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Reversible Encephalopathy Induced by Systemic High Dose Methotrexate

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Abstract Therapy induced leukoencephalopathy is a known complication for children receiving high dose intravenous methotrexate. It may present as seizure or focal neurological deficit but fortunately the neurological deficits are often transient. We reported 2 local patients who had this complication and no gross persistent neurological complication were noted. From the literature and our experience, MRI is a more sensitive modality in picking up such complication and aminophylline may have a role as a prophylactic agent. A prospective study with appropriate neuropsychological assessment and long term follow-up on patients with this complication is needed to delineate the actual impact of this clinical phenomenon.

Key words Leukoencephalopathy; Methotrexate

Therapy related leukoencephalopathy can be induced by either chemotherapy or cranial irradiation. Among the chemotherapeutic agents reported as causative agents for this complication, intrathecal or high dose systemic methotrexate are the most commonly described. Methotrexate induced leukoencephalopathy has a very diverse clinical manifestation ranging from asymptomatic to seizure or focal neurological deficit. Whether this complication is reversible remains unpredictable. We have two teenage boys who developed an acute neurological deficit 4 to 8 days after receiving high dose intravenous methotrexate and none of them had cranial irradiation. Complete neurological recovery was observed within 3 weeks and long term follow-up showed no residual neurological deficit or intellectual impairment, conventional MRI revealed complete resolution of the lesions.

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Case 1

A previously healthy 16-year-old boy presented with fever, general malaise and bilateral knee pain for 4 weeks. Complete blood picture revealed marked leukocytosis. Marrow showed blast cells of FAB-L2 morphology and immunophenotyping was consistent with common phenotype acute lymphoblastic leukaemia. Cytogenetic and molecular studies did not show any abnormality. His urate was slightly elevated and his renal function was normal. There was no central nervous system or testicular

involvement. He was treated with the modified ALL-BFM-95 protocol that consisted of 12 weeks' of induction therapy with prednisolone, vincristine, L-asparaginase, daunorubicin, cyclophosphamide, cytarabine, 6-mercaptopurine, intrathecal (IT) methotrexate (MTX) on first day and 4 more doses of triple IT therapy of methotrexate, hydrocortisone and Ara-C. He tolerated the treatment well with no major complications.

Then he proceeded to consolidation therapy, which consisted of oral 6-mercaptopurine together with four 2-weekly cycles of 24 hours intravenous infusion of high dose MTX at 5 gm/m^2 and triple IT. Folinic acid 15 mg/m^2 every 6 hours for a minimum of 3 doses were administered 42 hours from the start of MTX infusion as rescue. MTX levels was checked at 24 hourly after MTX infusion till it returned to <0.25 μmol/L. His renal function and creatinine clearance prior to and after the MTX infusion was within normal limit and his 24 & 48 hours MTX levels were 82 μmol/L & 0.3 μmol/L respectively. There was no additional folinic acid rescue required. Eight days after the second cycle of consolidation, he had sudden onset of right hemiparesis with ipsilateral upper motor neuron facial palsy. There was no dysphasia or change in sensorium. He was fully conscious with normal vital signs but with slurring speech. Urgent computer tomography (CT) of the brain, echocardiogram, ultrasonic doppler of carotid arteries were all normal. Thrombophilic screening including protein C, protein S, anti-thrombin III and lupus anti-coagulant were unremarkable. The neurological deficit resolved one week later. Because of swift neurological recovery, the third cycle of consolidation therapy was given as scheduled. However, magnetic resonance imaging (MRI) of the brain performed 2 weeks afterwards showed subtle area of T2 hyperintensity at left centrum semi-ovale and bilateral corona radiata especially with fluid attenuated inversion recovery (FLAIR) images (Figure 1). As the white matter changes were most likely related to the administration of high dose MTX, the drug was withheld in the fourth cycle. Repeated MRI towards the end of re-induction therapy (16 weeks from the second cycle of high dose MTX) showed mild progression of the leukoencephalopathy. There had not been any new complaints since he recovered from the neurological deficits. Cranial irradiation was withheld in view of the untoward central nervous system event.

During the maintenance therapy consisting of 6-mercaptopurine and weekly oral MTX 20 mg/m^2, six triple IT were given at every 10-week cycle in additional to vincristine and steroid. Folinic acid was administered for at least 3 doses after every TIT. His neurological problem did not recur with low dose oral and IT MTX. Follow-up MRI brain during the maintenance therapy showed resolution of the lesion over the right side while the left sided white matter changes were less conglomerated. Subsequently, another scan performed at the completion of therapy (72 weeks from the 2nd cycle of high dose MTX) revealed complete resolution of the lesions. Patient remained asymptomatic since recovery from the event and long-term follow-up assessment at 2 years after completion of therapy showed normal mental and physical functions. He has been off treatment for almost 3 years at the time of this review.

Case 2

A 17-year-old male with a right fibular osteosarcoma presented with large swelling of right lower leg complicated by deep vein thrombosis (DVT). He required low molecular weight heparin treatment and was then treated according to the modified Rosen T10 protocol. Each block of chemotherapy consists of adriamycin plus cisplatin

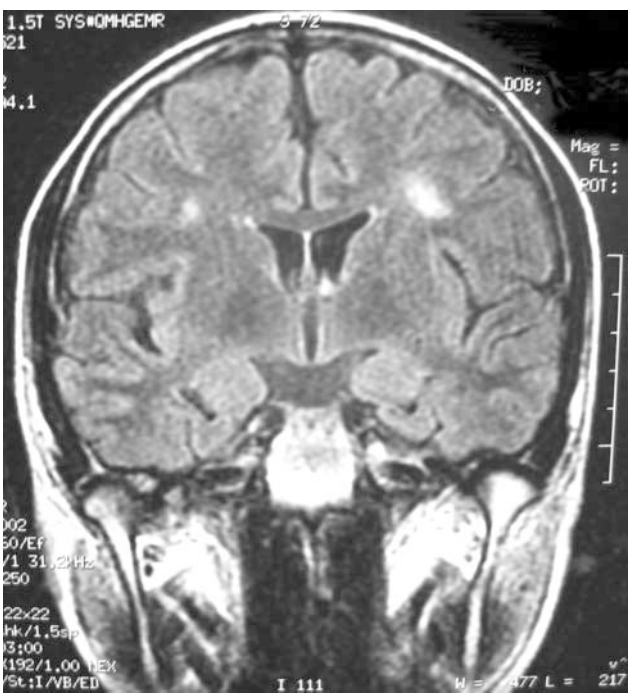

Figure 1 Coronal fluid-attenuation inversion recovery (FLAIR) MR image shows focal areas of hyperintensity at the bilateral corona radiata.

alternating with 2 weekly 24 hours intravenous infusion of high dose MTX at 12 gm/m^2 at 4 weekly interval. Folinic acid rescue was given according to the protocol until the MTX level dropped to <0.1 μmol/L. After he received 2 blocks of treatment, he suddenly developed right-sided hemiplegia. There was no associated cranial nerve palsy. The last dose of MTX was given 4 days before the incident when the MTX level already dropped to <0.1 μmol/L. His renal function and creatinine clearance prior to and after the MTX infusion was within normal limit and his 6 hours post-MTX level was 980 μmol/L with a satisfactory drop of MTX level at 24, 48 & 72 hours without additional folinic acid rescue added. At that time, he had been receiving 2000 units of daily subcutaneous enoxaparin as prophylactic therapy against DVT. The drug was immediately withheld. Urgent CT brain did not show any intracranial haemorrhage. MRI brain performed 18 hours after the incident showed subtle T1 hypointense and T2 hyperintense signal in the white matter of left high parietal lobe. This corresponded to an area of focal restricted diffusion on DWI sequence. (Figure 2). At 21 hours, he developed right-sided weakness as well and progressive left hemiplegia resulting in quadriplegia. Intravenous folinic acid was empirically restarted at 15 mg/m^2 every 6 hours. At 26 hours, the patient developed upper motor neuron lesion of left facial nerve followed by dysarthria and swallowing difficulties though he was fully conscious with stable vital signs. Repeated MRI brain showed high signal intensity areas at bilateral centrum semi-ovale on T2-weighted images (Figure 3), but resolution of restricted diffusion. The MR arteriogram showed patent intracranial arteries and the MR venogram showed no evidence of dural venous sinus thrombosis. The patient regained full power on the right side with resolution of bulbar dysfunction 3 days later. The residual left hemiplegia resolved within 3 weeks' of time though there was remaining problem of fine motor coordination of the left hand. Folinic acid was given for one week. Repeated MRI brain 3 weeks later still showed patchy bilateral symmetrical areas of white matter hyperintensity in centrum semi-ovale and in the periventricular white matter. The extent of lesions was unchanged. These features are compatible with treatment related leukoencephalopathy. Above-knee amputation was carried out one month after the last cycle of high dose MTX. Following the operation, the patient received 3 cycles of etoposide/ifosfamide alternating with adriamycin/cisplatin without MTX. The patient has been off treatment for 10 months now and he recovered completely with no residual neurological deficit.

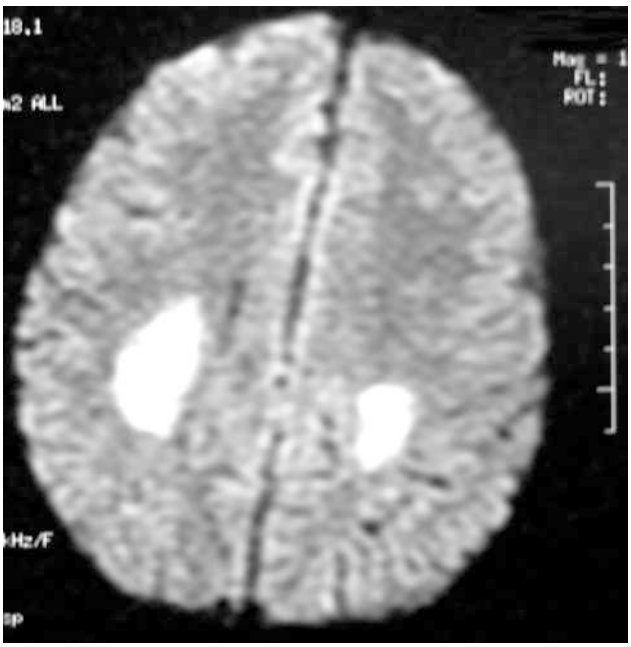

Figure 2 Axial diffusion-weighted MR image shows hyperintensities in the bilateral posterior corona radiata, in keeping with areas of restricted diffusion.

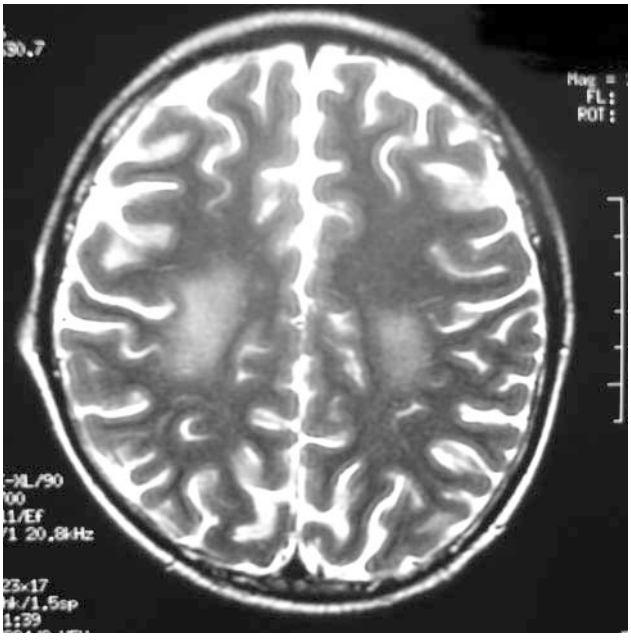

Figure 3 Axial T2-weighted MR image of shows corresponding areas of hyperintensities in the posterior corona radiata.

Discussion

Central nervous system (CNS) prophylaxis by either cranial irradiation or intrathecal and systemic MTX are crucial component for the prevention of CNS relapse in childhood leukaemia but they are also capable of inducing neurological complications themselves. CNS toxic effect has been reported with cyclosporin A, methotrexate, cytarabine and 5-fluorouracil.[1,2] Such neurotoxicity can be found in both children and adults.[3,4] Among them, MTX is the most frequently reported and it has been applied to a wide range of clinical conditions, including both neoplastic and non-neoplastic diseases. When used in low dose, symptomatic CNS toxicity mainly in the form of headache, dizziness, depression and transient-ischaemic-attack like syndromes was reported in 1 to 35% of cases.[5] When used in higher dose (>1 gm/m^2), more severe neurotoxicity including confusion, seizure, paraplegia or even coma and death can occur.

Using different diagnostic means, the incidence of leukoencephalopathy varied and occurs in 0 to 68% of ALL patients treated by systemic and intrathecal chemotherapy with or without cranial irradiation.[1,6,7] On the other hand, in patients with osteosarcoma in which treatment regimen involved even higher dose MTX, the incidence of leukoencephalopathy shown on MRI varied from 50 to 64%. But clinically, only 3.7 to 11.2% of patients were symptomatic when treated with high dose MTX.[8-10] Table 1 summarised the dose of intravenous (IV) and intrathecal (IT) MTX and occurrence of neurological complications in patients who received no cranial irradiation.

High dose MTX was the only common drug found in both ALL and osteosarcoma protocols. Our ALL patients received a total of 10 g/m^2 of IV MTX and a total of 84 mg of IT MTX, both of which was at the intermediate dosage range as compared to those described (Table 1). Our osteosarcoma patients, although did not receive any intrathecal chemotherapy, had been given a much larger dose of 48 mg/m^2 IV MTX. In our recent review of the HKPHOSG data on patients with osteosarcoma, 9 cases of methotrexate induced leukoencephalopathy was recorded out of 75 patients treated with the protocol (HKPHOSG, non-published data) and the incidence appeared to be more common than what we encountered in ALL patients. The incidence of this complication is likely associated with the higher dose of methotrexate given.

An increased risk of leukoencephalopathy is observed in patients who received 6 or more doses of 12 mg IT MTX post-transplantation; more than 50 mg IT MTX; more than 2000 cGy cranial radiation; or more that 40-80 mg/m^2 per week of IV MTX.[11] In the very young (<5 years) or in those who received high dose, multi-drug or combined with radiotherapy, the severity of leukoencephalopathy would also be higher.[2] The finding was echoed by another study showing even moderate dose MTX (42 to 72 mg IT MTX and 120 mg to 3233 mg oral MTX) in combination of cranial radiotherapy could result in significant incidence of magnetic resonance detectable leukoencephalopathy, particularly in those less than 6 years or younger receiving 2400 cGy of irradiation. A randomised phase III trial[10] involving 1300 children suggested that greater cumulative systemic exposure to MTX and a high MTX-folinic acid ratio posed an increased risk of leukoencephalopathy, especially in those who received concomitant TIT.

Recently aminophylline has been proposed to be able to salvage the neurological damaging effects of methotrexate.[12,13] The proposed mechanism of methotrexate induced neurotoxicity and aminophylline rescue has been postulated.[14] The cytotoxic effect of methotrexate is mainly due to the inhibition of dihydrofolate

Table 1 Summary on the dosage ranges, means of administration and outcome of MTX induced encephalopathy

Reference	Diagnosis	Year	Cases	Imaging	Total dose IV-MTX	Total dose IT-MTX	Residual defect
5	ALL/NHL	92	2	MRI	NA	NA	No
6	ALL	92	1	CT/MRI	3 g/m^2	30 mg	No
7	ALL	97	3	SPECT	0-72 g/m^2	36-204 mg	No
1	ALL	98	4	CT/MRI	NA	NA	NA
8	ALL	98	95	CT/MRI	12 g/m^2	128-240 mg	Yes
2	ALL	02	1	CT/MRI	Nil	3 doses	No
Case 1	ALL	00	1	CT/MRI	10 g/m^2	84 mg	No
Case 2	Osteosarcoma	03	1	CT/MRI	48 g/m^2	Nil	No

Studies with confounding variable of concomitant cranial irradiation are excluded.

reductase which recycles oxidized folates to their reduced state. Individual variation in polyglutamation of methotrexate may lead to purine synthesis inhibition and prolongs the intracellular retention of the drug resulting to an increase in adenosine in the cerebrospinal fluid. Because adenosine dilates cerebral blood vessels, alters neurotransmitter release and postsynaptic responses, and slows the discharge rate of neurons, it is possible that raised adenosine levels account for the neurotoxicity of methotrexate. Aminophylline, a methylxanthine, acts as a competitive adenosine antagonist and theoretically may relieve the neurotoxicity of methotrexate. However, the clinical efficacy remains controversial at the moment. The standard treatment approach of methotrexate induced encephalopathy remains to be supportive. It involves removal of the offending chemotherapeutic agent, administration of steroid in an attempt to reduce white matter oedema and use of antidote such as folinic acid.[2,11] In the patient with osteosarcoma, we tried to avoid using high dose MTX again for the rest of the chemotherapy regimen. In addition, folinic acid was empirically given for one more week although the drug level had been non-toxic already at the time of presentation. In the ALL patient, cranial radiotherapy was withheld to avoid further insult to the brain.

Except for a few patients with serious permanent deficit, majority of children including ours are reported to recover from the encephalopathy without residual neurological deficits. However, there has been report suggested up to 23% of their patients suffered from recurrent seizure but such high incidence of symptomatic leukoencephalopathy has not been observed in most large collaborative studies including our local study.[15-17] There is an argument saying that subtle complication of MTX induced leukoencephalopathy might be discovered if long-term follow-up is performed in larger number of patients. This is unlikely for most recent studies by MRI suggested these change are regressing rather than progressing.[6,18,19]

But subtle cognitive impairments in terms of change in concentration, attention, and memory without obvious structural abnormality have been identified, especially in those patients who received cranial irradiation.[20] Formal neuropsychological tests instead of simple neurological and mental state examination may be necessary to obtain a more accurate assessment for long-term survivors. In addition, the improvement in the sensitivity of the imaging technique may also help to detect earlier changes previously unidentified. Advanced functional imaging tools such as Single Photon Emission Computer Tomography (SPECT) to look at regional blood flow,[21] Proton Magnetic Resonance Spectroscopy (^{1}H-MRS)[22] to look at aspects of cerebral metabolism, may be helpful in the future. A recent study employed functional MRI including perfusion, diffusion, and blood-oxygen-level-dependent (BOLD) contrast imaging to look at MTX exposed swine brain.[23] Other new MRI technique such as diffusion tensor MR imaging may also help in early detection and quantification of treatment-induced leukoencephalopathy as it can detect subtle changes that occur in the microstructure and organisation of white matter fiber tracts. Whether all these more sensitive imaging will eventually assist us to a better clinical care has to be evaluated in future study.

In conclusion, drug induced leukoencephalopathy can be found in local children receiving high dose intravenous methotrexate. It may present as seizure or focal neurological deficit. Most children with this complication have favourable outcome and the neurological deficits are completely reversible. However, long-term neurological effects remain unknown especially in terms of cognitive function. MRI is a more sensitive modality in picking up such complication and aminophylline may have a role as a prophylactic agent but its therapeutic effect remains controversial.

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