Neuroimaging Findings in Children with Acute Lymphoblastic Leukemia: A Case Series and Review of Literature

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Abstract

Background and purpose: Acute Lymphoblastic Leukemia is the commonest form of childhood cancer. ALL is most common in early childhood, peaking between 2 and 4 years of age. Cases of AML are more spread out across the childhood years, but it is slightly more common during the first 2 years of life and during teenage years. No doubt, advanced neuroimaging technologies continue to improve and perfect the detection of CNS complications in children with ALL, and the issue of validity becomes steadily addressed. However, radiology literature concerning imaging in children with acute lymphoblastic leukemia (ALL) is sparse. We aim to review the neuroimaging findings in patients with ALL at the Children’s Cancer Center at our institution. Pediatric oncologists, neurologists, and radiologists need to be familiar with the neurologic complications and corresponding imaging findings in ALL patients in order to provide early intervention.

Materials and methods: Data were obtained from retrospective chart review of 196 pediatric patients with ALL treated at our institution between January 2002 and July 2012.

Results: 94 patients had neuroimaging studies; of those, 60 were normal, and 34 patients had abnormalities. The most encountered findings were brain atrophy (n=11 patients), venous sinus thrombosis (n=10), non-specific foci of abnormal signal or hypodensities (n=9), central nervous system infiltration by leukemia (n=7), hemorrhages (n=3 extra-axial hemorrhages, and n=2 parenchymal and subarachnoid hemorrhages), posterior reversible encephalopathy syndrome (n=4), arterial stroke (n=2), venous infarct (n=1), hydrocephalus (n=2), Wernicke encephalopathy (n=1), progressive multifocal leukoencephalopathy (n=1), and glioblastoma multiforme (n=1).

Conclusion: Neuroimaging abnormalities are frequent during and after treatment in pediatric patients with ALL (36.17%). CNS complications are common in ALL patients during therapy and require prompt diagnosis and timely intervention for a better outcome and can provide essential information for delineating priorities for neuroimaging in the detection of CNS complications and early intervention.

Keywords: Neuroimaging; Pediatrics; Leukemia; Complications; Thrombosis; Atrophy

Abbreviations: ALL: Acute Lymphoblastic Leukemia; PRES: Posterior Reversible Encephalopathy Syndrome; PML: Progressive Multifocal Leukoencephalopathy; CMV: cytomegalovirus; GBM: Glioblastoma Multiforme; CNS: Central Nervous System; LP: Lumbar Puncture; TPN: Total Parenteral Nutrition; WE: Wernicke’s Encephalopathy; CT: Computed Tomography; MRI: Magnetic Resonance Imaging

Introduction

Acute lymphoblastic leukemia (ALL) is the most common diagnosed cancer in children, constituting nearly one fourth of all pediatric malignancies and 80% of pediatric leukemia’s [1].

Neurologic complications are common in ALL, both during and after completion of therapy. CNS complications of ALL can be divided into those that result directly from the underlying leukemic process and those that are secondary to immunosuppression or to the therapeutic drug regimen. Direct CNS involvement by childhood leukemia is reported to occur in 3-6%, and may affect the leptomeninges, brain parenchyma, or Intracranial vessels [2,3]. This form of leukemic infiltrate manifests as meningeal involvement, and less commonly as choroma or cranial nerve infiltration [3].

Treatment related neurotoxicity occurs in 3-13% of children [4-6]. The most common complications include stroke, posterior reversible leukoencephalopathy syndrome (PRES), temporal lobe epilepsy, high-dose methotrexate toxicity, syndrome of inappropriate antidiuretic hormone secretion, and other abnormalities [7]. Several reports and case series describe cerebral venous sinus thrombosis in ALL patients, mostly but not exclusively, secondary to treatment with L-asparaginase [8]. Some of these patients had concurrent pro-thrombotic states such as protein S deficiency [9] or hypertriglyceridemia [10]. Increased incidence of hemosiderin deposition on brain MRI of ALL patients has been documented, especially in those patients with vascular malformations secondary to cranial irradiation [11].

The neurological complications of ALL are frequent and limited studies are available on this topic [7,12,13]. The purpose of this study is to present the radiological findings of CNS pathologies in children with ALL that have developed due to leukemia or to anti-leukemic therapy.

Materials and Methods

We retrospectively reviewed the imaging files for all pediatric
patients diagnosed with ALL at the Children’s Cancer Center of Lebanon at the American University of Beirut Medical Center (AUBMC) between January 2002 and July 2012. Images and reports for all cranial and spinal neuro-imaging studies, including MRI and computed tomography (CT) scan, were retrieved, re-evaluated and analyzed for the study. Abnormal imaging findings were consequently correlated with the medical records or the histopathologic diagnosis, when available. The American University of Beirut institutional review board approved the study.

Treatment consisted of three main phases: Induction, Consolidation, and Maintenance.

Three drug induction therapy (Prednisone, Vincristine, L-asparaginase) was administered over (4 weeks) in order to achieve a first remission (the absence of active cancer). Consolidation therapy consisted of four doses of high dose methotrexate and daily mercaptopurine. Maintenance therapy included weekly methotrexate, daily mercaptopurine with pulses of vincristine, and dexamethasone. Two re-induction treatments were also given during maintenance. Only one patient received radiotherapy, he was on the old treatment protocol.

All imaging studies were done, or submitted for official reading, at our institution. For each patient, the reports for all cranial and spinal neuroimaging studies, including MRI and CT scan were retrieved through the hospital Radiology Information System; the images were re-evaluated, and analyzed by one experienced neuroradiologist (10 years of experience) and one experienced general radiologist. All abnormal findings were documented, correlated with the patient’s clinical condition, dates and regimens of treatment, and with the histopathologic diagnosis, when applicable. The spectrum of abnormal findings and the frequency of occurrence, as well as their relation to any predisposing factors were analyzed.

CT scans were obtained using a spiral CT (AVE 1 Tomoscan, Philips) or a multidetector scanner. Scanning for the brain was performed in the standard axial plane with the following parameters: 120 kV, 250 mAs, section thickness of 3 mm, reconstructed at 1.5 mm, matrix 512 x 512. The enhanced scans were obtained after the injection of 100 mL of Ioversol (Optiray300, Mallinckrodt Medical, Inc.) using a power injector at a rate of 0.8 ml/s for younger pediatric patients and 1.4 ml/s for older patients depending on patient weight and catheter gauge, followed by 15 cc bolus of saline.

The MR examinations were performed on a 1.5 Tesla MR unit with axial gradient-echo T1W (TR/TE/NEX 539/12/2 or 147/1.8/2), transverse and coronal T2W images (TR/TE/NEX between 4847 and 7115/100/1), transverse and coronal FLAIR images (TR/TE/TI/NEX 6000/150/2000/2) and transverse DWI. For contrast-enhanced studies, transverse, sagittal and coronal gadolinium-enhanced gradient-echo T1W images (TR/TE/Nex, 147/1.8/2) were obtained.

For MRV, the 3 dimensions phase contrast technique was used (TR/TE 500/10 ms; FA=10 °; sagittal sections, slice thickness =1 mm; FOV, 230 mm; matrix, 256 × 256; TA, 5.25 minutes). All MRV source images obtained were post-processed using the MIP method, generating 12 MIP projections at 15° increments.

Results

A total of 196 charts were evaluated. A total of 94 patients underwent neurological imaging, 60 were normal and 34 patients had at least one CNS abnormality detected. The number of studies for each patient ranged between 1 and 22 imaging studies performed. Of those 34 patients, 21 patients had one abnormality, and 13 patients had two or more abnormalities, as described in (Table 1).

The abnormalities present were either related to the leukemic process itself or to post treatment complications. No doubt that in most

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Thrombosis</th>
<th>Atrophy</th>
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<th>Non-specific abnormal signal or hypodensities</th>
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<td>Spinal extra-axial hematoma post-LP</td>
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<td>Hydrocephalus</td>
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<tr>
<td>1</td>
<td>x</td>
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<td></td>
<td></td>
<td>x</td>
<td>Fever and elevated liver enzymes, radiologically like Wernicke</td>
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<td>Venous infarct, leptomeningeal disease</td>
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<td>Small embolic infarct; E coli sepsis</td>
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<td>Wernicke’s encephalopathy; typical</td>
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Table 1: Details of abnormalities encountered on neuroimaging studies.
cases diagnosis does not require histological analysis such as brain atrophy, venous sinus thrombosis were resolution of thrombus can confirm the diagnosis, CNS hemorrhage, PRES, WE. However, in cases such as chloroma a biopsy was done in addition to radiologic findings for confirmation.

Disease related findings

CNS involvement by leukemia was seen in seven patients, none of which were found at the time of diagnosis. One of these cases demonstrated as a chloroma and confirmed by biopsy (Figure 1). In another patient, the parenchymal leukemic infiltrates appeared as rim-enhancing lesions in the right basal ganglia surrounded by abnormal high T2 signal intensity denoting edema.

A third patient had evidence of a destructive process involving the temporal bones on CT scan which was attributed to leukemic infiltration which occurred 3 years after diagnosis, and was considered disease recurrence. On MRI, the temporal bone lesion was of intermediate signal on T2 and FLAIR images, and was accompanied by involvement of right VII- VIII nerve complex which appeared thicker and showed enhancement post intravenous gadolinium injection, in keeping with leptomeningeal involvement. Leptomeningeal disease was also seen in the rest of the seven patients, confirmed by CSF analysis and they occurred 1-2 years after diagnosis, one of which was during treatment and considered disease recurrence (Figure 2).

Treatment related findings

There were 11 patients who had brain atrophy. The atrophy in these patients persisted on follow-up scans, and therefore was a permanent finding rather than a transient shrinkage. They all occurred after diagnosis of ALL has been made, four of those of patients developed brain atrophy 1-2 year after diagnosis of ALL. The atrophy progressed initially and then persisted on follow-up scans four years from the time of diagnosis. Another six patients developed atrophy at an interval of 3 to 12 months after diagnosis and the atrophy persisted on follow-up scans. One patient developed brain atrophy 2 years after diagnosis but lost follow-up.

There were 10 patients with venous sinus thrombosis (two cases complicated by subarachnoid and intra-parenchymal hemorrhages, and one by venous infarction). In our study, all the patients developed SVT post L-asparaginase treatment. Three of those patients developed thrombosis during the first 3 months of diagnosis, two of them manifesting as transverse sinus thrombosis and one as superior sagittal sinus thrombosis. The rest developed venous thrombosis 1 year after diagnosis with an exception of one occurring after 3 years. The diagnosis of dural venous sinus thrombosis was established on CTV in four patients, on enhanced CT scan in three patients (Figure 3), and on MRV in three patients.

Five patients developed CNS hemorrhage, two of which were
secondary to dural venous sinus thrombosis as mentioned above (Figure 4). Two other patients presented with subdural hemorrhage, one of which developed post lumbar puncture. One patient presented with spinal epidural hemorrhage, also secondary to lumbar puncture.

Five episodes of posterior reversible encephalopathy syndrome (PRES) were encountered in four patients. All the cases were treated with L-asparaginase when they developed PRES. In one patient, it occurred 3 months after diagnosis. The rest had PRES 1-2 years after diagnosis. Clinically, patients presented with seizures and altered sensorium. MRI showed increased T2 signal intensity predominantly in the cortex and subcortical white matter, mainly in the posterior regions of the brain, and to a lesser extent in the frontal lobes. There was no evidence of restricted diffusion, and no involvement of the brainstem, basal ganglia, or cerebellum (Figure 5).

Two patients in our series suffered from arterial stroke. One of these patients presented with septic shock due to E-Coli septicaemia and turned out to have an embolic infarct in the left parietal lobe that occurred within a month of initial diagnosis with ALL. The other patient had third degree atroventricular block. CTA showed an infarct in the left basal ganglia that occurred 4 years after the initial diagnosis was established.

One patient had progressive multifocal leukoencephalopathy (PML) (JC virus) that occurred 10 months after starting treatment. The imaging findings were highly suggestive and MRI demonstrated multifocal progressive abnormal high T2 signal in the subcortical white matter extending to the periventricular white matter and basal ganglia (Figure 6). The patient had minimal partial recovery and significant residual neurological deficit.

Eight patients had nonspecific foci of high T2 signal intensity on MRI, mainly in the periventricular white matter and centrum semiovale (Figure 7). Another patient had ill-defined small hypodensity on CT scan. Most of these findings occurred at an interval of 2 months – 1 year after diagnosis and treatment initiation. One patient had nonspecific abnormal high FLAIR along the medial longitudinal fasciculus in the pons and medulla bilaterally, with restricted diffusion, occurring 3 months after diagnosis.

Hydrocephalus was encountered in two of our patients, occurring at the time of diagnosis, and the CSF study done at the same point of time demonstrated the presence of a mixture of blasts and few normal lymphocytes. The blasts were positive for CD10, dim CD22, dim TdT and partial CD34, suggestive of meningeal involvement.

One patient in our series had histologically proven glioblastoma multiforme that occurred 5-6 years after diagnosis. This patient was diagnosed with ALL at the age of five years, received craniospinal radiation at the age of 8 years, and presented at the age of 13 years with a bifrontal tumor invading the genu of the corpus callosum (Figure 8). This is the only patient that received radiation therapy.

One patient in our series had acute pancreatitis and developed Wernicke’s encephalopathy (WE) (radiologic) 10 months after diagnosis, secondary to prolonged total parenteral nutrition (TPN).
Disease related complications

CNS complication in Leukemic patients is frequent affecting 25-50% of this population [14]. Disease infiltration of the central nervous system is one of the direct complications seen secondary to ALL.

Our incidence estimate is, as would be expected, 20.58% CNS involvement by Leukemia.

Meningeal involvement was the most common; especially the leptomeninges. Intracranial masses called chloroma or granulocytic sarcoma may occur in leukemia, although they are rare. These masses may be a presenting sign of leukemia or develop during the course of the disease [12]. They mainly occur in patients with acute myelogenous leukemia, although they can be seen in other myeloproliferative disorders but are rare in patients with acute lymphoblastic leukemia. Children are more often affected than adults [15].

Radiologically, CNS involvement may be diffuse or focal, with abnormal meningeal enhancement demonstrated on contrast-enhanced CT or better by MRI [16]. The chloroma may arise within the parenchyma or be dural-based. On non-contrastCT scan, it is isodense or hyperdense and enhances strongly after contrast administration. On MRI, it is isointense or hyperintense relative to the brain on T1 and T2-weighted images, and enhances prominently with gadolinium.

Another intracranial complication of leukemia is the development of spontaneous cerebral hemorrhage. Intracranial hemorrhage accounts for around 20% of the mortality associated with ALL. The location of the bleed is variable, preferentially subcortical lobar hemorrhage, however, it can present as subarachnoid as in our review. ALL patients have increased risk for bleeding and thrombosis.

Complications during treatment

The most common radiologic abnormality documented in our study was that of brain atrophy. The number of patients may be underestimated since non-imaged patients may have brain atrophy. This complication may be seen as a late finding after irradiation, often due to a diffuse white matter injury [17], or due to chemotherapy [18]. Only one of our patients had received brain irradiation. This suggests that brain atrophy was mainly secondary to high dose methotrexate and triple intrathecal injections (methotrexate, Ara-C, and hydrocortisone). Brain atrophy can be transient attributed to the use of hydrocortisone. However, the shrinkage noted in our patients was present on follow-up (1-4 years) and was permanent. The atrophy occurred at 1-2 years post treatment.

In our series, venous sinus thrombosis was the second most commonly detected neurologic complication (29.41%). Our incidence is higher than the average of thromboembolic events in ALL children under chemotherapy (3.2%). Although this is a generally rare event, it is common in patients with ALL especially those receiving remission induction treatment in a percentage ranging from less than 1% to 36.7% [19]. However, in our study, all the patients developed SVT post L-aspa treatment. The diagnosis of SVT is based on radiologic findings. Contrast enhanced CT and CTV show the empty delta sign corresponding to the venous filling defect. Both CTV and contrast enhanced MRV are considered the diagnostic modality of choice for SVT. Subarachnoid and intraparenchymal hemorrhages, and venous infarct are the most common complications, seen in 10-50% of cases of venous thrombosis [20].

Ischemic stroke can be seen in ALL patients. This is contributed by the disease itself, which may mimic a chronic state of disseminated

that lacked vitamin B12 supplementation. His WE showed complete resolution upon therapy with thiamine. Brain MRI revealed abnormal high T2 signal intensity in both mammillary bodies and the medial aspect of both thalami (Figure 9).

Discussion

The major improvements in treatment of pediatric ALL are a result of more aggressive and risk stratified protocols. Advanced therapy nowadays has improved prognosis of ALL leading to an increase in survival, thus more CNS abnormalities are encountered on MRI, related to the disease itself or treatment. No doubt, ALL is diagnosed based on various tests (Histologic examination, neuroimaging). Our diagnosis was based on radiographic features with or without tissue confirmation based on the clinical presentation. Improved neuroimaging techniques especially high resolution MRI, have helped in diagnosing and differentiating those abnormalities. The majority of the neurological complications of leukemia are treatable if they are detected at an early stage.
intravascular coagulation state, as well as chemotherapeutic agents that increase the risk of both bleeding and thrombosis. The risk factors include the presence of a blast crisis, thrombocytopenia, leukocytosis and disseminated intravascular coagulopathy [12,21,22].

Posterior reversible encephalopathy syndrome (PRES) has been reported in childhood leukemia patients increasingly. It was initially described by Hinchey et al. clinically the patients present with headache, seizures, altered mental status, and visual disturbances that correlate with transient, posterior bilateral lesions in the cerebral white matter on neuroimaging [23]. The pathogenesis of PRES is still unknown, but it can be secondary to high blood pressure or direct cytotoxicity of chemotherapy drugs [7]. It was described in patients with renal diseases, pre-eclampsia / eclampsia, after transplantation and in acute systemic hypertension. It is seen frequently in patients receiving immunosuppressive and cytotoxic drugs such as cyclosporine, cisplatin, cytarabine, high dose methotrexate, gemicetabine, FK506, interferon, erythropoietin, tarcolimus and L-asparginase [24-26]. The cases from our institution were all being treated with L-asparaginase when they developed PRES. PRES commonly resolves in 48 hours, yet the radiological findings disappear after one week to one month [27]. The typical imaging findings of PRES are hyperintense signal on FLAIR involving the cortex and subcortical white matter of the posterior regions of the brain, the parietooccipital lobes and cerebellum [7]. Less commonly, the frontal lobes, brainstem and basal ganglia are involved.

Infectious complications are a significant cause of morbidity and mortality in pediatric cancer patients [3]. The most frequent causal pathogens of febrile neutropenia (FN) are bacterial or fungal infections; they are identified and confirmed by culture in only 25–30% of the cases. Candida and Aspergillus species are the organisms most frequently identified. None were encountered in our series [28]. Patients with FN may develop also bacterial, fungal or viral infections [29]. CMV-related encephalitis should remain an important concern in immunocompromised patients who demonstrate a change in mental status, and imaging may aid in the diagnosis of this condition. In some cases, the neuroimaging findings are not specific, presenting as foci of high T2 signal in the white matter like in our case.

PML is a subacute demyelinating disorder of the CNS caused by JC virus that infects oligodendrocytes and leads to failure in maintaining myelination [30]. The virus usually remains in a latent form after primary infection, but can be reactivated in cases of impaired immune system [30-32]. One patient in our series developed PML. The typical appearance of PML is multifocal, patchy usually non-enhancing subcortical white matter lesions, more often bilateral and asymmetric involving the subcortical U-fibers. The lesions are hypointense on T1W images and hyperintense on T2W images. Increased signal alteration has been suggested to indicate an aggressive form of the disease. There is restricted diffusion in the regions of active infection and the advancing edge of large lesions distinguishing them from areas of reparative gliosis in the center of large lesions [33].

Non-specific foci of high T2 and FLAIR signal intensity or small hypodensities on CT scan in the white matter was seen in ALL patients. These white matter changes can be attributed to leukoencephalopathy, which is one of the most common manifestations of toxic effect of MTX on the CNS [34]. It is seen as white matter hyperintensities on T2-weighted MR imaging and it may be either persistent or transient. In a study by Redrick et al, authors show that higher doses of IV MTX placed ALL patients at a higher risk for leukoencephalopathy and many of the changes resolved after the completion of therapy [35].

Radiation induced vascular damage is an uncommon cause of thrombosis and hemorrhage in pediatric patients treated with radiation therapy. The complications are seen several years after radiation, however, this was not encountered in our series [12] since just one patient received radiotherapy.

The development of secondary CNS neoplasms in ALL patients who receive cranial irradiation is approximately 1%, and the most common malignancies to arise are sarcomas and meningiomas [13], in our series, it was a glioblastoma multiforme (GBM). In a cohort study by neglia et al. in 1991, the overall estimated proportion of patients with a second neoplasm was approximately 2.5 percent 15 years after diagnosis, with the tumors of the CNS (GBM, high grade astrocytoma) being the most common [36]. The occurrence of glioblastoma multiforme following radiation and chemotherapy in ALL is rarely reported [37]. Cranial irradiation has been clearly implicated in the development of secondary brain tumor [38] but cases of secondary malignant tumors in the CNS in ALL patients who had no history of irradiation have been reported [39].

Wernicke’s encephalopathy (WE) is a miscellaneous CNS finding found in one patient who had acute pancreatitis and prolonged TPN that lacked vitamin B12 supplementation. Characteristic findings on MRI are symmetric signal intensity alterations in the thalami, mammillary bodies, tectal plate, and periaqueductal area. Atypical MRI findings include signal intensity alterations in the cerebellum, cerebellar vermis, cranial nerve nuclei, red nuclei, dentate nuclei, caudate nuclei, splenium, and cerebral cortex. When acute, the cytotoxic edema can show restricted diffusion [40].

This series highlights the wide range of neurologic complications in pediatric patients with ALL, most CNS complications seen in our series of pediatric ALL patients were related to the neurotoxicity of different chemotherapeutic regimens, such as L-asparaginase or methotrexate. In addition, one should keep in mind thrombotic risks and coagulation problems in this population, as well as disease infiltration of the CNS.

Pediatric oncologists and neurologist as well as radiologists need to be aware of the wide range of neurologic complications and their corresponding imaging findings, allowing accurate diagnosis and timely intervention.

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Conflict of interest statement
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References


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