Etiology and Outcome of Seizures in Children during Induction Remission Chemotherapy for Acute Lymphoblastic Leukaemia

Shahinoor A. Soma¹  Chowdhury Y. Jamal²  Indira Chowdhury³

¹Junior Consultant (pediatrics), Upazila Health Complex, Nawabganj, Dhaka, Bangladesh
²Professor, Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh
³Junior Consultant (Pediatric Hematology and Oncology), Chittagong Maa-Sishu O General Hospital, Agrabad, Chittagong, Bangladesh.

Address for correspondence Shahinoor Akter Soma, Junior Consultant (pediatrics), Upazila Health Complex, Nawabganj 1320, Dhaka, Bangladesh (e-mail: somabd79@yahoo.com).

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Abstract

Seizure is one of the most frequent neurological complication and morbid phenomenon among children receiving chemotherapy for acute lymphoblastic leukemia. As overall survival of children with acute lymphoblastic leukemia is improving, now the challenge is to reduce treatment-related adverse effect. However, not much is known about the etiology and natural history of these seizure in our pediatric population. This is a single centered study conducted in the Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University. This prospective observational study was conducted over a period of 1 year from May 2017 to April 2018. A total of 105 patients aged 1 year to 17.9 years newly diagnosed as acute lymphoblastic leukemia were the study population. This study showed that in five (33.3%) patients, the underlying cause was suspected intracranial hemorrhage and it was the most common cause. All these five patients had features of severe sepsis and upper motor neuron sign associated with severe thrombocytopenia. Among them three had coagulopathy. Three (20%) patients had CNS leukemic infiltration. Suspected meningitis was attributed as the possible cause of seizure in two (13.33%) patients. Other identifiable causes were brain abscess in one patient, multiple cerebral infarction in one patient, hypertensive encephalopathy in one patient, and vincristine-induced neurotoxicity in one patient. In one patient no identifiable cause was found. Among 15 patients with seizure five (33.3%) patients were improved and completed induction remission chemotherapy. Ten (66.7%) patients died. In this study, we found sepsis and coagulopathy as the major underlying cause of seizure. Outcome was found very dismal in patients who developed seizure.

Keywords
► seizure
► acute lymphoblastic leukemia
► induction remission chemotherapy

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Introduction

The five year overall survival of children with acute lymphoblastic leukemia has dramatically improved over the past few decades. The advancement made in the treatment of childhood ALL is one of the successful milestones of the modern medicine. This improved survival is due to the use of more intensive and risk-directed chemotherapy in the treatment of children with acute lymphoblastic leukemia. Recently COG reported that the 5-year survival rate of children with ALL increased from 83.7% in 1990 to 1994 to more than 90% in 2000 to 2005 (p < 0.001). But with the use of more intensive chemotherapy the frequency of side effects has also increased.2,3

Acute neurological complications are among the most critical issues in children receiving chemotherapy for ALL.4–8 Seizures are reported in 8 to 13% of children with acute lymphoblastic leukemia.8–12 Most of the seizures occur during the induction and CNS system consolidation phases.5,8,10,13

Seizures may develop as a symptom of systemic complications or as isolated CNS toxicity.14,15 The most frequently reported neurotoxicity or systemic conditions that predispose patients to seizures are chemotherapeutic neurotoxicity, posterior reversible encephalopathy syndrome (PRES), cerebral hemorrhage, CNS infection, cerebral sinus venous thrombosis, methotrexate-related stroke-like syndrome, electrolyte disturbances including the syndrome of inappropriate antidiuretic hormone secretion, and leukemic infiltration.5,8,10,11,16

Knowledge of probable etiologies of seizure in children with ALL is very important for prompt diagnosis and optimal treatment to reduce seizure related morbidity and mortality. There is very little information about the etiology and natural history of these seizure in our population.

Thus, the objective of this study was to explore the etiology and outcome of seizures in children undergoing induction remission chemotherapy for acute lymphoblastic leukemia.

Materials and Methods

This is a single centered study conducted in the Department of Pediatric Hematology and Oncology, Bangabandhu Sheikh Mujib Medical University. This prospective observational study was conducted over a period of 1 year from May 2017 to April 2018. A total of 105 patients aged 1 year to 17.9 years newly diagnosed as acute lymphoblastic leukemia were the study population. Children who had any preexisting neurological abnormality were excluded from the study. Informed written consent were obtained from the parent or guardian at the time of study enrollment. Preformed data collection sheets (questionnaire) were used to collect data. The study protocol was approved by the institutional ethical committee. The patients were stratified and treated according to UK ALL 2003 protocol. Patients were considered as with standard risk who aged between 1 and 9.9 years with initial WBC of less than 50,000/mm³. On the other hand, patients aged > 10 years or initial WBC count > 50,000/mm³ were considered as high risk.17 Standard risk group patients got regimen-A and high risk group was treated with regimen-B. In both regimen the chemotherapeutic agents used were oral dexamethasone, vincristine, L-asparaginase, and IT/IT (intrathecal methotrexate, hydrocortisone and/or cytosine-arabinoside). In addition to these drugs high-risk regimen also includes daunorubicin.

Each patient was observed routinely from the first day of chemotherapy up to 35 days of induction remission for the development of seizure. Attending physician verified each incidence of seizure and its type. Whenever a patient developed seizure then detailed physical examination were done including fever, heart rate, blood pressure measurement, upper motor neuron sign, and signs of meningeal irritation. To find out etiology complete blood count, S. electrolytes, S. calcium, random blood sugar, prothrombin time, activated partial thromboplastin time, D-dimer, blood culture and if patients condition permitted EEG, CSF study, computed tomography (CT), and/or magnetic resonance imaging (MRI) were done after development of seizure. Clinical outcomes that were measured included resolution of seizure and death.

Results

Our study was conducted on 105 children with newly diagnosed ALL who aged 1 year to 17.9 years. Mean age was 5.99 ± 3.89 years with a male predominance (60%) and ninety-four (89.5%) patients with B cell lineage and 11 (10.5%) patients with T cell lineage ALL. Regimen A was given to 56 (53.3%) patients, on the other hand 49 (46.7%) patients were treated with regimen B. Seizure were reported in 14.3% (15/105) patients.

Of the 15 patients with seizures, five had suspected intracranial hemorrhage, three had CNS leukemic infiltration, two had suspected meningitis, one cerebral abscess, one had hypertensive encephalopathy, one had multiple cerebral infarction, and one had vincristine-induced neurotoxicity. In one patient with isolated seizure no cause was found (Table 1).

Among 15 patients with seizure, five (33.3%) patients were improved and completed induction remission chemotherapy. Ten (66.7%) patients died (Fig. 1).

Majority of cases were due to suspected intracranial hemorrhage: five (33.3%). All of them had feature of severe sepsis, upper motor neuron signs, and external bleeding from different sites of body associated with severe thrombocytopenia. Among them three had coagulopathy. In all these five patients death occurred within 4 hours to 54 hours of convulsion and their physical condition did not permit CT/MRI to be done to confirm the cause of seizure.

Next most common cause was CNS leukemic infiltration which was found in three (20%) patients and confirmed by CT scan. Among them condition of two patients was eventually improved and they completed induction remission therapy but one patient died. Two (13.3%) patients with suspected meningitis had signs of meningeal irritation but CSF study...
was not done to confirm meningitis as their vitals were not stable and both succumbed to death in a short time.

The condition of the patients with cerebral abscess and hypertensive encephalopathy was improved with appropriate treatment but the patient with multiple cerebral infarction died.

In rest of the two patients one patient developed seizure on second day of induction remission therapy shortly after receiving vincristine. As no other metabolic and structural factors were found, seizure in this patient was postulated to be due to vincristine-induced neurotoxicity. Seizure in this patient subsided by proper treatment and rest of the induction period was uneventful.

In another patient no definitive cause could be identified but the child had severe sepsis. Sepsis-induced brain dysfunction (SIBD) may be the underlying cause of seizure in this patient. We were not able to do neuroimaging to rule out other differential diagnosis in this patient as her physical condition did not permit. So the diagnosis of SIBD was not confirmed in this patient. In this study among the 15 patients who developed seizure, three had associated hypocalcemia, one had hyponatremia, and one had hypomagnesaemia. But none of the electrolyte abnormality was found in such level that could lead to development of seizure. So, they were not considered as the cause of seizure (∼Tables 2 and 3).

**Discussion**

Seizure is one of the most frequent CNS complication and morbid phenomenon among patients receiving ALL therapy.

### Table 1

<table>
<thead>
<tr>
<th>Cause of seizure</th>
<th>Number of patient (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspected intracranial hemorrhage</td>
<td>5 (33.33%)</td>
</tr>
<tr>
<td>CNS leukemic infiltration</td>
<td>3 (20%)</td>
</tr>
<tr>
<td>Suspected meningitis</td>
<td>2 (13.33%)</td>
</tr>
<tr>
<td>Brain abscess</td>
<td>1 (6.66%)</td>
</tr>
<tr>
<td>CNS infarction</td>
<td>1 (6.66%)</td>
</tr>
<tr>
<td>Hypertensive encephalopathy</td>
<td>1 (6.66%)</td>
</tr>
<tr>
<td>Vincristine-induced neurotoxicity</td>
<td>1 (6.66%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (6.66%)</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; CSF, cerebrospinal fluid.

*In all these five patients death occurred within 4 h to 54 h of convulsion and their physical condition did not permit CT/MRI to be done to confirm the cause of seizure.

**CSF study was not done to confirm meningitis as their vitals were not stable and both succumbed to death in a short time.**

### Table 2

<table>
<thead>
<tr>
<th>Sl no</th>
<th>Age/Sex</th>
<th>Signs and symptoms</th>
<th>CT/MRI</th>
<th>Other investigations</th>
<th>Etiological diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3/F</td>
<td>Focal seizure, signs of meningeval irritation</td>
<td>Not done</td>
<td>Hypocalcemia</td>
<td>Suspected meningitis</td>
</tr>
<tr>
<td>2</td>
<td>5/F</td>
<td>Generalized seizure, features of sepsis, UMN sign, melena</td>
<td>Not done</td>
<td>Thrombocytopenia</td>
<td>Suspected ICH</td>
</tr>
<tr>
<td>3</td>
<td>3/M</td>
<td>Generalized seizure, features of sepsis, ecchymosis</td>
<td>Not done</td>
<td>Normal EEG, Thrombocytopenia</td>
<td>Suspected ICH</td>
</tr>
<tr>
<td>4</td>
<td>4/F</td>
<td>Focal seizure, features of sepsis, UMN sign</td>
<td>Normal</td>
<td>Hypocalcemia</td>
<td>Suspected meningitis</td>
</tr>
<tr>
<td>5</td>
<td>8/F</td>
<td>Focal seizure, signs of meningeval irritation, melena</td>
<td>Not done</td>
<td>Thrombocytopenia, coagulopathy</td>
<td>Suspected ICH</td>
</tr>
<tr>
<td>6</td>
<td>3.5/F</td>
<td>Focal seizure</td>
<td>Leukemic infiltrate</td>
<td>Coagulopathy, hypocalcemia</td>
<td>CNS leukemic infiltration</td>
</tr>
<tr>
<td>7</td>
<td>12/M</td>
<td>Generalized seizure, features of sepsis, UMN sign, hematemesis</td>
<td>Not done</td>
<td>Thrombocytopenia, Coagulopathy</td>
<td>Suspected ICH</td>
</tr>
<tr>
<td>8</td>
<td>6/F</td>
<td>Generalized seizure, features of sepsis</td>
<td>Not done</td>
<td>Hypomagnesaemia</td>
<td>Unknown</td>
</tr>
<tr>
<td>9</td>
<td>6/F</td>
<td>Generalized seizure,</td>
<td>Multiple cerebral infarcts</td>
<td></td>
<td>CNS infarction</td>
</tr>
<tr>
<td>10</td>
<td>6/F</td>
<td>Generalized seizure, features of sepsis, hematemesis</td>
<td>Not done</td>
<td>Thrombocytopenia, coagulopathy</td>
<td>Suspected ICH</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; EEG, electroencephalography; ICH, intracranial hemorrhage.
chemotherapeutic treatment. Seizure is a serious complication associated with significant morbidity and mortality. In this study seizures were reported in 14.3% (15/105) children with ALL getting induction remission chemotherapy.

Seizure may be triggered by chemotherapeutic neurotoxicity, cerebral hemorrhage, CNS infection, metabolic complications, PRES, cerebral vascular disorders, and leukemic infiltration.

This present study showed that in five (33.3%) patients, the underlying cause was suspected intracranial hemorrhage and it was the most common cause. A retrospective study performed in 792 recently diagnosed patients with acute leukemia developed a risk score model for fatal ICH. The frequency of fatal ICH was 5.2% in patients with acute leukemia. They demonstrate that female gender, thrombocytopenia, prolonged prothrombin time and hyperleukocytosis are significantly associated with the occurrence of this complication.18

Another retrospective study of 494 children diagnosed with acute leukemia during 2003 to 2016 at a hospital in Thailand showed that the incidence rate of intracranial hemorrhage was 5.1 in acute lymphoblastic leukemia. Case fatality rate was 75% and fatality rate was 100% with early ICH. Early intracranial hemorrhage was associated with prolonged INR and higher WBC count, whereas late intracranial hemorrhage was associated with concurrent systemic infections.19 In our study all the five patients with suspected intracranial hemorrhage had severe sepsis. Among them three had coagulopathy.

Three (20%) patients had CNS leukemic infiltration, which was diagnosed on the basis of CT/MRI findings. A retrospective cohort study done in Indonesia found that among 128 newly diagnosed children with ALL, 23 (18.0%) patients suffered from CNS leukemia. Decrease level of consciousness (61%), vomiting (48%), cranial nerve palsy (44%), and seizures (39%), were the most frequently found clinical manifestations. They found that early CNS leukemia cause low survival of ALL patients than those without early CNS leukemia (p = 0.0005).20

Liu et al evaluated 14 patients with leukemia and CNS lesions. They conclude that MRI aided in the characterization of CNS lesions caused by the leukemic involvement of CNS structures but brain biopsy remains the gold standard for diagnosis.21

In our study suspected meningitis was attributed as the possible cause of seizure in two (13.33%) patients.

Kuskonnaz et al in a retrospective study of 203 ALL patients showed that 9.9% patients developed neurological complication of which 25% were meningitis.6

McCullers et al described a series of 12 children with leukemia who developed candida meningitis. Duration of profound neutropenia and use of total parenteral nutrition were significantly associated with candidal meningitis in children with leukemia. Candida tropicalis, was responsible for 11 cases, indicating increased pathogenicity of this organism in CNS disease. The cases were invariably fatal.22

Other identifiable causes were cerebral abscess in one patient, hypertensive encephalopathy in one patient, and CNS infarction in one patient. The condition of the patients with cerebral abscess and hypertensive encephalopathy was improved after appropriate treatment and both of them completed induction remission chemotherapy. Steroid-induced HTN is a frequent adverse effect of induction therapy in pediatric ALL, occurring in almost 15% of all patients.23

Hypertensive encephalopathy is a rare neurological manifestation in children. It is characterized by rapid onset of severe hypertension and complete recovery if promptly treated. Typical clinical findings include headache, vomiting, mental changes, seizures, and visual abnormalities. This syndrome can be fatal if unrecognized and not properly addressed. Therefore it should be considered as a medical emergency.24

The patient with CNS infarction had convulsion after nine doses of L-asparaginase. As one of the side effect of this drug is thrombosis, it can be attributed as the cause of CNS infarction in this patient. A meta-analysis of 17 prospective studies done by Caruso et al showed that the rate of thrombosis in 1,752 children with ALL was 5.2%. Most of the events occurred during the induction remission phase of chemotherapy. There were several risk factors. Patients who received lower doses of L-asparaginase (£6,000 U/m²) for longer periods (>9 days) were associated with the highest
incidence of thrombosis. Anthracyclines and prednisone are also associated with thrombosis.²⁵

In one patient seizure developed on 2nd day of induction remission therapy shortly after receiving vincristine. In this patient seizure was postulated to be due to vincristine-induced neurotoxicity. Gomber et al in their study show that 10 out of 20 children, treated with usual doses of vincristine for various types of childhood cancers, developed neurotoxicity during treatment. Two of them developed encephalopathy in the form of seizures, confusion, and aphasia. They show a relatively higher incidence of vincristine-induced neuropathy in Indian children, which was probably due to coexistence of severe malnutrition in them.²⁶

In the remaining one patient no definitive cause could be identified. The child had severe sepsis and we assumed sepsis-induced brain dysfunction may be the underlying cause of seizure in this patient. SIBD is characterized by alteration of consciousness, which ranges from delirium to coma, seizure or focal neurological signs. Although its pathophysiology is not well-understood, neuroinflammatory process and impairment of cerebral perfusion may play the role. These two processes leads to microcirculatory dysfunction and ultimately SIBD. Clinical examination is the basis for diagnosis of brain dysfunction. For detecting subclinical brain alteration EEG can be helpful. Other investigations are virtually performed to rule out differential diagnoses.²⁷

As neuroimaging was not done so the diagnosis of SIBD was not confirmed in our patient.

This present study showed that the outcome was very dismal in patients who developed seizure. Among 15 patients who developed seizure, 10 (66.7%) patients died. Kuskonmaz et al in their study found that among 203 children with ALL, 9 (4.4%) patients developed seizure. Three (33.33%) of them died within a median time of 12 days after development of seizure. But in some other studies the outcome was not so poor. In a retrospective study performed in 204 Italian children with ALL, 12 (5.8%) patients developed seizures. Among these 12 patients only one patient died, and the others had no neurological sequelae.³⁹ Parasole et al in their study of 253 children with ALL showed that 24 (9.4%) patients developed seizures. In long-term follow-up all patients were alive except one who died from progression of disease due to ALL combined relapse.¹²

The previous studies done in abroad showed that the underlying cause of most of the seizures developed during ALL therapy was attributed to chemotherapeutic toxicity. But in present study most of the seizures developed directly or indirectly as a complication of severe sepsis. So, these patients had grave outcome.

Limitations of the Study

This study was not without limitation. The limitations of the studies were as follows:

- Calculated sample size could not be achieved.
- Neuroimaging and EEG could not be done in most of the patient in this study.

Conclusion

Among the neurological complications that develop in children who receive chemotherapy for acute lymphoblastic leukemia, seizure is the most devastating one. In our study we found sepsis and coagulopathy as the main underlying cause of seizure. Outcome was found very poor in patients who developed seizure.

Conflict of Interest

None declared.

Acknowledgment

The authors would like to thank the patients and their parents who participated in this study.

References