

**Research Article**

Role of CT & MRI in the Imaging Spectrum of Central Nervous System Complications in Paediatric Leukemias

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Abstract

Leukemia is the most common childhood malignancy representing nearly 30% of all malignancies in children. With advances in treatment, prognosis and survival rates have vastly increased, resulting in a similar increase in the number of adverse effects and complications as well. There is an increased risk of CNS complications in acute leukemia either resulting from direct effects of leukemia or from antileukemic therapy. Bone marrow transplantation requires suppression of the recipient's immune system and administration of cytotoxic drugs like cyclophosphamide. Early recognition of CNS complications is important, in order to ensure timely treatment and to avoid grave consequences, thereby improving the overall survival benefits. Most of the neurologic complications have similar overlapping clinical presentations resulting in a diagnostic dilemma. Here imaging, especially CT & MRI has a major role to play and helps to arrive at a reasonable diagnosis. This study retrospectively analyzed neuroimaging of 149 pediatric leukemic patients who underwent CT/MRI with a clinical suspicion of neurological complication. Of the 149 children, CT brain was done for 90 children, MRI brain was done for 40 children and 10 of them had both CT and MRI done. Positive findings were recorded in 44 children on CT and 24 children on MRI. The diverse pathologic entities that we came across in CT/MRI of these patients have been grouped into different categories. The major complications encountered were cerebrovascular complications including venous sinus thrombosis, intracranial haemorrhages and infarcts, CNS infections, leukaemic involvement, miscellaneous conditions like hydrocephalous and treatment complications. These included mainly, leukoencephalopathy, methotrexate related complications and PRES.

Introduction

Leukemia is the most common childhood malignancy representing nearly 30% of all malignancies in children ^[1]. In the past, CNS

complications were rarely seen due to the rapid course of the disease. Today, prognosis and survival rates have vastly increased, thanks to the availability of advanced therapeutic options and

supportive care. But yet, there has been a similar increase in the number of adverse effects and complications. There is an increased risk of CNS complications in acute leukemia either resulting from direct effects of leukemia or from antileukemic therapy^[2]. Bone marrow transplantation and prophylactic treatment for CNS have revolutionized outcome in leukemic children, with overall cure rates for children with ALL now approaching 80%^[3]. CNS prophylaxis involves using intrathecal methotrexate, high-dose chemotherapy, radiotherapy, or a combination of any of these. Bone marrow transplantation requires suppression of the recipient's immune system and administration of cytotoxic drugs like cyclophosphamide. All these do not come without significant acute side effects^[4]. Early recognition of CNS complications is important, in order to ensure timely treatment and to avoid grave consequences, thereby improving the overall survival benefits. Most of the neurologic complications have similar overlapping clinical presentations resulting in a diagnostic dilemma. Here imaging has a major role to play and helps to arrive at a reasonable diagnosis.

Materials and Methods

The study was designed as a combined retrospective and prospective observational study from December 2012 to June 2016 in the Department of Imageology, Regional Cancer Centre, Trivandrum. The study population included all pediatric patients with ALL registered in RCC.

Inclusion Criteria: All pediatric leukemia cases with neurological symptoms, who underwent CT/MRI Brain in our department.

Exclusion Criteria: Any contraindication for CT/MRI.

Sample Size Estimation: Pilot study was done retrospectively with the aid of PACS for a period of December 2012 to March 2014. There were 65 cases of CT/MRI Brain done for paediatric leukemic patients with neurological symptoms. 28 patients were found to have imaging features of

CNS complications. Sample size was calculated using the formula: $n = Z^2 p (1-p) / d^2$

Where, Z= 1.96, for a confidence interval of 95% , p = 0.43 (from pilot study) , d is precision, taken as 20% of p (<1/4 p). Sample size was estimated as 147 using the statistical formula for descriptive studies.

All pediatric ALL cases with neurologic symptoms, who underwent CT/MRI brain in our department were collected and studied during the period from December 2012 and continued till June 2016. Socio-demographic features like name, age sex, neurological symptoms, imaging study done of the cases studied were obtained by the aid of PACS and RIS. (PACS –Picture Archiving and Communication System, RIS Radiology Information System). Imaging features of the complications were evaluated .Plain and Post contrast CT/ MRI Brain taken were studied for CNS complications. Imaging features were identified and characterized for each complication detected. In patients with CNS complications with MR/CT BRAIN available in PACS were studied. Variables evaluated were: Age of the patient , Sex of the patient, Phase of treatment, Investigation done, Follow up imaging, Imaging features, Imaging Diagnosis. Data was collected using the case sheets obtained from the pediatric department and imaging features were obtained from the CENTRICITY PACS. Study variables included socio-demographic features like age, sex. Patient features like presenting symptoms, phase of treatment. CT/MRI brain of each children was studied for imaging features and diagnosis.

Study variables were analysed and percentage of each were presented in a descriptive format. All MR examinations were performed in a 1.5 Tesla MR (GE Medical systems) using dedicated head coils. Following sequences were routinely studied:

- Axial T2 propeller, T2 FLAIR, T1 FLAIR, T1 post contrast, SWI and DWI
- Sagittal T1 post contrast
- Coronal T2, T1 post contrast.

ADC maps obtained using post processing software. A few cases were done using limited

screening sequences, Sequences studied were: Axial T2 FLAIR, SWI and DWI. All CT examinations were performed in a 16 slice scanner (GE Medical Systems). Examinations were done using a kV of 100, with variable mAS of 150-250 (auto ma).

Observations & Results

We retrospectively analyzed neuro imaging of 149 pediatric leukemic patients who underwent CT/MRI with a clinical suspicion of neurological complication. Head ache, seizures, weakness of limbs, altered behaviour were the major symptoms for which they were imaged. Of the 149 children, CT brain was done for 90 children, MRI brain was done for 40 children and 10 of them had both CT and MRI done. Positive findings were recorded in 44 children on CT and 24 children on MRI. The diverse pathologic entities that we came across in CT/MRI of these patients have been grouped into different categories to simplify the approach and representative cases have been selected for illustration (Fig. 1).

I. Cerebrovascular complications

Leukostasis associated with leukemia can cause vascular damage leading to thrombosis or hemorrhage. Thrombocytopenia, sepsis and coagulopathy are other contributing factors [2]. Cerebrovascular complications are particularly common during induction phase of chemotherapy where drugs like glucocorticoids and L-asparaginase further predispose. Asparaginase can cause depletion of plasma proteins involved in both coagulation and fibrinolysis and hence predispose to both thrombosis and hemorrhage [5]. In our observation, cerebrovascular complications accounted for 37% of total neurological abnormalities. 61% of cerebrovascular complications occurred during induction / reinduction phases of chemotherapy. These included sinovenous thrombosis (n=13), intracranial hemorrhages (n=7) and infarcts (n=10).

a. Sinovenous thrombosis:

9 cases were detected on CT and 4 cases on MRI. 3 of them had associated venous infarcts. 6 of

them were on chemotherapy. (Table 1) (Figs.2,3, 4).

b. Intra cranial hemorrhage

Intracranial hemorrhage was detected on CT in 5 children and on MRI in 2 children. 5 children had low platelet counts, 2 of them with counts below 10,000. 2 of them also had abnormal coagulation profile. 5 of them were on chemotherapy. (Figs.5,6)

c. Infarcts

There were 10 children who developed infarcts (4 on CT and 6 on MRI). One case of acute infarct was not evident on CT, and was picked up on subsequent MR. Of the 10 cases, 3 were venous infarcts associated with sinovenous thrombosis. 6 children developed infarcts while on chemotherapy. (Fig.7).

II. Infections

Both the disease per se and therapeutic agents can result in immunosuppression making the child susceptible to various infections, especially fungal. Poor nutrition, indwelling catheters, prolonged hospital stay are other contributing factors [3]. Usual mode of spread to the CNS is via haematogeneous route. Direct spread from adjacent focus of infection is also possible. In our study, infections accounted for 6% of complications on neuroimaging. All children who developed infectious complications were on chemotherapy and had neutropenia. (Figs.8-14).

III. CNS involvement by leukemia

Leukemic cells may infiltrate the dura, leptomeninges, calvarial bone marrow and rarely parenchyma. Granulocytic sarcomas, also known as chloromas or extramedullary myeloblastomas, refer to masses of granulocytic precursors cells. They are usually seen in children with acute myelogenous leukemia and can involve any part of body, but commonly seen in orbits, subcutaneous tissue and other sites like paranasal sinuses, lymph nodes, bone, spine, brain [6]. They are seen as isodense or hyperdense well defined masses on unenhanced CT, hypointense or isointense on T1-weighted MR images, isointense or hyperintense on T2-weighted MR images

showing homogeneous contrast enhancement. Imaging is enough for diagnosis in the setting of myeloid leukemia, biopsy can be avoided [7]. They also show rapid response to treatment. We had a case of calvarial leukemic deposits and an orbital chloroma. (Figs.15,16).

IV. Side effects of therapeutic measures

Excluding cerebrovascular events (where chemotherapeutic measures are again a risk factor), we had 34 cases of other therapy related complications. Table 2. In 5 children CT was normal /inconclusive and subsequent MRI revealed the abnormality . These included 2 cases of PRES and 3 case of methotrexate toxicity. (Table 2).

a. Leukoencephalopathy

Chemotherapeutic agents, particularly methotrexate, cisplatin, cytosine arabinoside, carmustine, and thiotepa, occasionally cause cerebral white matter abnormalities characterized by diffuse, symmetrical involvement of central and periventricular white matter with sparing of subcortical U fibers [8]. On MRI there is diffuse T2 and T2 FLAIR hyperintensity involving periventricular white matter with sparing of subcortical U fibers. Usually there is no diffusion restriction.(Fig 18)

b. Methotrexate related neurotoxicity:

Methotrexate associated early neurotoxicity has been described in literature characterized by diffusion restriction on MRI in the centrum semiovale that preceded abnormality in the same region on FLAIR sequences. The exact pathophysiology is not known, direct neurotoxic effect on the cells is the proposed mechanism [9]. Intrathecal use of methotrexate, young age, associated cranial irradiation are all considered risk factors [10,11]. Usual symptoms include hemiparesis, aphasia, seizures, head ache. This acute, methotrexate-induced neurotoxicity is not necessarily irreversible. Resolution of symptoms is often seen [9].(Figs 19,20).

c. Posterior Reversible Encephalopathy Syndrome (PRES)

It is an acute neurological complication occurring secondary to the inability of posterior circulation to auto-regulate in response to acute changes in blood pressure resulting in vasogenic edema. It is a recognised complication of paediatric leukemia treatment, often associated with steroid induced hypertension. Other drugs like L-asparaginase, cytarabine and immunosuppressants like cyclosporine and tacrolimus are also associated with PRES [3]. Clinical features include headache, seizures, visual disturbance, altered sensorium, and/or neurological deficit, accompanied by elevated blood pressure. This condition and its imaging features are potentially reversible with prompt control of blood pressure and withdrawal of the culprit drug. But, delay in intervention can result in progression to cytotoxic edema with infarction or hemorrhage and possible irreversible neurologic deficit [12]. (Fig.21).

V. Miscellaneous

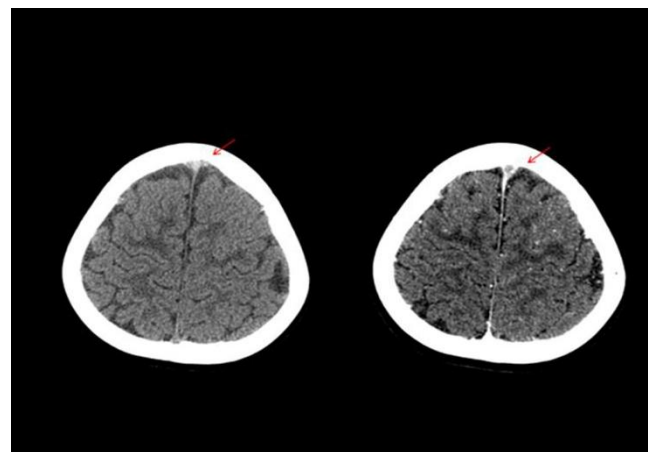
Hydrocephalus and subdural hygroma are included here. Hydrocephalus is postulated to be caused by leukemic cells impeding the drainage of CSF from the ventricles. It may also be an indicator of CNS relapse. Sub dural hygroma in leukemia can arise from multiple causes like meningitis, trauma, coagulopathy. (Fig. 22.)

Table 1: Sinovenous thrombosis

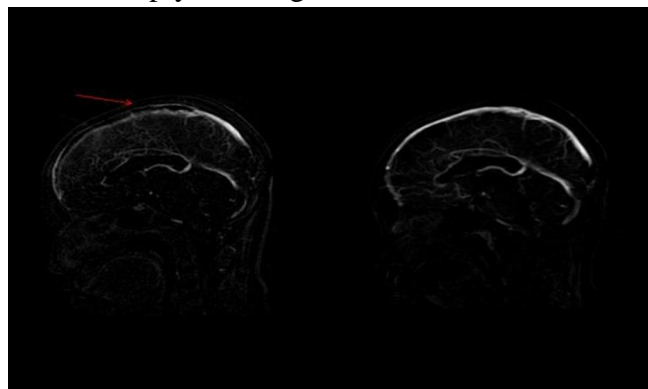
	IMAGING FEATURE	NUMBER OF CASES:
SITE OF INVOLVEMENT:	Transverse/Sigmoid Sinus	4
	Superior Sagittal Sinus	9
	Cortical vein involvement	2
CT SCAN:	Hyper dense sinus	4
	Filling defect/empty delta sign	6
	Cord sign	2
MRI scan	Filling Defect within the sinus	2
	Associated venous infarct:	3

Table 2: Therapy related CNS complications detected on CT/ MRI.

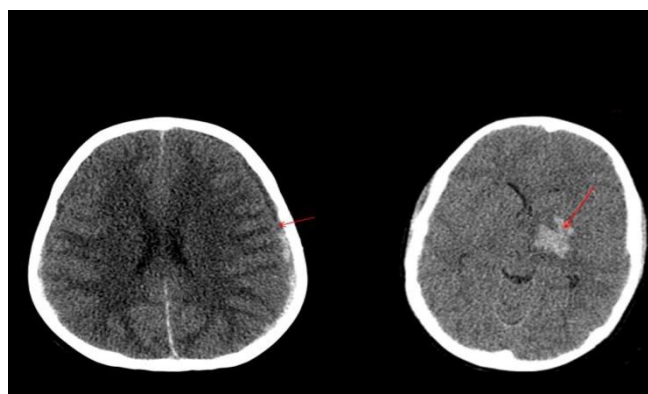
	CT	MRI
Methotrexate Toxicity	2	14
PRES	5	8
Leukoencephalopathy	0	2
Atrophic changes	1	4
Mineralising	1	0
Microangiopathy		



CASE 2: 14 yr old boy with ALL having head ache, receiving asparaginase. Non contrast CT (left)– dilated hyperdense superior sagittal sinus. CECT (right)- filling defect in superior sagittal sinus - "empty delta sign".



CASE 3: 13 year old girl, ALL on re-induction phase of chemotherapy, with seizures. MR Venogram (left) - Filling defect in superior sagittal sinus - thrombus. MR Venogram (right) - Recanalised superior sagittal sinus on follow up MRV after 2 months.



CASE 4 (Left): 11 year old girl with ALL, had head ache and vomiting. Non contrast CT brain - Crescent shaped extraaxial hypodensity along left cerebral hemisphere with hyperdense layering- acute on chronic subdural hematoma. CASE 5

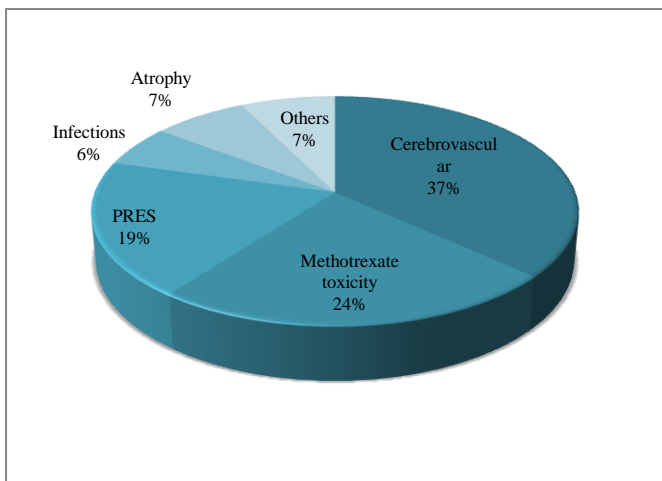
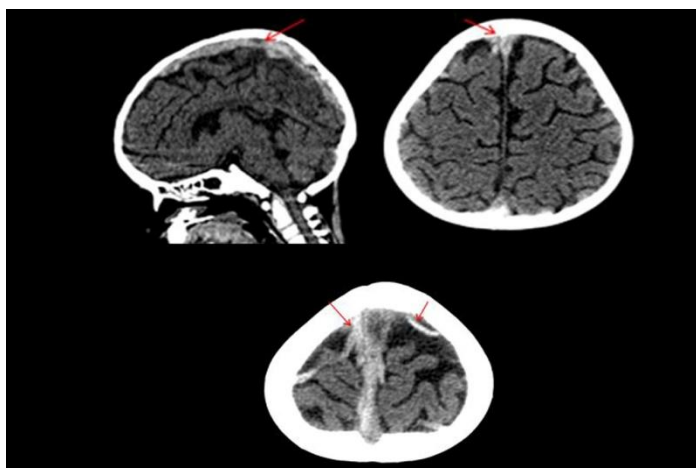
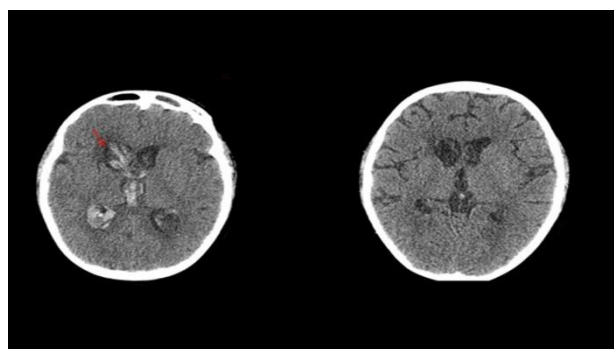


Fig 01 Distribution of CNS complications in pediatric leukemia detected on CT/ MRI

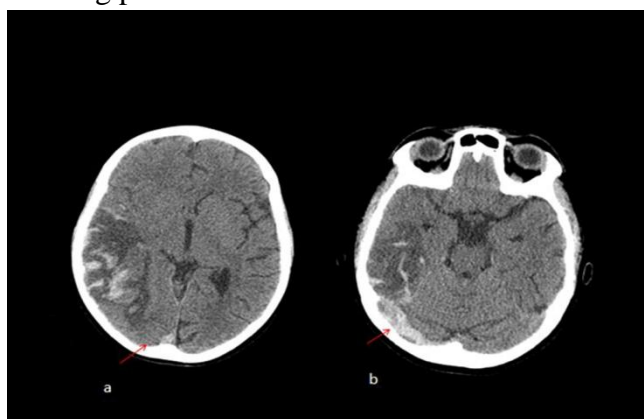


CASE 1: 5 year old boy with ALL, on chemotherapy, developed seizures. Non contrast CT brain showing hyperdensity within superior sagittal sinus and bilateral cortical veins – sinovenous thrombosis.

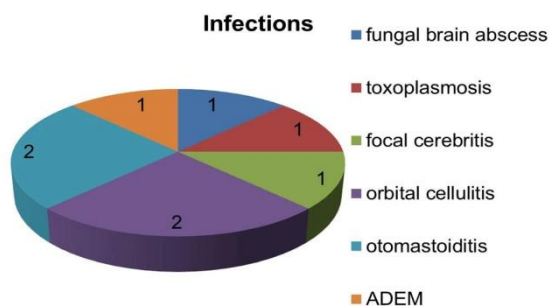
(Right) : 16 year old boy with ALL relapse, on chemotherapy, developed seizures. Non contrast CT brain - Hyperdense lesion in left basal ganglia with surrounding edema – basal ganglia hematoma



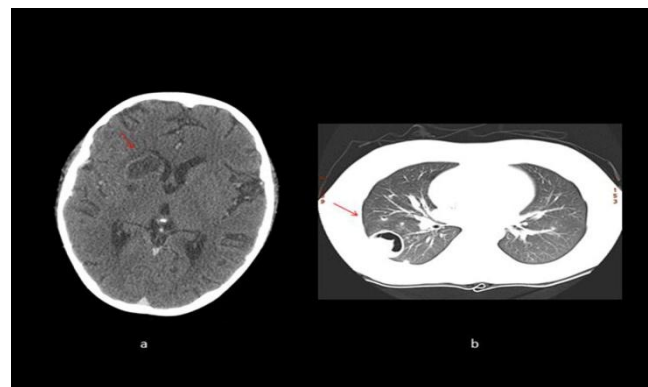
CASE 5: 15 year old boy with ALL on maintenance chemotherapy had seizures. (Left) Non contrast CT brain showing intraventricular hemorrhage. (Right) CT taken 1 week later showing partial resolution.



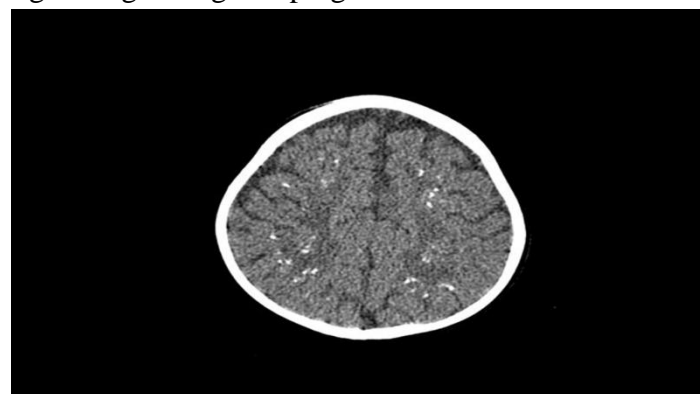
CASE 6: 8 year old boy with ALL on induction chemotherapy developed headache and photophobia. Non contrast CT brain showing superior sagittal sinus and right transverse sinus thrombosis with a large haemorrhagic venous infarct in the right temporal and parietal lobes.



Pie chart showing distribution of Infections.



CASE 7. 15 year old boy with ALL on chemotherapy, developed head ache and facial palsy. (a) CECT brain - ring enhancing hypodense lesion in right gangliocapsular region involving right caudate and lentiform nuclei and anterior limb of internal capsule - fungal brain abscess. CSF culture yielded filamentous fungal hyphae. (b) CT chest - Cavitary mass with air crescent sign in right lung - Aspergillosis.

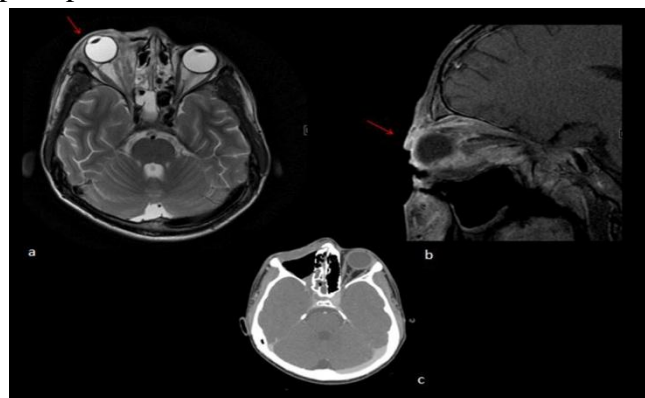


CASE 8: 3 year old girl with ALL, presented with status epilepticus. Non contrast CT brain - Multiple discrete foci of calcifications in the white matter at the grey white matter interface, periventricular white matter - toxoplasmosis (serology was positive).

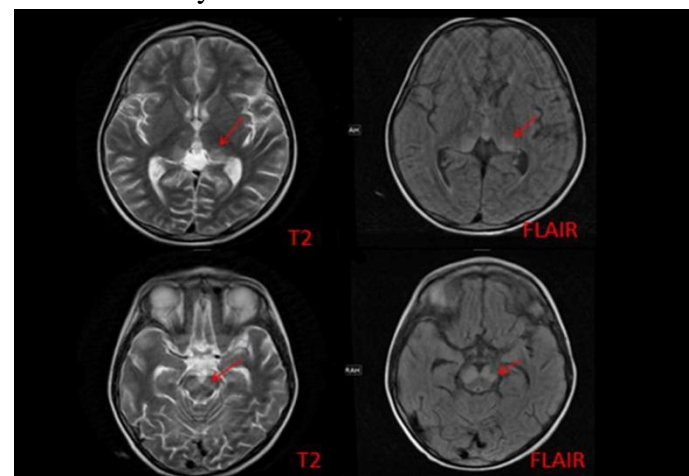


CASE 9: 14 year old boy with ALL having proptosis of right eye. CECT head - proptosis of

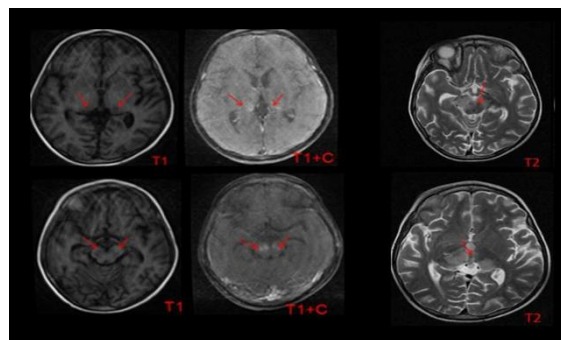
the right eye with soft tissue thickening and oedema in the right preseptal space, premaxillary and infratemporal region and right side of nose – preseptal orbital cellulitis.



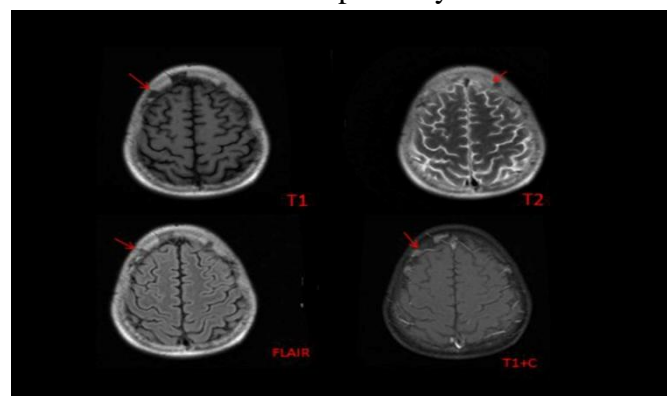
CASE 9 cont. MRI (a and b) taken 2 weeks later showed orbital cellulitis with optic neuritis. T2 hyperintensity in the right preseptal space and right side of nose. Bulky right medial rectus muscle showing heterogeneous contrast enhancement. Mild peripheral enhancement seen within right optic nerve suggestive of involvement. CT (c) - post exenteration of right orbit. Mucormycosis



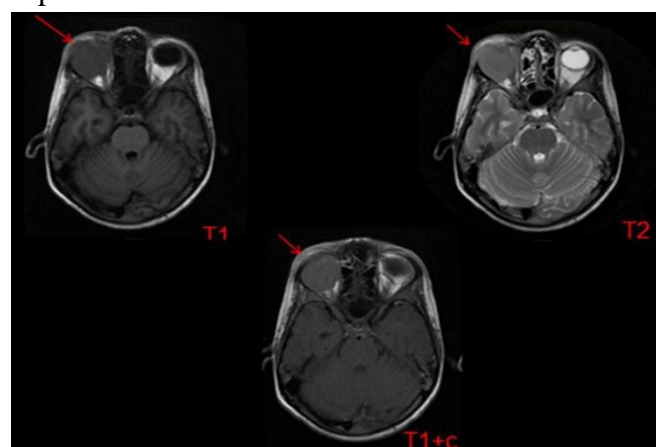
CASE 10: 5 year old boy, ALL, with fever, photophobia and irritability. MRI - T2, FLAIR: Ill-defined hyperintensity is seen involving the posteromedial aspect of bilateral thalami and the midbrain.



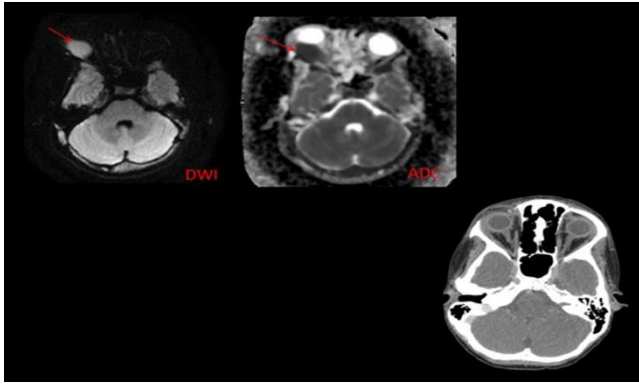
CASE 10 Cont. MRI - The lesions are hypointense on T1 and shows patchy ill- defined heterogeneous contrast enhancement. Progression of lesions in subsequent MRI (T2 images). Acute Disseminated Encephalomyelitis.



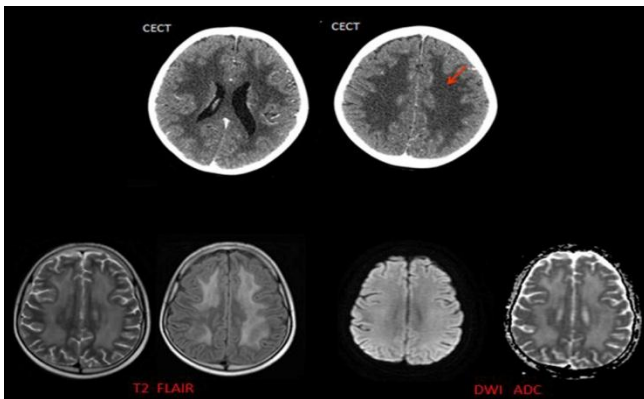
CASE 11: Calvarial leukemic deposits in a 13 year old boy with ALL. MRI Brain - Skull vault shows T1, T2 and FLAIR hypointense enhancing lesions in bilateral frontal bones - leukemic deposits.



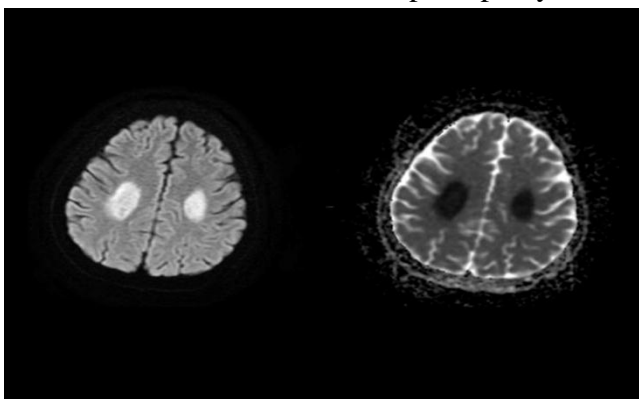
CASE 12: 14 year old boy, AML, presented with proptosis. MRI brain - A well defined lesion in the right orbit supero-laterally, isointense on T1 and hyperintense on T2 images with uniform contrast enhancement.



CASE 12 Cont. MRI - lesion in right orbit shows restriction of diffusion. Post chemotherapy CT shows resolution of the lesion. Chloroma

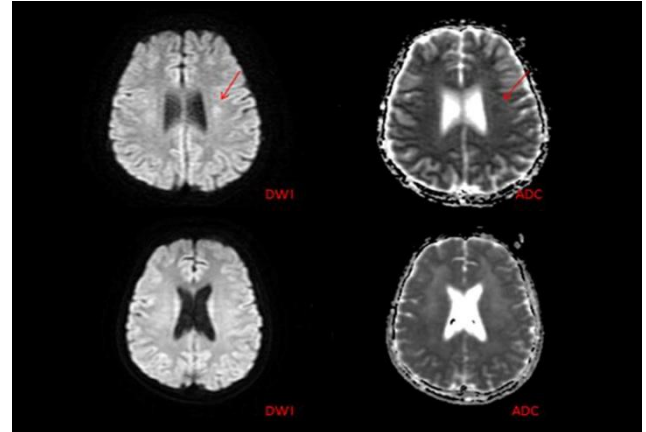


CASE 13: 10 yr child, case of B-ALL on reconsolidation phase of chemo presented with head ache. CT images showing diffuse hypodensity involving bilateral periventricular and centrum semiovale white matter. MRI- T2 and T2 FLAIR sequences showed diffuse hyperintensity involving periventricular white matter with sparing of subcortical U fibres. No diffusion restriction. Leukoencephalopathy

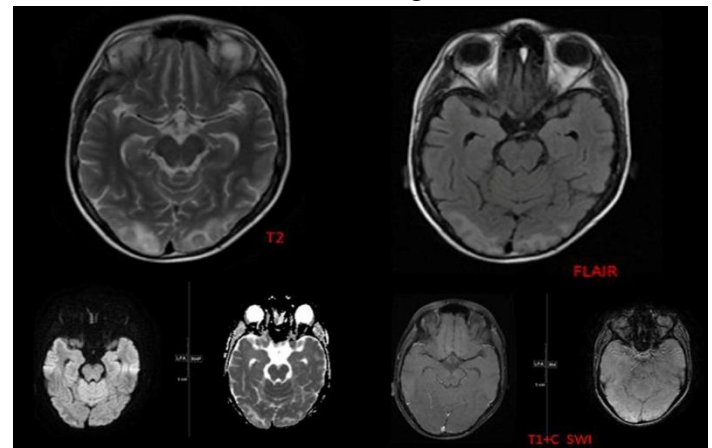


CASE 14: 14 year old girl, ALL on consolidation chemotherapy with left hemiplegia. MRI brain (DWI and ADC) - Altered signal intensity lesions with strong diffusion restriction in bilateral centrum semi ovale suggestive of drug-induced

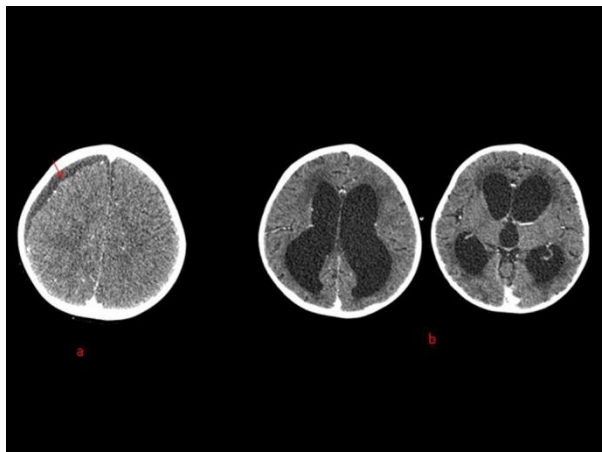
white matter changes - Methotrexate related neurotoxicity.



CASE 15: Another case of methotrexate neurotoxicity in a 14 year old girl with ALL, on consolidation phase of chemotherapy. MRI - Small foci of diffusion restriction noted in bilateral centrum semi ovale and corona radiata. Follow up MRI 3 months later (bottom images) showed resolution of the findings.



CASE 16: 15 year old boy, ALL post induction chemotherapy, developed seizures. MRI- T2 and FLAIR revealed white matter hyperintensities involving bilateral occipital lobes. DWI-ADC images show T2 shine through at affected regions. No post contrast enhancement. No hemorrhage on SWI. Posterior Reversible Encephalopathy Syndrome



CASE 17: 3yr old boy, ALL, on chemo, complained of head ache. CT brain (a)- Subdural hygroma along right cerebral convexity . **CASE 18:** 2 year old boy, ALL, with seizures, altered sensorium. CT brain (b)- Hydrocephalus.

Discussion and Conclusion

With recent advances in management, prognosis and survival rates in leukemia have improved. However, due to the same reason, therapy related and disease related neurologic complications have also increased. Modern imaging techniques facilitate prompt detection and characterisation of these complications and allow timely intervention thereby reducing morbidity and mortality.

Major neurological complications include cerebrovascular events, infections, PRES and drug toxicity. MRI is preferred for detecting drug toxicity and other complications related to treatment, while CT brain is usually sufficient in detecting cerebrovascular events. MR outweighed CT in detecting PRES and methotrexate toxicity.

A tailored investigation protocol based on clinical suspicion helps in early detection of these complications promoting prompt management. Considering radiation risks, time and overall accuracy, we would recommend a concise MRI protocol comprising of Axial FLAIR, DWI and GRE sequences as the initial investigation of choice for detecting all major CNS complications in pediatric leukemia.

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