizures, and a diffuse, irregular spike-and-wave pattern was observed on interictal EEG. A clinical picture of MTLE-HS developed 2 years later. Such atypical EEG findings may indicate MTLE-HS during follow-up of leukemia patients. MTLE-HS develops several years after an initial precipitating incident such as prolonged seizures, central nervous system infection, and brain trauma. In our cases, the initial precipitating incident may have been chemotherapy and/or prolonged seizures. Thus, MTLE-HS associated with leukemia may not be as rare as generally believed. A large cohort study of late neurologic complications is warranted.
Acute lymphoblastic leukemia (ALL) is the most common childhood cancer. Fortunately, its long-term survival rate has significantly improved due to systemic multagent antileukemia chemotherapy and central nervous system (CNS) prophylaxis, including intrathecal chemotherapy and cranial irradiation. However, significant side effects of the therapy, such as acute neurotoxicity and epilepsy, occasionally occur as late neurologic sequelae.\(^1\) Approximately 10% of children with ALL experience \(\geq 1\) seizures, typically during antileukemia therapy. Such events are triggered by acute treatment toxicity, which might be related to chemotherapeutic neurotoxicity, cranial radiation, metabolic complications, cerebral hemorrhage, CNS infection, cerebral vascular disorders, and leukemic infiltration.\(^2,3\)

Mesial temporal lobe epilepsy with hippocampal sclerosis (MTLE-HS) is characterized by intractable epilepsy with complex partial seizures (CPSs) of temporal origin and temporal sclerosis and represents the final common pathway of several processes.\(^4\) Early detection of MTLE-HS is important, because these children are likely candidates for brain surgery and have an excellent chance of a subsequent normal life.\(^5\) Thus far, only 8 cases of children with MTLE-HS in hematologic cancers have been reported.\(^6-10\) We experienced 2 such cases at our institute and believe that MTLE-HS is probably not as rare as generally deemed. This is the first report to our knowledge that describes the clinical course of patients who were longitudinally followed throughout the latent period until the manifestation of MTLE-HS by EEG and MRI.

**PATIENT PRESENTATIONS**

**Patient 1**

A 6-year-old girl with an uneventful medical history was diagnosed with precursor B ALL. She was treated with chemotherapy comprising prednisone, vincristine, 4′-O-tetrahydropropyranyl-adriamycin, L-asparaginase, cytarabine, 6-mercaptoprine, cyclophosphamide, and methotrexate in accordance with the Tokyo Children Cancer Study Group protocol (TCCSG L99-15).\(^11\) She had no CNS involvement at diagnosis and had complete remission after induction therapy. At age 6 years 4 months, after starting consolidation therapy comprising cyclophosphamide, cytarabine, 6-mercaptopurine, triple intrathecal administration of methotrexate, hydrocortisone, and cytarabine, the patient experienced her first seizure: tonic-clonic convulsions of the right extremities lasting 10 minutes. MRI performed 2 days after the seizure revealed a high-intensity area by T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging over the left temporal lobe, medial occipital lobe, and vermis of the cerebellum (Fig 1A). Blood and cerebrospinal fluid examination revealed unremarkable results, and EEG showed increased slow waves in the left hemisphere. The mass gradually diminished during treatment, eventually disappearing after 3 months (Fig 1B).

Six months after the first seizure, the patient complained of nausea and headache during infusion of intravenous methotrexate. Shortly after triple intrathecal therapy, she lost consciousness, followed by a cluster of tonic-clonic convulsions of the right extremities lasting 3 to 5 minutes, which were arrested after 30 minutes by continuous injection of midazolam. Throughout the course of chemotherapy, repeated lumbar punctures revealed no abnormalities. Carbamazepine therapy was started, and the seizures did not recur for \(\sim\)5 years. The patient received 11 courses of intrathecal methotrexate without cranial radiation. Her EEGs remained normal for the following 3 years, until diffuse, irregular spike-and-wave patterns in the left hemisphere were observed at age 9 (Fig 1E). MRI performed at age 9 revealed normal results (Fig 1C). At age 10, spike-and-wave activity on EEG became localized to the anterior head area (Fig 1F).

At age 11, she started having CPSs, which comprised paroxysmal episodes of epigastric rising sensations followed by unconsciousness. Multiple antiepileptic drugs, including zonisamide, clobazam, and gabapentin, were unsuccessfully used to control the seizures. Intercital EEGs were unremarkable, leading to the suspicion of pseudoseizures. At age 12, after reducing antiepileptic drugs, CPSs occurred, with ictal EEGs showing a cluster of spikes in the left temporal region (Fig 1G). Thereafter, seizures continued daily or weekly despite combination treatment with valproate, zonisamide, and clonazepam. Finally, surgery was performed; multiple subpial transections on the left mesial temporal lobe were selected instead of amygdalohippocampectomy to preserve memory function. She has been seizure-free for 18 months since the surgery.

MRI performed regularly since the diagnosis of ALL did not indicate hippocampal abnormalities between the first and second attacks. It was not until the patient was 12 years old that sclerosis of the left hippocampus was recognized by FLAIR imaging (Fig 1D). However, a retrospective review of MRI scans indicated that the lesion had been apparent at age 11, 2 years after the appearance of EEG abnormalities, when she started having refractory CPSs.

**Patient 2**

A 5-year-old boy was diagnosed with precursor B ALL and was treated according to the TCCSG L99-15 protocol,\(^11\) similar to patient 1. He had no CNS involvement at diagnosis. After induction therapy, he went into remission and experienced no seizures.
during antileukemia therapy. Cranial irradiation was not used. Brain MRI performed at age 6 revealed normal results.

At age 11, the boy experienced an episode of vomiting followed by ambulatory automatism and became unconscious for 10 minutes. Again, MRI revealed no abnormalities (Fig 2A), but EEG showed a diffuse, irregular spike-and-wave pattern (Fig 2C). His family was unwilling to start anticonvulsant therapy; therefore, he was observed without medication. At age 13, he experienced 5 episodes of CPSs. We initiated carbamazepine therapy, but the therapy was discontinued after 1 week due to withdrawal of parental consent. As the frequency of seizures increased, interictal EEGs obtained every 2 months showed diffuse, irregular spike-and-wave activity. At age 13, 2 years after the appearance of EEG abnormalities, MRI revealed atrophy of the left temporal lobe and hyperintensity of the left hippocampal formation by FLAIR imaging (Fig 2B), and EEG showed high-voltage slow waves dominant in the left hemisphere (Fig 2D). Subsequently, MTLE-HS was diagnosed on the basis of clinical symptoms, that is, nausea and loss of consciousness, and hippocampal sclerosis (HS) on MRI. He has been seizure-free for 5 months since the resumption of carbamazepine treatment. Currently, brain surgery is scheduled in case his seizures become uncontrolled.

**DISCUSSION**

MTLE-HS generally develops during the latent period and appears several years after an initial precipitating incident (IPI). Recently, cases of very rare MTLE-HS associated with hematologic malignancies have been reported, wherein seizures induced by chemotherapy or cranial irradiation were suspected as IPIs.

In our patients, cranial irradiation was not used, and neither CNS infection nor cerebrovascular disease was observed. In patient 1, the IPIs may be “atypical methotrexate encephalopathy” and/or...
seizure clusters. This type of encephalopathy is characterized by the presence of a T2 high-intensity area in the cortex and subcortical white matter, seizures lasting several days, and normalization of the MRI within 3 months. With regard to differential diagnosis, patient 1’s MRI abnormalities were also suspected to be the result of direct invasion of leukemic cells, despite the lack of leukemic cells in the cerebrospinal fluid, due to the presence of gadolinium-enhanced nodules. In patient 2, seizures did not occur during chemotherapy, and no abnormalities were observed on MRI. In this case, the IPI might have been the anti-leukemia chemotherapy itself, similar to a case reported by Goyal et al. The current literature describes only 10 patients, including the present cases, with MTLE-HS after treatment of hematologic cancer. Seizure during chemotherapy occurred in 8 of 10 patients; CNS leukemic invasion occurred in 2 patients; cranial irradiation occurred in 2 patients; encephalopathy, such as posterior reversible encephalopathy syndrome, occurred in 2 patients; and methotrexate leukoencephalopathy occurred in 2 patients. Notably, intrathecal methotrexate was administered in all except 2 cases. These observations suggest that among the anticancer agents, methotrexate may be related to the development of MTLE-HS, although multiple factors are involved in the formation of HS.

Methotrexate is a key drug in the management of ALL, and recently, intrathecal methotrexate therapy has been used as an alternative to cranial radiation, without compromising patient outcome. However, methotrexate is known to exhibit critical neurotoxicity, probably through the following mechanisms. First, methotrexate depletes intracellular folate, which increases homocysteine levels and damages the vascular endothelium. Increased homocysteine is additionally metabolized to yield an N-methyl-D-aspartate receptor agonist, leading to seizures and excitotoxic neuronal death. Second, methotrexate decreases tetrahydrobiopterin, which limits γ-aminobutyric acid availability, thereby increasing the susceptibility to seizures. Another study, however, reported that systemic or intrathecal methotrexate therapy did not increase the risk of seizures during chemotherapy. Conceivably, methotrexate may cause MTLE-HS but not any other type of epilepsy.

Interictal EEG findings generally show anterior-temporal spikes in adults with mesial temporal lobe epilepsy. Mohamed et al reported that interictal EEGs in children revealed anterior-temporal spikes associated with extratemporal or generalized discharges in 60% of cases. Harvey et al reported that focal temporal spikes were detected on the first EEG only in 56% of newly diagnosed temporal lobe epilepsy cases occurring before 15 years of age. The present cases showed only diffuse, irregular spike waves on
EEG during the latent period, which may have emerged from the subcortical thalamus induced by secondary bilateral synchrony. We believe that interictal EEGs in cases of mesial temporal lobe epilepsy are likely to show diffuse epileptic discharges in the latent period during infancy, becoming localized to anterior-temporal spikes with age. Interestingly, both patients developed HS, 2 years after the detection of diffuse spike-and-wave activity. On the basis of only 2 cases, however, we hypothesize that such nonspecific EEG findings after chemotherapy are important for the prediction of MTLE-HS in clinical practice. Therefore, these cases should prompt a call for additional study on the EEG findings in the years after ALL treatment and study of the rate of MTLE-HS.

Treatment regimens for ALL patients have progressed over the past 30 years, resulting in increased numbers of survivors of leukemia. Consequently, the number of patients with late neurologic complications after leukemia therapy is also increasing. In the past 10 years, we experienced 2 children developing MTLE-HS out of 85 patients with ALL treated in our institute (71 patients are alive). It is possible that leukemia therapy itself is an IPI, and a future cohort study is required to investigate the morbidity of late complications of childhood leukemia.

REFERENCES


**Temporal Lobe Epilepsy With Hippocampal Sclerosis in Acute Lymphoblastic Leukemia**

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