

Methotrexate induced leucoencephalopathy: A stroke mimic

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Abstract

With increasing usage of thrombolysis in the treatment of acute ischemic strokes within 4.5- hour window, it is becoming more important to recognize stroke mimics. Though the incidence of stroke mimics being thrombolysed is less than 3%, it is essential to diagnose them so as to avoid wrong thrombolytic treatment which carries potential complications of bleeding. We describe the case of a 17 year old girl with acute lymphoblastic leukemia, who developed stroke like episodes on two consecutive challenges with a chemotherapeutic regime which included intravenous and intrathecal methotrexate. She had MRI changes consistent with acute ischemic stroke on both occasions. Her deficits recovered completely and spontaneously, as did the MRI changes. She did not have any further episodes when methotrexate was excluded from the chemotherapeutic regime.

Key Words

Leucoencephalopathy, methotrexate, stroke mimic

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Case Report

A 16-year-old girl diagnosed to have acute lymphocytic leukaemia (ALL) was admitted for consolidation phase of chemotherapy. Her previous chemotherapy cycles were uneventful. Nine days after the second cycle of consolidation chemotherapy which included IV-Methotrexate (IV-MTX) and Intrathecal-Methotrexate (IT-MTX) she developed sudden onset of paresthesias over left face and left side of body while watching television in her hospital bed. On trying to move her limbs immediately after these symptoms, she noticed clumsiness in using her left upper limb and weakness in her left lower limb. An urgent neurology referral was made for possible stroke. Her power was grade 4/5 in the left upper limb and 4+/5 in the left lower limb. There was no significant ataxia. The deep tendon reflexes were normal and symmetrical in all four limbs. Plantar reflexes were flexors. The abdominal reflexes were present and bilaterally symmetrical. There was approximately 20% reduction

in pinprick sensations in left half of face. There was no objective sensory sign in the limbs. Due to sudden onset of the symptoms, a clinical impression of sensory motor neurological deficits due to a cerebrovascular event was made and an urgent MRI brain was requested.

MRI Brain was done 3.5 hours after onset of symptoms [Figure 1]. On FLAIR images, a 2 cm × 1.5 cm minimally hyper-intense oval-shape lesion was noted in the right fronto-parietal subcortical region. The lesion showed restricted diffusion on DWI images. MRA was normal [Figure 2a,b]. The lesion was reported as lacunar infarct. The patient was started on antiplatelet agents. Her neurological deficits subsided when she woke up next morning, about 16 hours after their onset.

Carotid and transcranial Doppler study, 2DECHO, ECG were normal. Thrombophilia screens, ANA, dsDNA, lupus anticoagulant were negative. Lipid panel and homocysteine levels were normal. EEG was unremarkable. Antiplatelet agents were continued.

Five days after the above neurologic event, the patient received her third cycle of consolidation chemotherapy also consisting of IV-MTX and IT-MTX. She developed thrombocytopenia secondary to chemotherapy and her antiplatelet agents were stopped. On day 11 of this chemotherapy cycle and 3 days after stopping antiplatelet agents, she had another episode of acute onset of left upper and lower limb numbness and weakness along with numbness over left side of face.

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She woke up with these symptoms which she described to be exactly similar to the first episode. Clinical examination revealed mild weakness in the left upper and lower limb (grade 4+/5). There was no ataxia. The deep tendon reflexes were normal and symmetrical in all 4 limbs, plantars were flexors bilaterally and there was slight reduction in pin prick sensation over left half of her face.

Repeat MRI of the brain [Figure 3] again showed an area of restricted diffusion around the area of the initial lesion. Because of the temporal relation to methotrexate treatment, a clinical diagnosis of methotrexate neurotoxicity was made. This time her neurological deficits resolved within 6 hours. Five days later, MRI of brain was repeated and it showed near complete resolution of the lesions [Figure 4] [For timeline of events see Figure 5].

Discussion

Our patient had 2 clinical events which were consistent with sensory-motor lacunar syndrome. She also had definite MRI lesions consistent with an acute infarct.

Stroke is the commonest but not the only cause of restricted diffusion on MRI. Restricted diffusion can occur in any setting of cytotoxic edema. Bacterial abscesses, certain epidermoid tumors, central portions of some primary and secondary brain tumors (as they outgrow their blood supply and become ischemic), an acute MS plaque may exhibit restriction diffusion. Differential diagnoses of cortical diffusion restriction include venous infarct, viral encephalitis, meningitis, CJD, mitochondrial cytopathies and postictal state.^[1]

A transient or a delayed-reversible methotrexate leucoencephalopathy mimicking cerebrovascular accident has been described as a complication of chemotherapy, most commonly in recipients of intrathecal methotrexate for childhood leukaemia.^[2,3] Our patient presented with hemiparesis and sensory symptoms which were attributed to the involvement of corticospinal tract and the third order sensory fibres in the corona radiata. The temporal relation of symptoms to administration of MTX was reproduced on consecutive exposures and the lesion recurred at the same place.

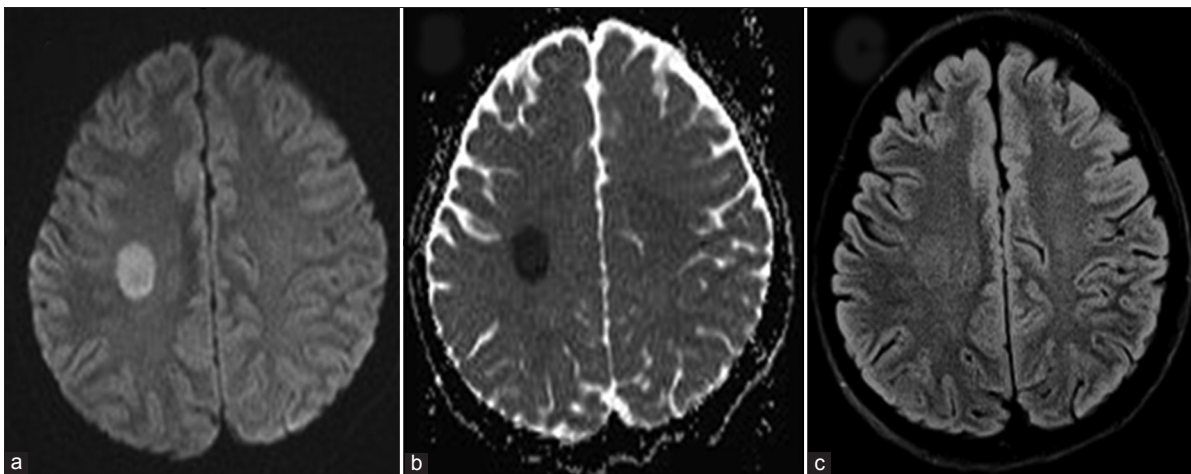


Figure 1: MRI scan after the first onset of symptoms. (a) Diffusion weighted MRI image showing an area of restricted diffusion in the right fronto-parietal subcortical white matter. (b) The area of restricted diffusion is hypointense on ADC map. (c) FLAIR image showed minimal hyperintensity in the same region



Figure 2 (a-b): Normal MR angiogram

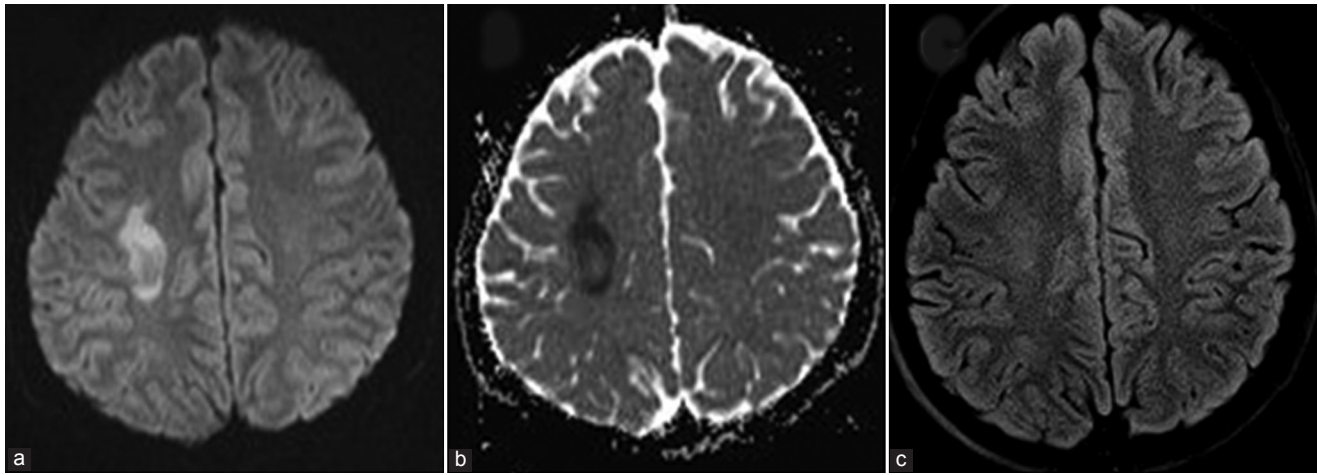


Figure 3: Repeat MRI after recurrence of symptoms. (a) Diffusion weighted image showing restricted diffusion in the fronto-parietal subcortex surrounding the area of initial insult seen in Figure 1. (b) The area of restricted diffusion was hypointense on ADC map. (c) FLAIR image showed minimal hyperintensity

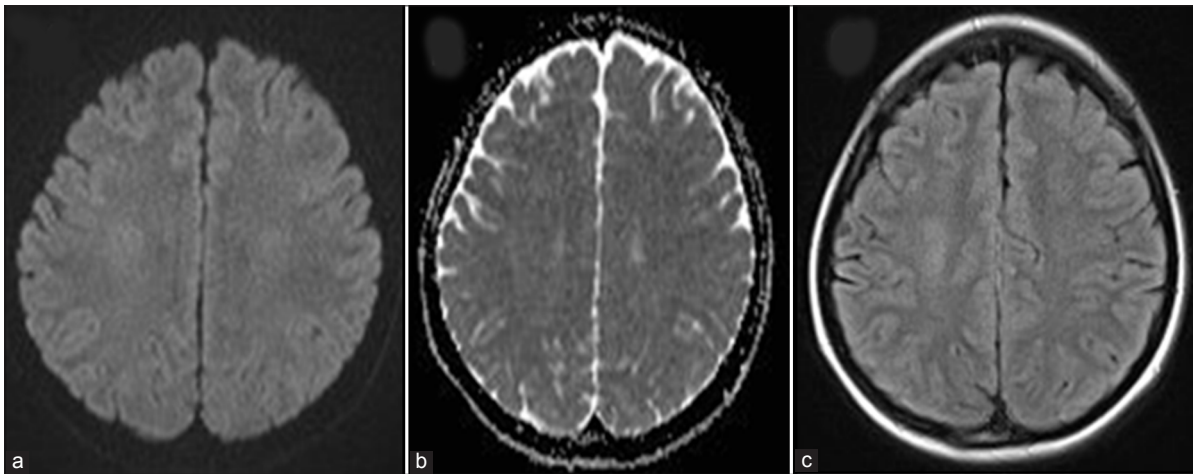


Figure 4: Repeat MRI after resolution of neurologic deficits and 5 days after MRI shown in Figure 2. DWI (a) ADC. (b) and FLAIR (c) images show near complete resolution of lesions

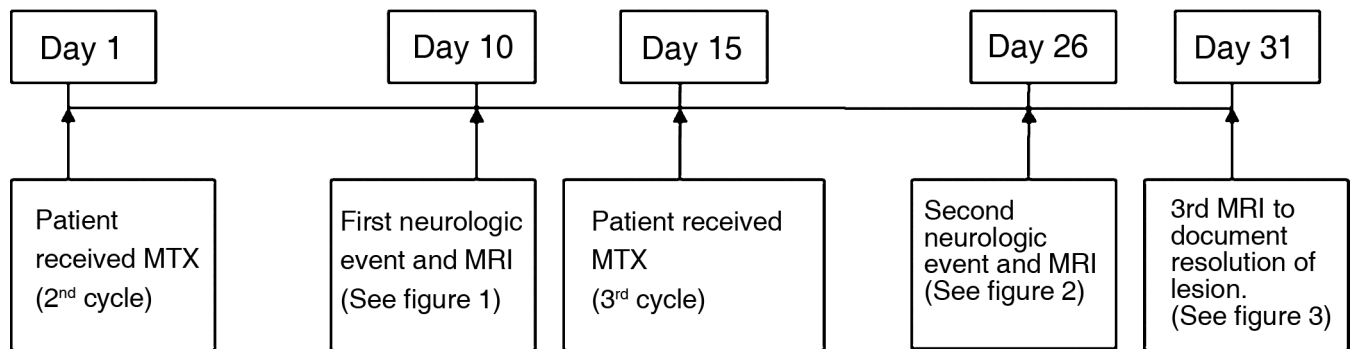


Figure 5: Summary of timeline of events

In methotrexate-induced leucoencephalopathies, the exact histologic and pathophysiologic correlate of the lesion with diffusion restriction is unknown. In previous reports, a reversible metabolic encephalopathy leading to cytotoxic edema in cerebral white matter was postulated.^[2] Other hypothesis included focal demyelination, microinfarctions

and direct toxic effects to the CNS by damaging the neuronal tissue.^[4] In animal studies, an intraventricular infusion of toxic metabolites of chemotherapeutic agents was shown to cause myelin swelling and vacuolation in an early, possibly reversible stage. These were followed by fragmentation, granularity and myelin loss in the later, possibly partially

reversible or irreversible, stage.^[5] Whether this could be extrapolated to methotrexate leucoencephalopathy needs further investigations. Polymorphisms in the enzyme 5, 10-methylene tetrahydrofolate reductase may predispose an individual to leucoencephalopathy following methotrexate exposure,^[6] which might partly explain why only a few patients exposed to methotrexate develop leucoencephalopathy.

On the first occasion our patient developed symptoms 9 days after completion of her methotrexate dose, while the second episode occurred 11 days after the methotrexate. Previous studies have reported a variable time of onset of clinical features ranging from 6 hours to 11 days after administration of chemotherapy.^[2] The mechanism as to why the clinical onset is delayed and variable after the initial exposure is still unknown. Interestingly, in our patient, the focal diffusion abnormality recurred at the same site on both occasions. Why particularly this area of the brain was predisposed remains an unanswered.

Our patient had spontaneous clinical and radiological resolution of the neurotoxicity. However, the standard treatment for methotrexate-induced encephalopathy remains supportive and includes 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.^[7,8]

Conclusion

A clinical and radiological stroke like episode can be a presentation of MTX neurotoxicity. A high index of suspicion

should be kept in an appropriate clinical setting to avoid unwarranted antiplatelet or thrombolytic therapy in this stroke mimic.

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