NEURORADIOLOGY

Pictorial essay: Acute neurological complications in children with acute lymphoblastic leukemia

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Abstract

Acute lymphoblastic leukemia (ALL) is the commonest childhood malignancy with high cure rates due to recent advances in central nervous system (CNS) prophylaxis. The disease per se, as well as the prophylactic therapy, predisposes the child to complications such as cerebrovascular events, infections, drug toxicities, etc. The purpose of this study is to highlight the pathophysiology and the imaging features (with appropriate examples) of these complications and to propose a diagnostic algorithm based on MRI. Interpreting these scans in the light of clinical inputs very often helps the radiologist reach an appropriate diagnosis and help treatment and management.

Key words: ALL; neurological complications; methotrexate induced leucoencephalopathy; PRES; immunocompromised patient

Introduction

Acute lymphoblastic leukemia (ALL) is the most common malignancy in children, accounting for about 75% of childhood leukemias and one-fourth of all pediatric cancers. The overall cure rates for children with ALL now approach 80%, prophylactic therapy of the central nervous system (CNS) being the cornerstone of this success. This therapy is administered using intrathecal methotrexate, high-dose chemotherapy, radiotherapy, or a combination of any of these. However, patients with ALL can present with neurological complications as a result of this therapy and the underlying systemic effects of leukemia.

The neurological complications in ALL can be divided into two broad categories: Infiltration of the CNS by leukemic cells (primary involvement) and complications due to disease *per se* and/or therapy (secondary manifestations). The latter have been divided into seven categories as shown in Table 1. Our review focuses on the complications that have an acute presentation and can be promptly recognized on imaging.

Cerebrovascular Complications

Pathophysiology

Leukemia is often associated with leucocytosis, thrombocytopenia, sepsis, or coagulopathy.[1] The stasis of a large numbers of cells within small arterioles causes vascular damage and massive hemorrhage or thrombosis. These factors and certain therapeutic agents like glucocorticoids and L-asparginase used in the management of these tumors, predispose the patient to cerebrovascular events. Asparginase leads to depletion of plasma proteins involved in both coagulation and fibrinolysis and thus is linked to both thrombosis of dural sinuses/infarction as well as hemorrhage.[2] The acute promyelocytic form of myeloid leukemia is particularly associated with an increased risk of massive brain hemorrhage due to disseminated intravascular coagulation, which can cause death in more than 60% of these patients.[3] Patients can present with headaches, altered sensorium, focal neurological deficit, seizures, or unconsciousness.

Imaging

Hemorrhage is seen commonly and is often fatal.[4] It is seen as hyperdense lesions on plain CT scans, and has a complex appearance, depending on its stage, on MRI [Figure 1]. The mass effect associated with these lesions leads to complications.

Table 1: Secondary manifestations of leukemia in brain

Cerebrovascular complications (may be due to leukemia or induced by chemotherapy)
    Hemorrhage
    Infarction
    Dural sinus thrombosis

Infections (may be due to leukemia or induced by chemotherapy)
    Parenchymal
    Meningitis

Drug-induced neurotoxicity
    Meningitis
    Leucoencephalopathy

Posterior reversible encephalopathy syndrome (PRES)

Radiotherapy-induced complications
    Leucoencephalopathy
    Mineralizing microangiopathy
    Radiation-induced cryptic malformations

Parenchymal atrophy (due to leukemia or induced by therapy)

Secondary brain tumors

The thrombosed dural sinuses appear hyperdense on CT scans, while on MRI they appear hyperintense on plain scans instead of showing the normal void caused by moving blood [Figure 2]. The 'empty delta sign' helps in making a reliable diagnosis of complete sagittal sinus thrombosis on postcontrast CT scans.[5] This is seen as a central filling defect with a peripherally enhancing wall. However, if the sinus is partially thrombosed, then the detection is better with MRI as compared to CT scan. Thrombosed cortical veins may be seen as hyperdense linear structures extending to the sinuses on plain CT scan (the 'cord sign') and as hyperintensities on T1W images. The resultant venous infarctions tend to be nonterritorial and are associated with reperfusion injury and hemorrhage [Figure 2C].

The arterial infarcts could be lacunar or larger and territorial [Figure 3]. Their imaging appearance is also dictated by the temporal evolution of the ischemic cells. Diffusion-weighted imaging (DWI) depicts a hyperacute infarct as an area of restricted diffusion even when it is not visible on routine sequences.

Infections

Pathophysiology

The disease and the therapy together can cause neutropenia
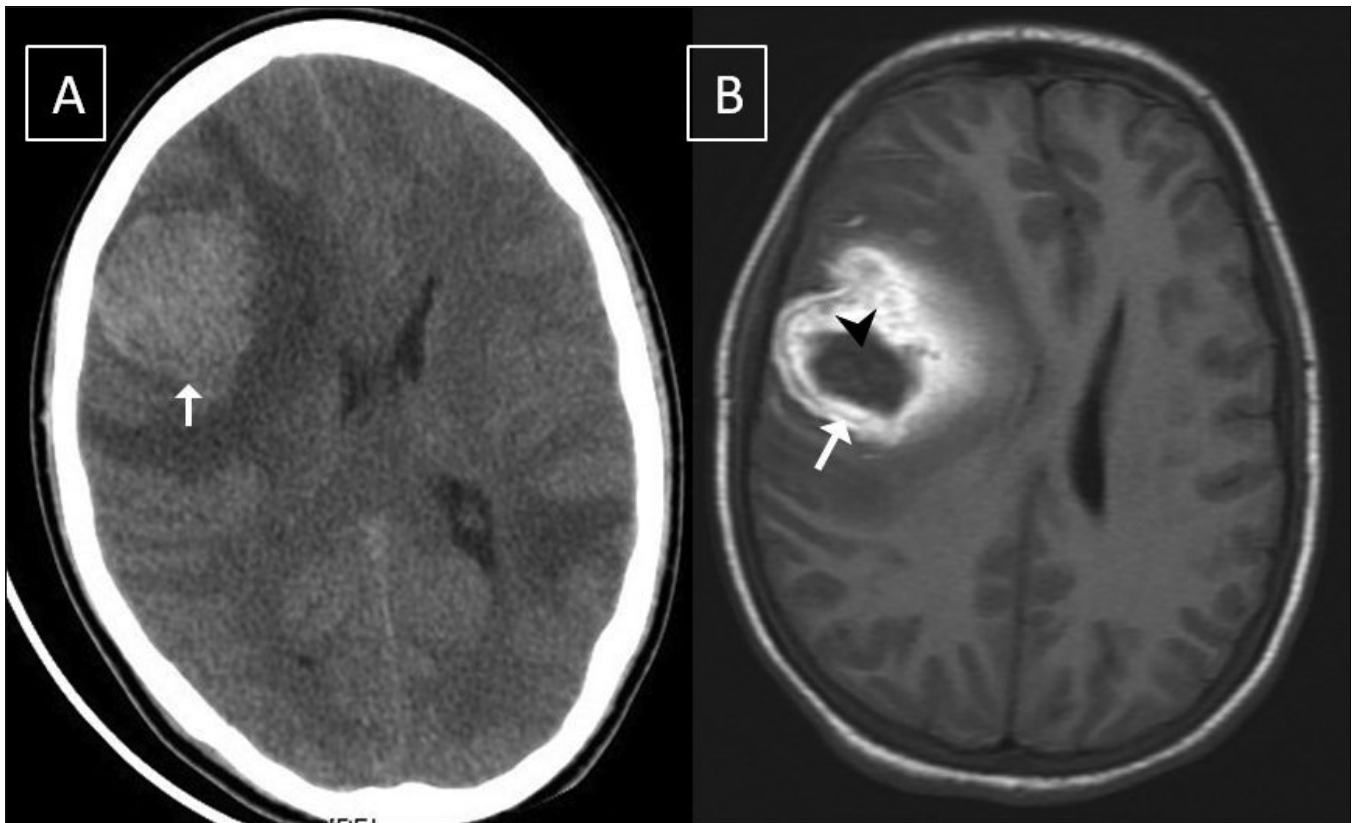
Figure 1 (A, B): A 16-year-old boy developed altered sensorium followed by loss of consciousness. Plain CT scan (A) shows a hyperdense lesion (arrow) in the right frontoparietal region, with surrounding white matter edema and mass effect. Axial plain T1W MRI (B) at the corresponding level shows a hyperintense periphery (arrow) due to presence of intracellular methemoglobin and central hypointensity (arrowhead) due to deoxyhemoglobin
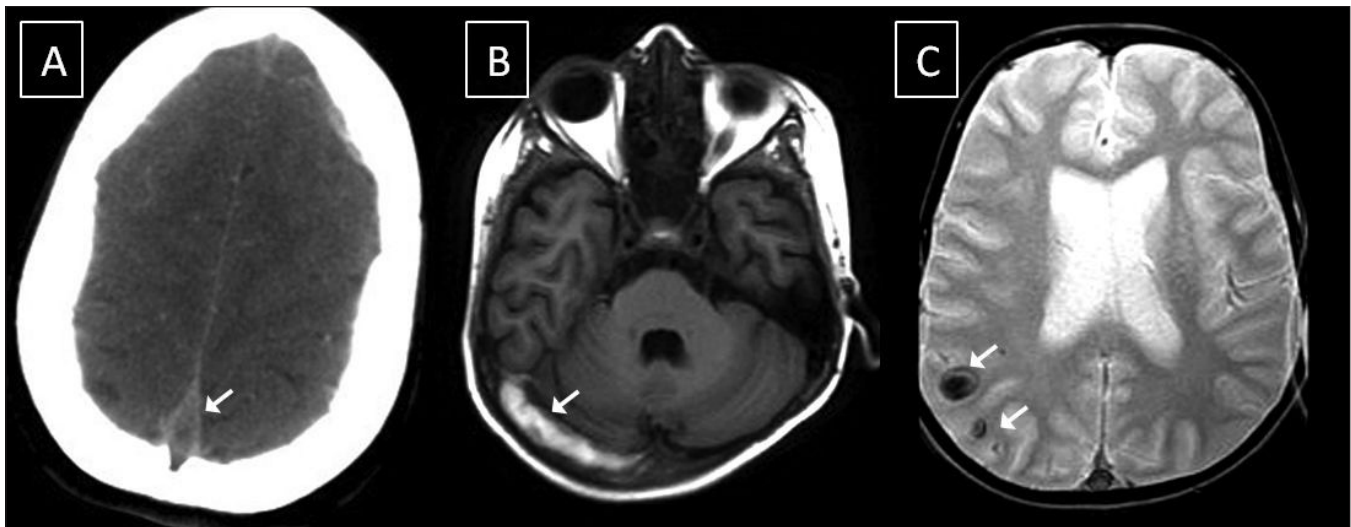
Figure 2 (A-C): A 17-year-old female was on induction chemotherapy and receiving L-asparaginase when she developed severe headache. The contrast-enhanced CT scan (A) shows an empty delta sign (arrow). The walls of the superior sagittal sinus show enhancement, while the center shows a filling defect. A 10-year-old male presented with headache while receiving induction chemotherapy. Axial plain T1W MRI (B) shows a dilated right lateral sinus (arrow) filled with a hyperintense clot suggestive of thrombosis. The patient also had thrombosis of the superior sagittal sinus; foci of subacute hemorrhage (arrow) seen as oval areas of altered signal intensity on this axial gradient-echo MRI (C)

and immunosuppression. This and other factors such as poor nutritional status, prolonged hospital stay, indwelling catheters, mucositis, etc., predispose the child to infections from a wide variety of organisms, especially nonpyogenic such as fungi, mycobacteria, virues, or parasites. The most frequently encountered fungi are *Aspergillus* and *Candida*,[4] while herpes simplex virus (HSV1 or 2) is the most common virus. Very often the organisms reach the CNS from another site of infection through hematogeneous spread. Less commonly, there may be direct extension from an adjacent focus of infection.

The pathogens may affect the brain parenchyma (focal or diffuse), the meningeal lining, or the extra-axial space. The signs and symptoms of CNS infection are likely to be subtle in the immunocompromised host because of the diminished inflammatory response; however, the disease tends to be more disseminated and refractory to treatment and needs to be managed aggressively. Patients can present with headache, seizures, altered sensorium, focal neurological deficits, etc.

Imaging
Gadolinium-enhanced MRI is the investigation of choice when CNS infection is suspected. MRI spectroscopy (MRS) and DWI may help in further characterization. The focal form of parenchymal infection is usually cerebritis which, untreated, evolves into an abscess.

CNS aspergillosis results in single or multiple abscesses. It is often angioinvasive, leading to hemorrhagic infarction and a fulminant course. *Candida* can lead to multiple ring-enhancing lesions [Figure 4]. The presence of projections from the walls of the abscesses showing restricted diffusion

is suggestive of a fungal etiology.[6]

Tubercular abscesses mimic other pyogenic lesions, but the presence of basal exudates and multiple granulomas can aid in diagnosis. MRI findings vary depending upon presence of caseation and necrosis. While the non-caseating non-necrotic lesions appear hyperintense on T2, occasionally one may see a solid caseating granulomas having a T2-iso to dark center, which is considered characteristic[7]

On MRS, the presence of cytosolic amino acids (0.9 ppm) and lipid–lactate (1.2–1.3) is seen in fungal as well as bacterial abscesses. However, it is proposed that multiple peaks between 3.6 and 3.8 ppm assignedto trehalose are specific for fungal infection.[6] The presence of a lipid peak in the absence of other amino acids, succinate, and acetate should suggest tubercular origin.[6]

Meningitis may be diagnosed because of obliterated subarachnoid spaces and cisterns due to exudates. This can cause altered signal intensity on FLAIR images and can be confirmed by enhancement seen on a contrast-enhanced scan. However, abnormal meningeal enhancement is not seen in every case of meningitis.[8] Imaging is more useful for detecting complications like infarctions, abscesses, hydrocephalus, or empyemas. Moreover, the appearance of all types of meningitis — chemical, aseptic, bacterial, or even leukemic infiltration is similar [Figure 5].

Drug Toxicity

Pathophysiology
The two common manifestations of neurotoxicity due to drugs are aseptic meningitis (also called chemical meningitis
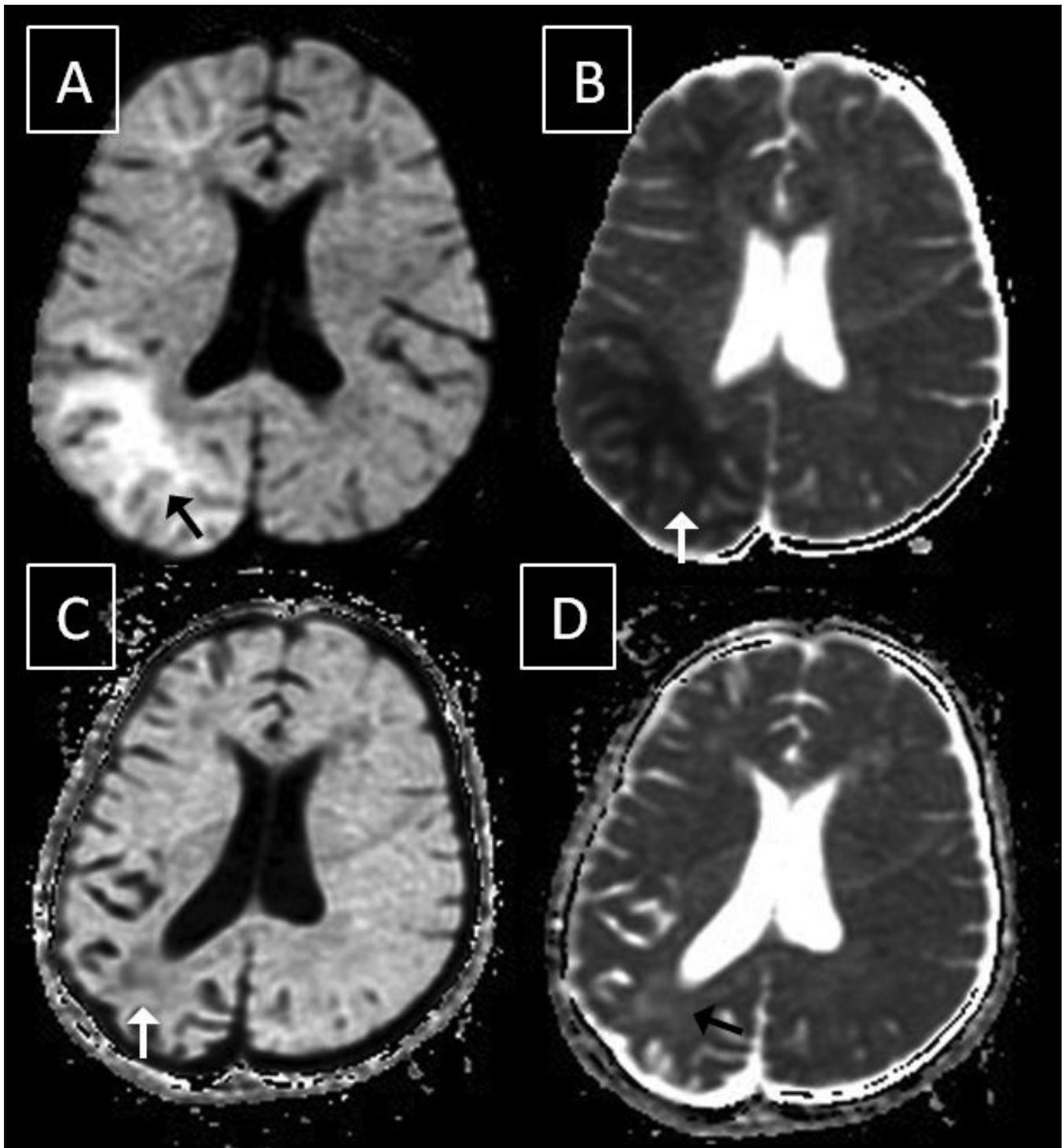
Figure 3 (A-D): A 10-year-old female was off therapy when she presented with gaze palsy and neck rigidity. These serial diffusion-weighted images of the patient depict the evolution of an infarct. eADC (A) and ADC (B) MRI images show an area of restricted diffusion (arrow) in the right parieto-occipital region suggestive of an acute infarct. eADC (C) and ADC (D) MRI images show evidence of parenchymal atrophy, prominence of subarachnoid space, and facilitated diffusion in the white matter (arrow), suggestive of gliosis in the same region

or arachnoiditis) and leucoencephalopathy (LE), in addition to cerebrovascular events like sinus thrombosis and posterior reversible encephalopathy syndrome (PRES). These toxicities are most commonly reported with methotrexate. The exact pathogenesis is not known; however, the LE is attributed to alteration in the blood–brain barrier, especially when the patient has also received radiotherapy. The meningeal irritation commonly occurs within 12–24 h of intrathecal administration. It is a self-limiting condition but, unusually, may progress to encephalopathy or myelopathy.
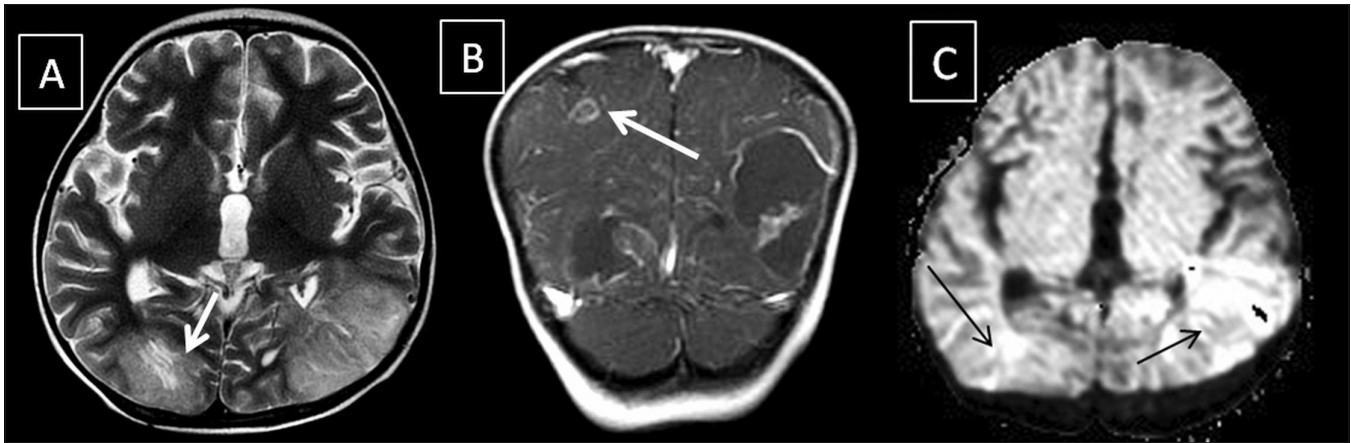
Figure 4 (A-C): MRI in a 3-year-old patient with seizures and visual complaints. Axial T2W image (A) shows two SOL-like lesions in bilateral occipital lobes, with heterogeneous signal intensity (arrow) due to gyral swelling and white matter edema. The postcontrast coronal T1W image (B) shows peripheral enhancement as well as gyral enhancement in these lesions; another focus is also noted in the right occipital lobe (arrow). The corresponding eADC image (C) shows that the lesion has intermixed areas of restricted and facilitated diffusion. This patient underwent decompression surgery as she was not responding to medical management. The surgical specimen showed presence of fungal hyphae

Figure 5: Contrast enhanced CT scan of this 4 year old boy with headache reveals meningeal enhancement in bilateral parieto-occipital regions (arrows). CT scan features are suggestive of meningitis and CSF sample revealed no evidence of infection. Patient had received intrathecal methotrexate 3 days prior to the scan, hence a possibility of chemical meningitis was raised. Patient responded to conservative management

LE can occur even after intravenous administration of the drug, and higher doses and more courses of treatment increase the risk of this complication.[9] This also is more often a reversible side effect. Similar toxicities can be seen with cytosine arabinoside.

Clinically, the patient presents with acute onset of a neurological deficit. Aphasia may be characteristically noted, as has been described in a study by Fisher *et al*.[10]

Imaging
The imaging appearance of chemical meningitis is similar to that of infective meningitis (described earlier in the section on infections). LE often presents as a single patch — or more often multiple patches — of altered signal intensity in the centrum semiovale or periventricular white matter on FLAIR and T2W images. The subcortical U-fibers are often spared. The lesions can be detected earliest using DWI, in which the affected white matter shows restricted diffusion[10] [Figure 6].

Posterior Reversible Encephalopathy Syndrome (PRES)

Pathophysiology
This is an increasingly recognized complication of treatment of many pediatric cancers, the commonest being leukemia.[11] Poor sympathetic innervation of the posterior circulation, which leads to loss of cerebral autoregulation, has been identified as a cause for this condition. Most often PRES is seen with hypertension. The steroids administered during induction therapy of leukemia often lead to elevated blood pressure. The other drugs used in the treatment of leukemia (L-asparginase, cytarabine) and immunosupressants (cyclosporine and tacrolimus)are also associated with PRES. It is believed that leak in the endothelial lining leads to vasogenic edema. The typical presenting features are headache, visual symptoms,
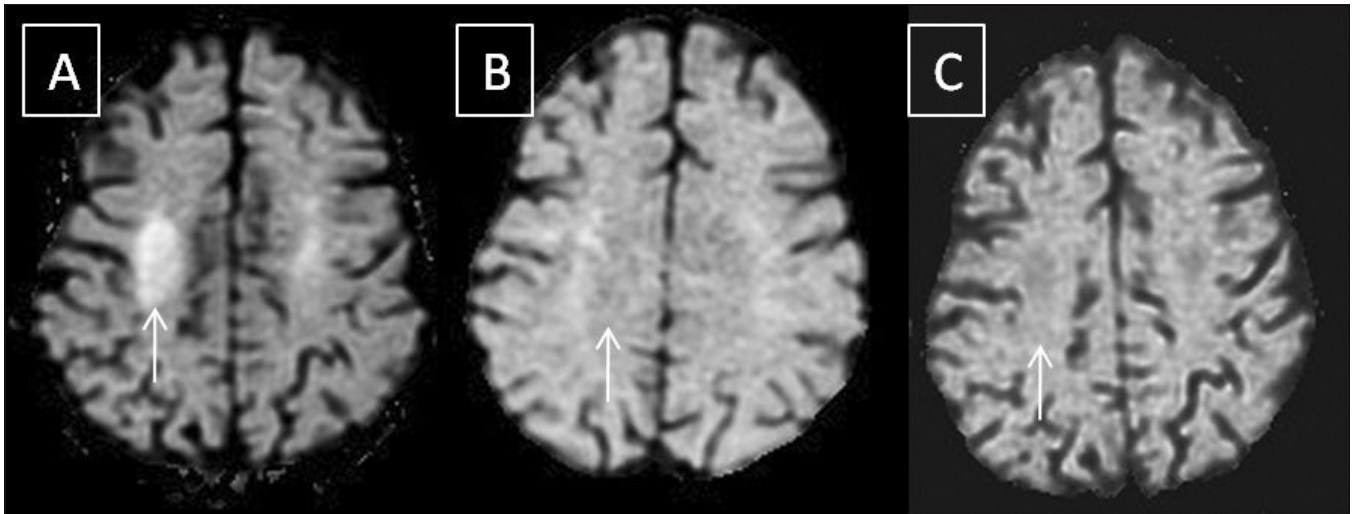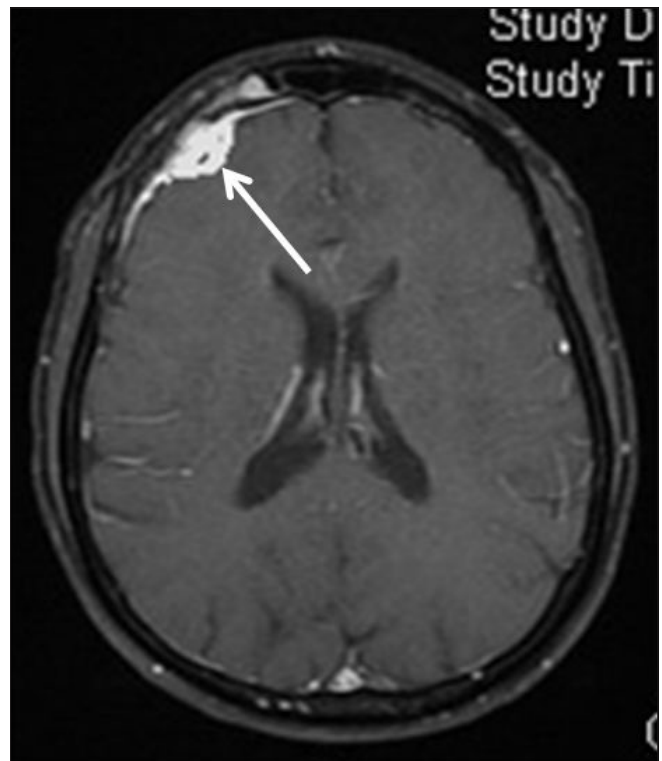
Figure 6 (A-C): Serial eADC MRI maps of a 5-year-old boy with leucoencephalopathy post intrathecal methotrexate show restricted diffusion in bilateral centrum semiovale (A), followed by pseudonormalization on day 7 (B) and facilitation after that (C)
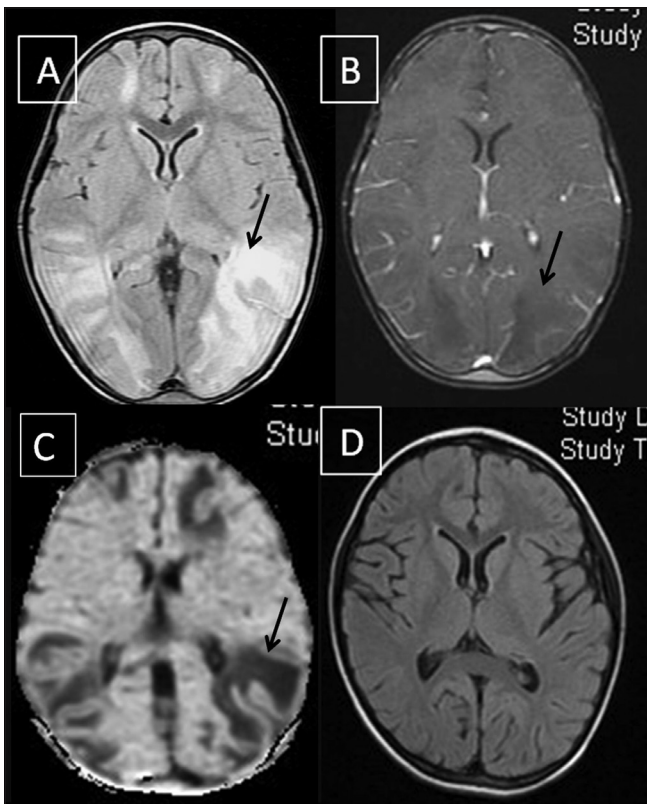
Figure 7 (A-D): A 9 year old boy with elevated BP on induction chemotherapy presented with sudden onset visual disturbances. MRI reveals bilaterally symmetrical hyperintensity in the white matter, predominantly in the parieto-occipital regions, on FLAIR image (A), which do not enhance on this axial T1W contrast-enhanced MRI (B) and have facilitated difuusion on the eADC map (C). These features represent posterior reversible encephalopathy syndrome. The follow up axial FLAIR image (D) shows complete reversal of this transient vasogenic oedema
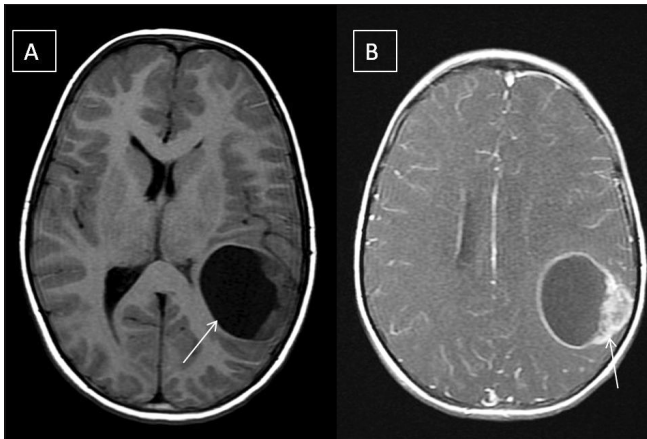

Figure 8: Axial contrast enhanced MRI image of this 23 year old adult treated for ALL 18 years ago reveals an enhancing extra-dural lesion having a dural tail on either side suggestive of a meningioma (arrow)

Imaging

At CT scan/MRI, the brain typically demonstrates focal regions of symmetric hemispheric edema. The parietal and occipital lobes are most commonly affected, followed by the frontal lobes, the inferior temporal-occipital junction, and the cerebellum.[12] This edema is best seen on FLAIR and T2W images [Figure 7]. Occasionally the lesions may show associated hemorrhage or contrast enhancement.

convulsions, altered sensorium, and/or neurodeficit, along with elevated blood pressure.

Figure 9 (A,B): Axial T1W (A) and contrast-enhanced T1W (B) MRI images in a 9-year-old boy who was treated for ALL 4 years back and now presented with seizures reveals a predominantly cystic space occupying lesion with an enhancing solid component along its lateral wall (arrow). The imaging features are suggestive of a low-grade brain tumor; this however turned out to be primitive neuroectodermal tumor

Figure 10 (A-B): This set of MRI mages shows relapse in the sanctuary sites: optic nerve and globe. An axial contrast enhanced T1W MRI (A) in a 4 year old child chows asymmetric thickening and mild enhancement of the left optic nerve (arrow). A 5-year-old patient who presented with acute onset of blindness was off therapy for 3 years; axial contrast-enhanced T1W MRI (B) shows bilateral subretinal enhancing deposits (arrow) and retinal detachment
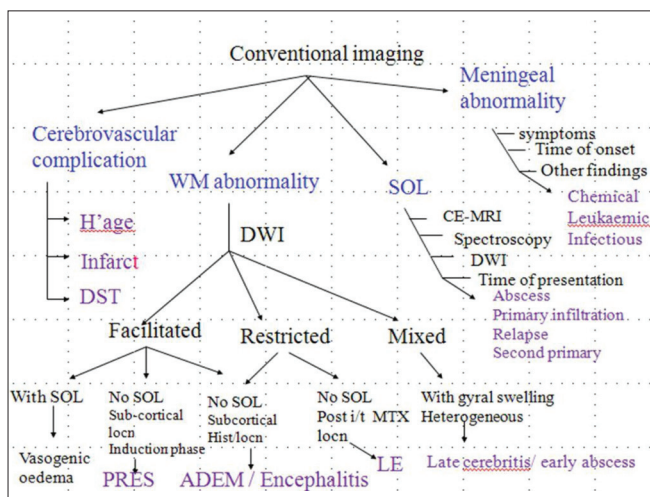
Figure 11: Proposed algorithm for approaching MRI. (WM: white matter, SOL: space occupying lesion, H'age: hemorrhage, DST: dural sinus thrombosis, DWI: diffusion-weighted imaging, locn: location, i/t MTX: intrathecal methotrexate, PRES: posterior reversible encephalopathy syndrome, ADEM: acute disseminated encephalomyelitis, LE: leucoencephalopathy, CE-MRI: contrast-enhanced MRI)

DWI reveals elevated apparent diffusion coefficient (ADC) in the acute stage. This is useful for differentiation from infarcts, which show restricted diffusion in the early stage. However, it has been proposed that pseudonormalization of ADC values in a patient with PRES is associated with cerebral infarction and may represent the earliest sign of nonreversibility, as severe vasogenic edema progresses to cytotoxic edema.[13]

Secondary Brain Tumors

Pathophysiology
Though secondary brain tumor cannot be considered as an acute complication, the presentation could be acute, for example, with seizures, and hence they are being discussed here. The incidence of second malignancy anywhere in the body in a patient treated for ALL is 62.3/100000 cases annually,[14] and CNS malignancy constitutes a small group. The occurrence of brain tumor is often attributed to radiotherapy;[15] however, they are also seen in patients who have not been irradiated[16] and, recently, have been reported even after bone marrow transplantation.[17] Glioma is the commonest tumor, followed by ependymomas, lymphoma, and meningioma.[18,19] Loss of immune surveillance and genetic factors have been proposed to be the etiological factors.[15] The presenting feature could be seizure, headache, altered sensorium, etc.

Imaging
These lesions will present like any other brain tumor, i.e., as space-occupying lesions (SOL), with enhancement and mass effect [Figures 8 and 9].

CNS infiltration

Pathophysiology
Primary CNS leukemia is found at diagnosis in fewer than 5% of children with ALL. It is more common in children with myeloid leukemias and is commonly called a chloroma or granulocytic sarcoma. It occurs due to hematogeneous spread or direct extension from involved cranial bone marrow (through cortical veins to superficial arachnid or perineurium).

CNS relapse occurs in about 15% of cases despite prophylactic treatment. It can present as intra-axial infiltration, meningeal involvement, or infiltration of the bone marrow, or all three. The disease may be diffuse or focal, which will dictate the presentation. The globe, the extraocular muscles, or the optic nerve may be involved. This area acts as a sanctuary site due to suboptimal penetration of chemotherapeutic agents into the retrobulbar optic nerve.[20]

Imaging
Parenchymal leukemic masses are very uncommon in ALL. When present, they appear hyperdense on CT scan, may

be contiguous with the meningeal lining, and enhance after administration of contrast material.[21] The presence of enhancing optic nerve enlargement in children with leukemia should suggest leukemic infiltration [Figure 10].

Conclusion

The various acute neurological complications in ALL have common presenting symptoms but varying imaging abnormalities. We believe that correct diagnosis needs inputs from the treating clinician (regarding signs/symptoms, phase of treatment, drugs used, etc) and a dedicated radiologist to read the scans. A diagnostic algorithm using plain and contrast-enhanced MRI along with spectroscopy and DWI as added investigations has been proposed [Figure 11], the ultimate goal being to make a correct diagnosis that allows prompt intervention.

Acknowledgements

References

1. Ginsberg LE, Leeds NE. Neuroradiology of leukaemia. AJR Am J Roentgenol 1995;165:525-34.

2. Ramsay NK, Coccia PF, Krivit W, Nesbit ME, Edson JR. The effect of L-asparaginase on plasma coagulation factors in acute lymphoblastic leukemia. Cancer 1977;40:1398-401.

3. Chen CY, Zimmerman RA, Faro S, Bilaniuk LT, Chou TY, Molloy PT. Childhood leukemia: Central nervous system abnormalities during and after treatment. AJNR Am J Neuroradiol 1996;17:295-310.

4. Vázquez E, Lucaya J, Castellote A, Piqueras J, Sainz P, Olivé T *et al.* Neuroimaging in pediatric leukemia and lymphoma: Differential diagnosis. Radiographics 2002;22:1411-28.

5. Lee EJ. The empty delta sign. Radiology 2002;224:788-9.

6. Luthra G, Parihar A, Nath K, Jaiswal S, Prasad KN, Husain N *et al.* Comparative evaluation of fungal, tubercular, and pyogenic brain abscesses with conventional and diffusion MR imaging and proton MR spectroscopy. AJNR Am. J. Neuroradiol 2007;28:1332-8.

7. Harisinghani HG, McLoud TC, Shepard JA, Ko JP, Shroff MM, Mueller PR. Tuberculosis from head to toe. Radiographics 2000;20:449-70.

8. Phillips ME, Ryals TJ, Kambhu SA, Yuh WT. Neoplastic vs inflammatory meningeal enhancement with Gd-DTPA. J Comput Assist Tomogr 1990;14:536-41.

9. Reddick WE, Glass JO, Helton KJ, Langston JW, Xiong X, Wu S, *et al.* Prevalence of Leukoencephalopathy in Children Treated for Acute Lymphoblastic Leukemia with High-Dose Methotrexate. AJNR Am J Neuroradiol 2005;26:1263–9.

10. Fisher MJ, Khademian ZP, Simon EM, Zimmerman RA, Bilaniuk LT. Diffusion-weighted MR imaging of early methotrexate-related neurotoxicity in children. AJNR Am J Neuroradiol 2005;26:1686-9.

11. Morris EB, Laningham FH, Sandlund JT, Khan RB. Posterior reversible encephalopathy syndrome in children with cancer. Pediatr Blood Cancer 2007;48:152-9.

12. Bartynski WS. Posterior reversible encephalopathy syndrome, part 1: Fundamental imaging and clinical features. AJNR Am J Neuroradiol 2008;29:1036-42.

13. Covarrubias DJ, Luetmer PH, Campeau NG. Posterior reversible encephalopathy syndrome: Prognostic utility of quantitative diffusion-weighted MR images. AJNR Am J Neuroradiol 2002;23:1038-48.

14. Miké V, Meadows AT, D'Angio GJ. Incidence of second malignant neoplasms in children: Results of an international study. Lancet 1982;2:1326-31.

15. Walter AW, Hancock ML, Pui CH, Hudson MM, Ochs JS, Rivera GK, *et al.* Secondary brain tumours in children treated for acute lymphoblastic leukemia at St Jude children's research hospital. J Clin Oncol 1998;16:3761-7.

16. Gilman PA, Miller RW. Cancer after acute lymphoblastic leukemia. Am J Dis Child 1981;135:311-2.

17. Witherspoon RP, Fisher LD, Schoch G, Martin P, Sullivan KM, Sanders J, *et al.* Secondary cancers after bone marrow transplantation for leukemia or aplastic anemia. N Engl J Med 1989;321:784-9.

18. Zarrabi MH, Rosner F, Grünwald HW. Second neoplasms in acute lymphoblastic leukemia. Cancer 1983;52:1712-9.

19. Relling MV, Rubnitz JE, Rivera GK, Boyett JM, Hancock ML, Felix CA, *et al.* High incidence of secondary brain tumours after radiotherapy and antimetabolites. Lancet 1999;354:34-9.

20. Madani A, Christophe C, Ferster A, Dan B. Perioptic nerve infiltration during leukaemic relapse: MRI diagnosis. Pediatr Radiol 2000;30:30-2.

21. Tomura N, Hirano H, Kato K, Sashi R, Hashimoto M, Watarai J, *et al.* Central nervous system involvement of leukemia and systemic lymphoma in children: CT and MR findings. No To Shinkei 1997;49:993-1000.