Methotrexate encephalopathy presenting as choreoathetosis

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DESCRIPTION

A 6-year-old boy with B-lineage acute lymphoblastic leukaemia was on intermediate risk Berlin-Frankfurt-Munster 2002 (BFM-2002) chemotherapy protocol. He had favourable response to chemotherapy at the end of induction, as suggested by a negative minimal residual disease. During interim maintenance course of chemotherapy, high-dose methotrexate (HD-MTX) comprising MTX at 5 g/m^2 and intrathecal MTX at 12 mg was administered. Seven days after the first cycle of HD-MTX, the patient was admitted with altered sensorium, irritability and generalised seizures. Central nervous system (CNS) examination did not show signs of meningeal irritation and there were no focal neurological deficits. Fundus evaluation showed grade 1 papilloedema. Contrast-enhanced CT scan was normal. Cerebrospinal fluid (CSF) was normal and did not reveal blasts. The patient was managed with anticonvulsants and anti-raised intracranial pressure measures and he improved in the next 48 hours. He was continued on oral levetiracetam and was subjected to a second cycle of HD-MTX three weeks later.

Ten days after the second cycle of HD-MTX, the patient was admitted with choreoathetoid movements with preserved sensorium (video 1). No other abnormality was noted on CNS examination. Complete blood count and biochemical parameters were normal. CSF was normal and did not reveal blasts. He was managed with oral trihexyphenidyl and clonazepam. Abnormal movements were controlled within 6 hours. MRI of the brain performed after 4 days was suggestive of MTX-induced leucoencephalopathy (figure 1A,B). Trihexyphenidyl and clonazepam were tapered and stopped, while levetiracetam was continued. Serum MTX levels at 36 hours after the start of MTX during cycles 1 and 2 were 1.82 µmol/L and 1.36 µmol/L (normal value <3 µmol/L). He was rechallenged with two more cycles of HD-MTX and did not have any recurrence of symptoms suggestive of MTX-induced encephalopathy.

HD-MTX plays an important role in the curative therapy for haematological malignancies. It is associated with toxicities in 2%–12% of cases.[1] MTX encephalopathy is seen in 0.8% of cases with haematological malignancies and presents within 2 weeks of exposure to MTX (intravenous and/or intrathecal). MTX encephalopathy has varied clinical manifestations and radiological findings. The general clinical manifestations are headache,

Video 1 Choreoathetoid movements with preserved sensorium in the index child.

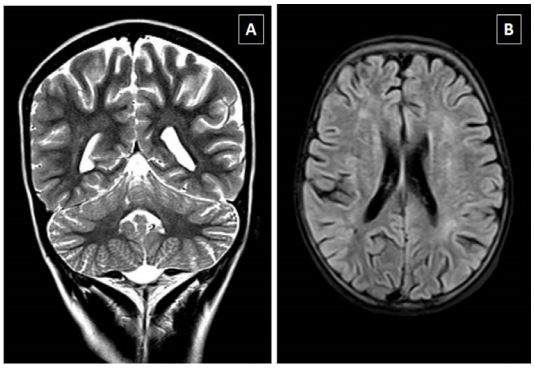

Figure 1 T2-weighted coronal (A)and axial fluid-attenuated inversion recovery (B) images showing ill-defined, irregular, scattered areas of periventricular and deep white matter hyperintensities involving the bilateral cerebral hemispheres, predominantly the peritrigonal regions and the bilateral frontal lobes.

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seizures, disorientation, confusion and focal neurological deficits. Extrapyramidal movements are extremely rare and are due to acute injury or disruption of the basal ganglia or its connections. Waxing-waning symptoms indicate progressive depolarisation of the axonal membranes rather than vascular occlusion. Re-exposure to MTX following episodes of resolved toxicity is generally safe. Classically, it presents with radiological changes in leucoencephalopathy (white matter hyperintensities on T2-weighted image and fluid-attenuated inversion recovery on MRI).[2 3] Although choreoathetoid movements are primarily due to involvement of the striatum, indirect involvement of the cortical, subcortical and thalamic pathway leading to loss of inhibition may explain extrapyramidal manifestations. Frontal cortical pathway involvement was seen in the index child. We diagnosed MTX encephalopathy in the index child based on the temporal association with MTX exposure, recurrent symptoms with MTX exposure, self-limiting nature, characteristic MRI findings and after ruling out other causes.

Learning points

- Methotrexate (MTX) encephalopathy is a rare toxicity associated with high-dose MTX which has varied clinical and radiological manifestations and should be considered in a child with fresh-onset neurological symptoms and MTX exposure within 2 weeks.
- Choreoathetosis is an extremely rare manifestation of MTX encephalopathy.

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