Reversible Leukoencephalopathy Following Intrathecal Methotrexate

H Xiong, SY Ha, AKS Chiang, YL Lau, Q Hu, GCF Chan

Abstract
Leukoencephalopathy is a severe but often reversible neurological complication with high dose intravenous methotrexate (MTX). It is much rarer after intrathecal MTX. We report a 13-year-old girl suffered from leukoencephalopathy 7 days after intrathecal MTX administration. The sequential MRI changes are highlighted in this report. Rescue therapy with aminophylline and high-dose folinic acid was given for 10 days. Her neurological status in terms of the speech and motor function gradually improved afterwards.

Key words
Intrathecal; Leukoencephalopathy; Magnetic resonance imaging; Methotrexate

Introduction
Methotrexate (MTX) is an antimetabolite with an important role in the treatment of acute lymphoblastic leukaemia (ALL). Intravenous (IV) high-dose (HD) MTX and intrathecal (IT) MTX have improved the prognosis and reduced the rate of CNS relapse. MTX induced leukoencephalopathy is an increasingly recognised complication following IV HD MTX or IT MTX. We report a patient who developed leukoencephalopathy following IT MTX and was rescued with aminophylline and HD folinic acid. The sequential MRI and CT imagings changes during different period in this unusual case are shown. The patient gradually recovered from the neurological deficit.

Case Report
A 13-year-old girl presented with symptoms of pallor, general malaise and decreased exercise tolerance. The diagnosis of precursor B cell leukaemia was made. Induction, early intensification, consolidation therapy had been performed in the first nine months, including IT chemotherapies of MTX, cytosine arabinoside and hydrocortisone according to the protocol of ALL CCLG-2008. After completed a systemic treatment (cyclophosphamide, cytosine arabinoside and thioguanine), she received the IT treatment. The cerebrospinal fluid examination was negative for malignant cells or other abnormal findings. On day 7 after the IT, the patient presented with right hemiparesis with mild headache. She then rapidly deteriorated in her neurological state with quadriplegias, bilateral facial weakness, bulbar palsy, expressive dysphasia and urinary retention. There were no clinical seizure or fever, thrill, vomit and she was able to obey simple commands. Her GCS remained 15/15.

Urgent biochemical tests, including blood glucose, electrolytes, renal and liver function were within normal limits. Peripheral blood count showed haemoglobin of 7.8 g/100 ml, total leukocyte count cells 560/mm³,
neutrophils 370/mm³, eosinophils 60/mm³, lymphocytes 90/mm³, and platelets 13,000/mm³.

Urgent MRI of brain and cervical spine were performed on day 7. Very mild reduction in T1W signal (Figure 1) and increase in T2W signal (Figure 2) were seen. An area of focal diffusion restriction on DWI image and ADC map (Figure 3) was seen in the deep white matter of left parietal lobe. No obvious signal change on FLAIR. No sign of haemorrhage, acute ischaemia or other focal signal abnormality were found. Re-examination of MR and MRA+MRV was executed on day 8 due to the deterioration of neurological status, which displayed interval progression of signal changes at bilateral subcortical white matter (Figures 1 to 3). No abnormal T2* (Figure 4) blooming focus was seen to suggest previous haemorrhage while major venous sinuses and branches of the Circle of Willis were patent. However, CT scans of brain failed to detect significant changes at the same two days.

She was started with intravenous folinic acid 1500 mg rescue over 24 hours together with aminophylline 0.5 mg/kg/hr infusion for 7 days. There was a gradual progressive improvement in neurological status with her 4 limbs power back to at least 4/5 and returning of spontaneous speech. She could stand up gradually, while remained to have facial nerve palsies, unsteady gait, hand tremor, cerebella ataxia and wasted distal limbs’ muscle with weakness. She was referred to physical therapist for neuro-rehabilitation after ten days of continuous treatment with folinic acid and aminophylline.

Subsequent chemotherapy was modified to omit MTX. On day 80 visit, the patient could walk via the assisted-tool while her fine motor movements remained poor. Her cognitive function including concentration, attention and memory seemed to return to normal. A repeated MR examination showed the typical periventricular white matter T2W hyperintense/T1W hypointense areas (Figures 1 & 2)
Reversible Leukoencephalopathy

Discussion

Common causes of acute progressive neurological deterioration in children and adolescent include cerebrovascular diseases (related to thrombosis due to the use of L-asparaginase or intracranial haemorrhage due to thrombocytopenia), CNS invasion by neoplastic cells, CNS infection, metabolic or electrolytic disturbances and drug neurotoxicity. We could exclude reasonably neoplastic, infectious and vascular diseases on the basis of history, clinical, biochemical and imaging findings of this 13-year-old girl. Upon review of her treatment around the time of the neurological disturbance, we identified MTX might be the likely drug that could explain the signs and symptoms. It was further proven by the demonstration of the typical leukoencephalopathy pattern and the possible response to aminophylline and folinic acid. Although MTX is almost always used in conjunction with other drugs, such as cytosine arabinoside, which by itself has a significant toxic potential, MTX is usually assumed to play the major role in the clinical scenario.
causative role in the development of leukoencephalopathy, with the other treatment modalities having only an additive effect.

MTX is an anti-cancer drug with anti-folate function by inhibiting dihydrofolate reductase, thereby depriving cells of tetrahydrofolate acid necessary for cellular production of folate. As a highly ionised and lipid-insoluble compound, MTX could hardly cross over the blood brain barrier, so it is commonly administered by intrathecal route for both treatment and prevention of CNS leukaemia. However, the drug also has a significant toxic effect on the CNS, which can potentially lead to severe neurological lesion known as leukoencephalopathy. Leukoencephalopathy commonly follows IT or IV MTX administration, though the exact mechanism is currently not fully understood, nor predictable of its occurrence. An increased risk of leukoencephalopathy has been observed in patients received more than 50 mg IT MTX, more than 40-48 mg/m² per week of IV MTX, or more doses of intrathecal 12 mg MTX post-transplantation. The reported case has been arranged for 9 months' chemotherapy and a total of intrathecal MTX as 132 mg for 11 doses, which was at the high dosage range as compared to those described in Table 1. Though prior successful MTX treatments, she presented with features of a reversible leukoencephalopathy after her repeated IT treatment. She had a rapidly deteriorating clinical course with progressive neurological deficits and a gradually improvement under rescue treatment with aminophylline and folic acid.

The mechanism of MTX-induced leukoencephalopathy remains unclear, and more than one mechanism may be involved, while increased adenosine levels and decreased biogenic amine neurotransmitter synthesis may be important in the pathogenesis of MTX toxicity. Aminophylline, acting as a competitive adenosine antagonist, has been used to relieving the neurotoxicity of methotrexate supportive by its increasing clinical efficacy. Folic acid was empirically given for two more weeks although the blood MTX level would have already been normalised.

MRI is very useful in the diagnosis of MTX-induced leukoencephalopathy, especially DWI/ADC map offering improved sensitivity in early detection and quantification of the distinctive syndrome, which is in concordance with our patient’s condition. However, our patient recovered clinically while her MRI remained to have a lag phase with the persistent periventricular white matter lesions even up to day 80 after the onset of her neurological event. This discrepancy in the relationship between MRI lesion and clinical syndromes resolution should be further evaluated. Also we found that CT scan might be not sensitive enough to detect early white-matte lesion.

Our case highlights the fact that intrathecal MTX can

### Table 1: Summary on the dosage ranges, interval of administration and outcome of IT-MTX induced leukoencephalopathy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Diagnosis</th>
<th>Year</th>
<th>Cases</th>
<th>CNS Leukaemia Infiltration</th>
<th>Imaging</th>
<th>Total Dose IT-MTX</th>
<th>Interval Between First IT and Syndrome</th>
<th>Interval Between Last IT and Syndrome</th>
<th>Residual Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>B-ALL</td>
<td>2003</td>
<td>1</td>
<td>No</td>
<td>DWI-MR</td>
<td>NA</td>
<td>3 weeks</td>
<td>6 hours</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>B-ALL</td>
<td>2004</td>
<td>1</td>
<td>No</td>
<td>MRI-T2</td>
<td>60 mg</td>
<td>19 days</td>
<td>4 days</td>
<td>Yes</td>
</tr>
<tr>
<td>13</td>
<td>ALL</td>
<td>2006</td>
<td>2</td>
<td>No</td>
<td>FLAIR+DWI+ADC MR</td>
<td>24~84 mg</td>
<td>12~15 days</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>14</td>
<td>2 B-ALL, 2 T-ALL</td>
<td>2006</td>
<td>4</td>
<td>No</td>
<td>DWI-MR</td>
<td>12 mg</td>
<td>NA</td>
<td>7~10 days</td>
<td>No</td>
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<tr>
<td>15</td>
<td>ALL</td>
<td>2008</td>
<td>1</td>
<td>No</td>
<td>MRI</td>
<td>84 mg</td>
<td>13 weeks</td>
<td>8 days</td>
<td>No</td>
</tr>
<tr>
<td>16</td>
<td>T-ALL</td>
<td>2008</td>
<td>1</td>
<td>Yes</td>
<td>DWI-MR</td>
<td>60 mg</td>
<td>20 days</td>
<td>5 days</td>
<td>Yes</td>
</tr>
<tr>
<td>17</td>
<td>2 B-ALL/2 T-ALL/1 lymphoblastic leukaemia/1 AML-M1</td>
<td>2008</td>
<td>6</td>
<td>No</td>
<td>DWI+FLAIR MR</td>
<td>24~96 mg</td>
<td>NA</td>
<td>4~9 days</td>
<td>Yes</td>
</tr>
<tr>
<td>Reported case</td>
<td>B ALL</td>
<td>2009</td>
<td>1</td>
<td>No</td>
<td>FLAIR+DWI+ADC MR/CT</td>
<td>132 mg</td>
<td>9 months</td>
<td>7 days</td>
<td>Yes</td>
</tr>
</tbody>
</table>
also induced leukoencephalopathy. The clinical course can present with rapid neurological deterioration with gradually improvement in clinical status. The improvement in MRI findings may take a much longer time. However, we should also take note of the significant role of early MRI imaging with DWI sequence in detecting early changes of the disease. Further investigations are necessary to elucidate the exact role and mechanism of the antidote protocol with either aminophylline or folinic acid. Long term follow-up of residual neurological sequelae is essential to provide proper rehabilitating care.

Conclusion

Intrathecal MTX can induce reversible leukoencephalopathy similar to high dose systemic MTX. Prompt neuroimaging examination and appropriate treatment can help to render early rescue and intervention of this devastating complication.

Acknowledgements

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References