Hemiparesis and aphasia in a child with acute lymphoblastic leukemia

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Clinical Description

A 13-year-old child was presented with acute onset of left-sided hemiparesis progressing rapidly to hemiplegia and aphasia over 3 hours. She had been diagnosed with acute lymphoblastic leukemia and was started on induction chemotherapy with intrathecal methotrexate (MTX) 5 days before the episode. An emergent computed tomography scan of the brain was normal. This was followed by magnetic resonance imaging (MRI) which revealed restricted diffusion in bilateral periventricular white matter, particularly in the centrum semiovale, on diffusion-weighted images (DWI) [Figure 1a] with no corresponding abnormality on fluid-attenuated inversion recovery (FLAIR) [Figure 1b]. The T1 [Figure 2a] and T2 [Figure 2b] images were normal. Contrast-enhanced MR angiography was normal. In keeping with the clinical presentation and the DWI abnormalities, a diagnosis of MTX-induced transient acute neurotoxicity was considered. Over the next few days while there was improvement on the affected side, she developed contralateral (right-sided) weakness. The symptoms waned soon and complete resolution was seen by the seventh day. A repeat MRI showed "new" hyperintensities on the FLAIR [Figure 3a] with resolution of the DWI abnormalities [Figure 3b]. The corresponding areas showed subtle hypointensities on the T1-weighted image [Figure 4a] and appeared hyperintense on T2-weighted image [Figure 4b]. Subsequently she received full course of chemotherapy and is on follow-up since then with no residual neurological deficits or impairment.

Discussion

Neurological manifestations in patients with leukemia may be due to nervous system involvement or complications of treatment. Treatment-related neurotoxicity can in turn be due to chemotherapeutic agents, radiation therapy, or bone marrow transplantation. Methotrexate is frequently responsible for chemotherapy-induced acute neurotoxicity, which is observed in about 0.8% patients within 2 weeks of initiating high-dose intravenous or intrathecal MTX.[1] Hemiparesis (at times alternating) and aphasia are the commonest presenting symptoms, although headache, gait disturbance, bilateral weakness, emotional lability, and choreoathetoid movements may sometimes be the only manifestations. Similar signs and symptoms can also been seen in posterior reversible encephalopathy and stroke, which are in fact the commonest treatment-related neurological complications in leukemic patients.[2] The diagnosis and further management in patients with suspicious toxicity is thus largely dependent on accurate interpretation of neuroimaging studies. MTX-induced neurotoxicity, although infrequently seen, has characteristic imaging findings which a neurologist needs to be aware of. This also has prognostic implications because most patients with transient MTX-induced neurotoxicity will resume full function and do not show residual neurological deficits.[1] In a classical case the computed tomography is noncontributory and the diagnosis is rendered on MRI. At presentation restricted diffusion is seen in the deep cerebral white matter particularly as shown in our case. The MR findings are not always consistent with the clinical picture, and FLAIR, T2, and T1 images are unremarkable at this stage. Resolution of symptoms is associated with disappearance of DWI abnormalities and appearance of subtle T2 and FLAIR hyperintensities on the follow-up MRI study, which normalize over a variable duration of time.[3] Facilitated diffusion may be seen in some patients at this stage or later. In the relevant clinical setting, these imaging findings are pathognomic and unique to MTX-induced acute neurotoxicity. The imaging appearance of posterior reversible encephalopathy is distinctly different from MTX-induced acute neurotoxicity and is characterized by cortical and subcortical symmetric hyperintensities on T2-weighted and FLAIR images predominantly in the posterior parietal and occipital lobes. On the other hand, at presentation the T2-weighted and FLAIR images are often normal in MTX-induced neurotoxicity as shown.

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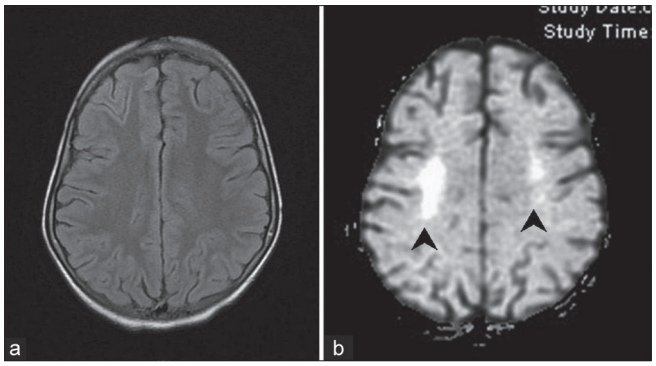

Figure 1: FLAIR- (a) and diffusion-weighted image (b) from the initial study shows areas of restricted diffusion in the deep white matter in the region of centrum semiovale (arrowheads). The corresponding areas on the FLAIR image are normal

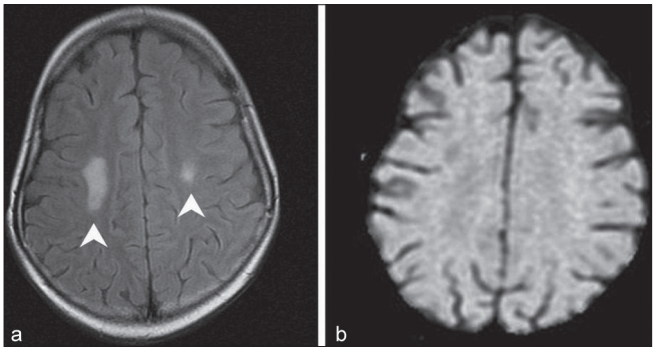

Figure 3: FLAIR- (a) and diffusion-weighted image (b) from the follow-up study shows appearance of hyperintensities in the region of the centrum semiovale (arrowheads in a) and resolution of restricted diffusion seen in the earlier study in Figure 1

The onset of symptoms is typically within 2 weeks of initiating intrathecal MTX, and symptoms often progress over minutes to hours. Complete resolution of symptoms seen in about a week in most patients and residual neurological impairment are unusual.[1] The pathogenetic event in the development of MTX-induced transient neurotoxicity is believed to be due to MTX-induced adenosine release, high levels of which dilate blood vessels alter neurotransmitter release and retard the neuronal discharge rate. This explains the rationale behind the universal use of aminophylline in the treatment, which acts by displacing adenosine from the receptors.[4]

Conclusions

MTX toxicity is an important differential in leukemic patients presenting with neurologic symptoms following initiation of treatment. DWI abnormalities in the deep white matter with no abnormality on FLAIR images at presentation and a reversal, that is, appearance of FLAIR hyperintensities and normalization of DW images coincident with clinical improvement, are pathognomic for MTX-induced transient acute neurotoxicity. Knowledge of these findings can thus be invaluable to the diagnosis, management, and prognostication of such patients.

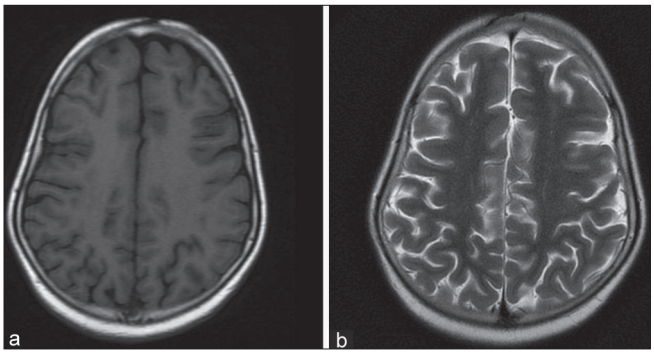

Figure 2: T1- (a) and T2-weighted images (b) at presentation are unremarkable

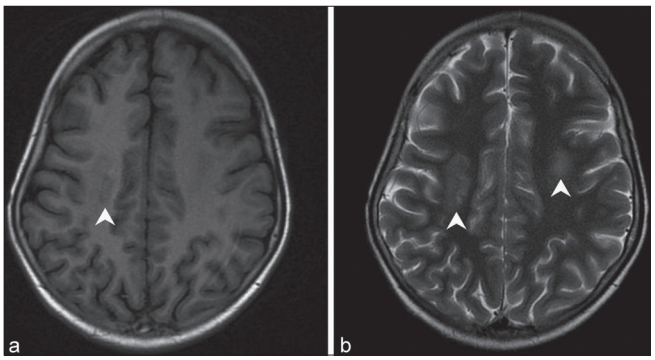

Figure 4: T1- (a) and T2-weighted images (b) from the follow-up study show subtle hypointensities (arrowhead in a) on the T1-weighted image with areas of hyperintensity of T2-weighted image (b)

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