Leukoencephalopathy in children treated with high-dose methotrexate

13-year-old male patient with acute lymphatic leukaemia undergoing treatment (the protocol used was an induction with daunorubicin, cyclophosphamide, vincristine, l-asparaginase and corticosteroids with intrathecal therapy with cytarabine, corticosteroids and methotrexate, and consolidation with methotrexate, cytarabine, 6 mercaptopurine). Acute clinical symptoms of dysarthria and blurred vision started three weeks later.

Imaging Findings:

T2-weighted and FLAIR MRI sequences show no abnormal findings. Axial diffusion image shows high signal intensity at site of restricted motion of water in the parietal white matter of both hemispheres, in the centrum semiovale. Axial ADC map shows hypointensity at affected sites, which reflects restricted diffusivity.

The MR imaging findings of increased signal intensity on DWI with hypointensity on apparent diffusion coefficient (ADC) map are indicative of cytotoxic oedema. This is consistent with the proposed mechanisms of a direct neurotoxic effect of methotrexate on the cell.

Discussion:

Acute lymphocytic leukaemia (ALL) is more commonly seen in children, methotrexate (MTX) is the mainstay of therapy for ALL given its permeability across the blood-brain barrier. There are different regimens of treatments which include MTX with different doses and types of administration (intrathecal or intravenous) and combined with other chemotherapeutic agents. [1] However, MTX has a significant toxic effect on the CNS and can potentially lead to severe neurologic morbidity. [2] Neurotoxic effects of MTX in CNS cause demyelination, necrosis of white matter, axonal swelling, and atrophy. These effects are more associated when MTX is administrated in high doses, with intrathecal administration, in young patients, and association with radiation therapy. [3, 4] The incidence of MTX neurotoxicity ranges from 3–10%. [3]

The acute neurotoxicity (within 24 hours after administration) consists of nausea, vomiting, drowsiness, confusion and seizures. Subacute (2–14 days after treatment) includes seizures, affective disorders, and the onset of encephalopathy with hypertension and neurological focal defects. Delayed neurotoxicity (months to years after treatment) includes the worsening of cognitive functions and, less often, progressive demyelinating
leukoencephalopathy with limb spasticity, dementia or coma. While acute encephalopathy is characterised by the presence of white matter hyperintensity on T2-weighted MR images (MRI), chronic neurotoxicity also shows ventricular dilatation with cortical atrophy. However, conventional MRI at the time of the neurologic event may show no abnormality. [1]

The presence of leukoencephalopathy, with findings in MRI, has been described in asymptomatic children treated with MTX. The reasons why some children, despite having white matter changes, do not develop neurologic symptoms are unknown. Some studies suggest that there may be a genetic factor. [5]

The pathophysiology of methotrexate neurotoxicity is unclear but several mechanisms have been proposed. The mechanism of action of MTX consists of inhibiting the enzyme dihydrofolate reductase, which causes depletion of folate and, consequently, a cellular incapacity to synthesize DNA and RNA. Vascular abnormalities, folate deficiency, and imbalances of adenosine and homocysteine are involved in direct axonal damage and demyelination.

MRI early shows restriction of diffusion in the white substance due to cytotoxic oedema produced in the cells. Although ADC maps show marked hypointensity associated with permanent injury, the resolution of symptoms suggests that this acute, MTX-induced cellular swelling is not necessarily irreversible. [4]

Various treatment options of questionable efficacy have been described, supportive therapy with corticosteroids, antioxidants [6], aminophylline, an adenosine antagonist, and dextromethorphan. [4] The suspicion of this clinical entity justifies the suspension of treatment with methotrexate to prevent fatal evolution. [7]

**Differential Diagnosis List:** Leukoencephalopathy related with methotrexate, Acute disseminated encephalomyelitis (ADEM), Ischaemic event, Drug abuse encephalopathy, CNS leukaemia

**Final Diagnosis:** Leukoencephalopathy related with methotrexate

**References:**


**Figure 1**

**a**

Description: Axial FLAIR image shows no abnormality. **Origin:** Salvador E, Department of Radiology, Madrid, Spain.

**b**

Description: Axial FLAIR image shows no abnormality. **Origin:** Salvador E, Department of Radiology, Madrid, Spain.
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**Figure 2**

**a**

*Description:* Axial diffusion image shows high signal intensity at site of restricted motion of water in the parietal white matter of both hemispheres. *Origin:* Salvador E, Department of Radiology, Madrid, Spain.

**b**

*Description:* Axial ADC map shows hypointensity areas at affected sites that reflects restricted diffusivity. *Origin:* Salvador E, Department of Radiology, Madrid, Spain.
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