ROLE OF DIFFUSION WEIGHTED IMAGING IN METHOTREXATE-INDUCED LEUKOENCEPHALOPATHY IN ADULT ACUTE LYMPHOBLASTIC LEUKAEMIA PATIENTS

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ABSTRACT

BACKGROUND

Methotrexate (MTX) is a chemotherapeutic agent commonly used in haematological malignancy. Its complication in childhood Acute Lymphoblastic Leukaemia (ALL) is well known to cause leukoencephalopathy. However, its complications in adults are uncommon. High doses of MTX is used to prevent CNS recurrence and haematological relapse. Diffusion weighted magnetic resonance imaging (DWI) plays an important role in early diagnosis. Aim of our study was to evaluate role of diffusion weighted MR imaging in Methotrexate-induced Leukoencephalopathy in adult acute lymphoblastic Leukaemia patients.

METHODS

A hospital based cross-sectional retrospective study was conducted. The study group comprised of 7 adult acute lymphoblastic leukaemia (ALL) patients presenting to the Departments of Radio-diagnosis, Medicine and Radiotherapy in a tertiary care hospital from April 2012 to May 2015.

RESULTS

In our study, 7 adult patients of acute lymphoblastic leukaemia (ALL), four patients (57.1%) developed MTX toxicity in interim maintenance phase and 3 patients (42.9%) developed in second maintenance phase of multidrug BFM-95 Regimen. Diffusion weighted images showed patchy multifocal restriction in 2 patients (28.6%) of acute MTX neurotoxicity and no diffusion restriction in rest 5 patients (71.4%). Acute MTX neurotoxicity in two patients (28.6%) had low apparent diffusion co-efficient (ADC) value while 3 patients (42.9%) of chronic MTX neurotoxicity had high ADC value and 2 patients (28.6%) of subacute MTX neurotoxicity had normal ADC value.

CONCLUSIONS

Prompt recognition of MTX neurotoxicity with diffusion weighted imaging and ADC value are essential to institute early treatment to improve the outcome after MTX overdose in adult ALL patients.

KEYWORDS

Methotrexate (MTX), Neurotoxicity, Apparent Diffusion Co-efficient (ADC), Acute Lymphoblastic Leukaemia (ALL).

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INTRODUCTION: Methotrexate (MTX) is a widely used drug in the treatment of malignancies, chiefly in the paediatric age group. Methotrexate is a folate analogue chemotherapeutic agent inhibiting dihydrofolate reductase enzyme. MTX toxicities are myelosuppression, mucositis, nephrotoxicity, hepatotoxicity and neurotoxicity.

The MTX neurotoxicity varies from acute to chronic encephalopathy.[1]

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Acute encephalopathy generally develops within 5–14 days after intrathecal MTX or high dose MTX. Acute MTX induced encephalopathy presented with headache, nausea, vomiting, altered mental status, aphasia, hemiparesis and seizure, etc. Transient acute encephalopathy develops in 3-15% of cancer patients after high dose MTX and can resume MTX therapy without permanent neurological sequelae.[2] The aim of this study was to evaluate role of diffusion weighted MR imaging in Methotrexate induced Leukoencephalopathy in adult acute lymphoblastic Leukaemia patients.

MATERIAL AND METHODS: After approval from the Institutional Ethics Review Committee, a hospital based cross-sectional retrospective study was conducted. The

study group comprised of 7 patients presenting to the departments of Radio-diagnosis, Medicine and Radiotherapy in a tertiary care hospital from April 2012 to May 2015.

Patient Selection: We included known adult ALL patients, both outpatients and inpatients. We included only those adult ALL patients in whom MR imaging was performed. Patients in whom MR imaging study was not done were excluded from the study. Informed consent was obtained from patient/parents/guardian before undergoing MRI scan.

MRI Protocols: All patients were subjected to MRI scan of brain and obtained axial T1WI, T2WI, FLAIR (Fluid attenuated inversion recovery), SWI (Susceptibility weighted image), DWI (Diffusion weighted image), Sagittal T1WI and Coronal T2WI sequences using 5 mm slice thickness. Post gadolinium fat suppressed T1W images were obtained in different planes. Intermediate TE (TE-135) MRI spectroscopy was done in all patients.

Evaluation: Seven adult ALL patients of MTX induced Leukoencephalopathy were examined to localised distribution of abnormal T2WI and FLAIR hyperintense lesions, DWI characteristics, ADC (apparent diffusion co-efficient) value in the affected altered signal intensities, post gadolinium enhancement pattern and chemical markers of MR spectroscopic findings.

STATISTICAL ANALYSIS: Data were presented in terms of percentage and mean. Calculations were done using Microsoft Excel.

RESULTS: In our study, 7 adult acute lymphoblastic leukaemia (ALL) patients were treated with multidrug treatment of Berlin-Frankfurt-Munster (BFM)-95 Regimen. In this regimen, initial 5 multidrug chemotherapy of Doxorubicin, Methyl prednisolone, Vincristine, Dexamethasone and L-asparaginase were given in both initial induction chemotherapy and initial intensification phases.

Four patients (57.1%) developed MTX neurotoxicity in interim maintenance phase while 3 patients (42.9%) developed MTX neurotoxicity in second maintenance phase after high dose MTX. Age of presentation varied from 22-35 years with mean age of 27.8 years. Female: Male sex ratio was 1:2.5. Four patients (57.1%) developed MTX neurotoxicity after intravenous administration of high dose MTX and 3 patients (42.9%) developed after oral administration of MTX. Six patients (85.7%) developed MTX neurotoxicity after IV administration of MTX dose of 5 mg/m^2 while one patient (14.3%) developed MTX toxicity after IV administration of MTX dose of 10 mg/m^2.

MRI revealed T1 iso to hypointense, T2WI and FLAIR hyperintense multifocal white matter lesions in bilateral cerebral hemispheres in 4 patients (57.1%), diffuse T2WI and FLAIR hyperintense lesions in bilateral cerebral hemispheric white matter in 2 patients (28.6%) and 1 patient (14.3%) had white matter abnormalities in bilateral cerebral and cerebellar white matter, brain stem and bilateral ganglio-thalamic regions.

Diffusion weighted images showed patchy multifocal diffusion restriction in 2 patients (28.6%) of acute MTX neurotoxicity [Figure 1] while no diffusion restriction were noted in 5 patients (71.4%) of subacute [Figure 2] and chronic [Figure 3] stages of MTX neurotoxicity. Two patients (28.6%) of acute MTX neurotoxicity had low ADC value while 3 patients (42.9%) had high ADC value in chronic MTX neurotoxicity and 2 patients (28.6%) in subacute MTX neurotoxicity had normal ADC value. Table: 1 showed ADC value in 7 patients.

Post gadolinium MR images showed patchy ill-defined enhancement in abnormal lesions in 3 patients (42.9%) and without abnormal enhancement in rest of 4 patients (57.1%).

On basis of DW imaging and ADC value, two patients (28.6%) were diagnosed as acute MTX neurotoxicity, 2 patients (28.6%) as subacute stage and 3 patients (42.9%) as chronic MTX neurotoxicity [Figure 4]. All 7 patients of MTX neurotoxicity were treated conservatively in the form of withdrawal of MTX, IV administration of Leucovorin and Dexamethasone, even though 4 patients in acute and subacute stages of MTX neurotoxicity died within 15 days of MRI scan.

Serial number	Age of patient (In years)	Sex of patient	Stage of MTX Neurotoxicity	DWI restriction	ADC value (x 10^{-3} mm^2/s)
1	22	F	Acute	Patchy multifocal	0.43
2	26	M	Subacute	no	0.5
3	27	M	Chronic	no	1.1
4	35	M	Chronic	no	1.13
5	25	F	Acute	Patchy multifocal	7.8
6	31	M	Subacute	no	7.9
7	29	M	Chronic	no	12.3

Table 1: Showed ADC Value of 7 Adult Onset ALL Patients of MTX Neurotoxicity

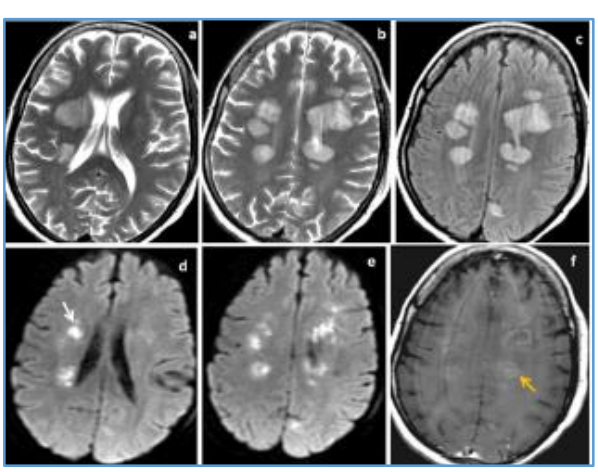

Figure 1

Figure 1: A 22-year-old female ALL patient on multidrug chemotherapy regimen BFM-95 had headache, vomiting and episodes of seizures after high second dose MTX in initial interim maintenance phase. Multifocal T1 hypo, T2 weighted and FLAIR hyperintense lesions were noted in bilateral deep periventricular white matter and right basal ganglia (Image a, b & c). Restricted diffusion was noted in these lesions (White arrow in image d) with low ADC value. Minimal peripheral enhancements were noted in these lesions on post gadolinium T1 images (yellow arrow in image f). These findings representing acute MTX induced Leukoencephalopathy.

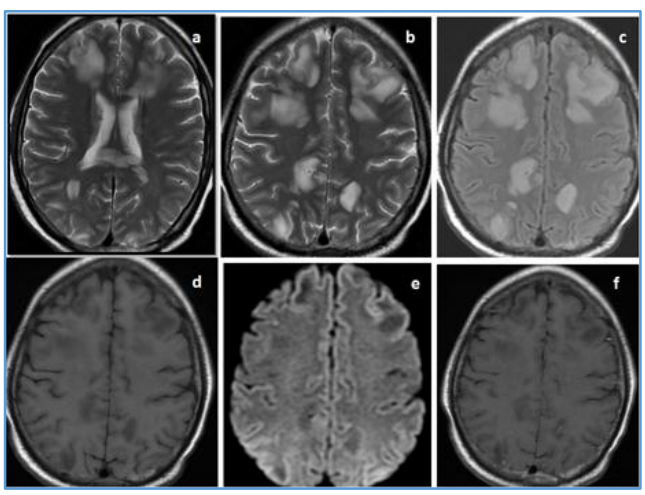

Figure 2

Figure 2: A 26-year-old male patient diagnosed with ALL on multidrug chemotherapy regimen presented with repeated episodes of seizures. Multifocal T1 hypointense, T2 and FLAIR hyperintense lesions were noted in subcortical and deep periventricular white matter of bilateral cerebral hemispheres and corpus callosum (Image a, b, c & d). No diffusion restriction was noted (Image e). Minimal irregular enhancements were noted in lesions on post gadolinium T1 images (Image f). These findings suggested subacute MTX induced Leukoencephalopathy.

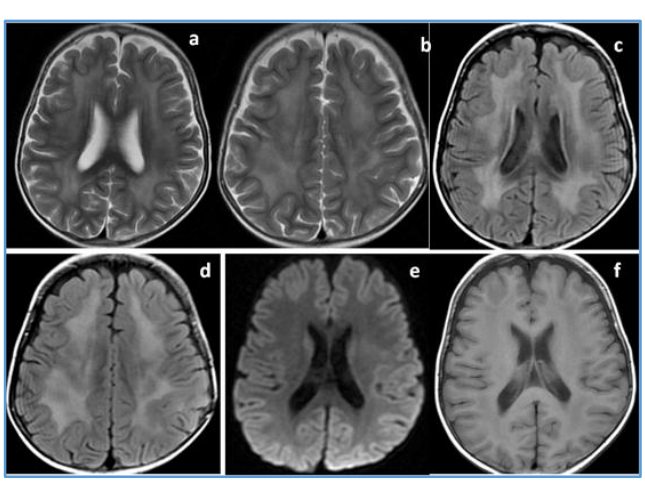

Figure 3

Figure 3: A 27-year-old patient of ALL initially treated with BFM-95 Regimen presented with gradual onset cognitive impairment and dementia after 9 months of treatment regimen. MRI revealed confluent T2WI (a & b) and FLAIR (c & d) hyperintense lesions in bilateral deep periventricular white matter and subcortical white matter of bilateral frontal and parietal lobes. No diffusion restriction was noted on DWI (e). These findings suggested chronic stage of MTX induced Leukoencephalopathy.

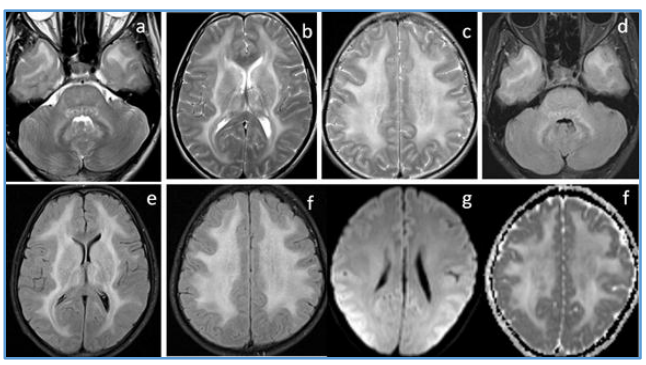

Figure 4

Figure 4: A 35-year-old male patient of ALL presented with gradual onset ataxia and rigidity. MRI revealed diffuse T2WI (a, b &c) and FLAIR (d, e &f) hyperintensities in bilateral middle cerebellar peduncles, brain stem, bilateral basal ganglio-thalamic regions, bilateral internal capsules, deep and subcortical white matter of bilateral cerebral hemispheres without perifocal oedema. No diffusion restriction was noted on DWI images (g) with higher signals on ADC map (h). These findings representing diffuse form of chronic MTX induced encephalopathy.

DISCUSSION: The main target of MTX is the inhibition of enzyme dihydrofolate reductase. This results in deficiency of folate and thereby decreased synthesis of both purines and pyrimidines.[3] Elevated levels of blood homocysteine after MTX administration induced endothelial cell injury and cerebrovascular infarcts may account for clinical focal neurological deficits and seizures as vascular-related phenomena of MTX neurotoxicity.[4]

The incidence of acute encephalopathy among Leukaemia/Lymphoma patients who received MTX was reported as 0.8%.[5] In children, the incidence of Leukoencephalopathy ranges from 1% to 45%. [6] Adult had lower MTX clearance which may contribute to the age risk for development of MTX toxicity.[2,7]

MTX can induce acute, subacute or chronic neurotoxicity. This toxicity is mainly observed after intrathecal or high dose IV administration of MTX.[8]

In acute MTX induced encephalopathy syndrome, MR images show discrete and confluent T2 and FLAIR hyperintense deep white matter lesions. These lesions show restricted diffusion with low ADC value.[9] Two patients in our study showed DWI restriction and low ADC value representing the acute MTX neurotoxicity.

Paraplegia, cerebellar dysfunction and seizures are reported as subacute MTX neurotoxicity[10] and usually occur a few weeks after initiation of MTX. No restricted diffusion noted on DWI. Similar changes were noticed in our two patients of subacute MTX neurotoxicity.

Chronic neurotoxicity is observed several months to years after MTX therapy.[8] The chronic MTX induced Leukoencephalopathy is characterised by a slow progressive cognitive deterioration, seizures, ataxia, spasticity or coma.[8] These chronic MTX induced neurologic deficits generally are irreversible. Intrathecal administration of MTX can also cause chronic MTX neurotoxicity. Few cases of chronic MTX leukoencephalopathy have been reported from high dose MTX or standard IV or oral dose of MTX.[11] Symptoms of chronic MTX neurotoxicity may appear months to years after MTX therapy.[12]

MTX neurotoxicity is usually treated with CSF drainage or CSF exchange, ventriculolumbar perfusion, intrathecal corticosteroids and IV Leucovorin in acute and/or subacute MTX neurotoxicity.[13] Adult patients with ALL who develop CNS recurrence have a very poor prognosis, like in our patients. Multifocal white matter changes denote poor prognosis than solitary white matter lesion. Intravenous Leucovorin rescues the MTX induced blockade of dihydrofolate reductase. Concurrent IV administration of Leucovorin rescue adapted to high dose MTX plasma concentrations in high dose MTX multidrug regimens; however, excessive Leucovorin administration as well as too early administration of Leucovorin[15] can impair the antitumor activity of high dose MTX.[14] Delayed and low dose Leucovorin rescue contributes to an increased overall therapeutic efficacy of high dose MTX.[16]

Sandoval et al, reported a known pre-B cell 13-year-old ALL female patient with acute MTX induced neurotoxicity occurring during consolidation phase as areas of restricted diffusion in bilateral centrum semiovale and corpus callosum.[17]

Diffusion weighted MR imaging is most sensitive imaging modality for identifying brain damage in MTX induced neurotoxicity.[5] T2WI and FLAIR images shows abnormal hyperintense lesions in affected white matter but these take time to appear; however, T2WI and FLAIR images may continue to show the residual altered signal intensities even after resolution of neurological deficits.[5,18] Diffusion weighted images show restricted diffusion with low ADC value in brain of the patients with acute lymphoblastic leukaemia who had stroke like symptoms after high dose MTX.[17,18,19] Hence MTX induced acute leukoencephalopathy syndrome can be diagnosed, where diffusion weighted images shows areas of diffusion restrictions with low ADC value across multiple cerebral vascular beds with involvement of cerebral/ cerebellar white matter, in the clinical background of waxing and waning neurological signs and symptoms after high dose MTX.

LIMITATIONS: In our study, we were not able to follow those three adult ALL patients who had chronic stage of MTX neurotoxicity.

CONCLUSION: MTX induced leukoencephalopathy varies from acute, subacute or chronic encephalopathy. The MTX neurotoxicity is more severe in adult patients than children. Hence, prompt recognition of MTX neurotoxicity with diffusion weighted imaging and ADC value are essential to institute early treatment to improve the outcome after MTX overdose in adult ALL patients.

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