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Acute Methotrexate Neurotoxicity: Findings on Diffusion-Weighted Imaging and Correlation with Clinical Outcome

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BACKGROUND AND PURPOSE: **Acute lymphocytic leukemia (ALL) is a common malignancy of childhood treated with methotrexate (MTX), which is associated with acute neurotoxicity. We evaluated diffusion-weighted (DW) and conventional MR images in children with ALL and acute MTX-induced neurotoxicity, with clinical correlation.**

METHODS: **Five patients aged 12–15 years underwent fluid-attenuated inversion recovery (FLAIR), T2-weighted fast spin-echo and gradient-echo, T1-weighted gadolinium-enhanced spin-echo, and DW imaging within 24 hours of symptom onset. Records were reviewed for the temporal relationship to MTX administration, strokelike symptoms, and neurologic outcome.**

RESULTS: **Six strokelike events were temporally related to intrathecal MTX given 6–11 days before symptom onset. FLAIR images showed abnormal hyperintensity in the callosal splenium in one patient but were otherwise normal. Diffusion abnormalities were frontoparietal in three events and frontal in one; nonfluent aphasia was seen in all. Bilateral frontoparietal diffusion abnormalities were associated with bilateral upper-extremity weakness, right-sided hemiparesis, or left-sided hemiparesis (one patient each); one patient had mild facial droop. Unilateral precentral subcortical diffusion abnormality was associated with contralateral motor deficit and ipsilateral upper-extremity sensory loss. Strokelike symptoms resolved rapidly and were not associated with other signs of encephalopathy. Subsequent intrathecal MTX administration was not associated with recurrence in four patients.**

CONCLUSION: **Diffusion abnormalities in acute MTX neurotoxicity indicated cerebral dysfunction but not necessarily overt structural injury to the cerebrum. Subsequent demyelination or gliosis could not be predicted on the basis of diffusion abnormalities. A single strokelike episode with diffusion abnormalities should not necessarily prompt modification of potentially curative chemotherapeutic regimens.**

Acute lymphocytic leukemia (ALL) is one of the most common malignancies of childhood with an incidence of four cases per 100,000 population (1). Chemotherapeutic regimens include methotrexate (MTX), as MTX crosses the blood-brain barrier and can be administered intravenously and via an intrathecal route to eradicate leukemic cells from the CNS and prevent CNS recurrence (2). Although multiple drugs are used in addition to MTX, the acute neurotoxicity reported in patients with ALL undergoing therapy is usually attributed to MTX. Acute MTX neurotoxicity usually results in strokelike symptoms, such as aphasia, weakness, sensory deficits, ataxia, and seizures (1, 2). MR imaging with diffusion-weighted (DW) imaging is widely available and used in routine clinical practice to identify acute stroke and to differentiate nonstroke conditions from ischemia.

The purpose of our study was to evaluate abnormalities on DW and routine MR images in five children with acute MTX neurotoxicity and to correlate the onset of acute neurotoxicity with the mode and frequency of MTX administration, diffusion abnormalities with neurologic problems, and long-term follow-up findings.

Methods

Since 1999, 194 children presented to our institution with ALL. Five had acute MTX neurotoxicity with signs or symptoms of sufficient severity and duration that the pediatric oncologist requested MR imaging. No clinically asymptomatic patients underwent MR imaging. Follow-up MR studies were

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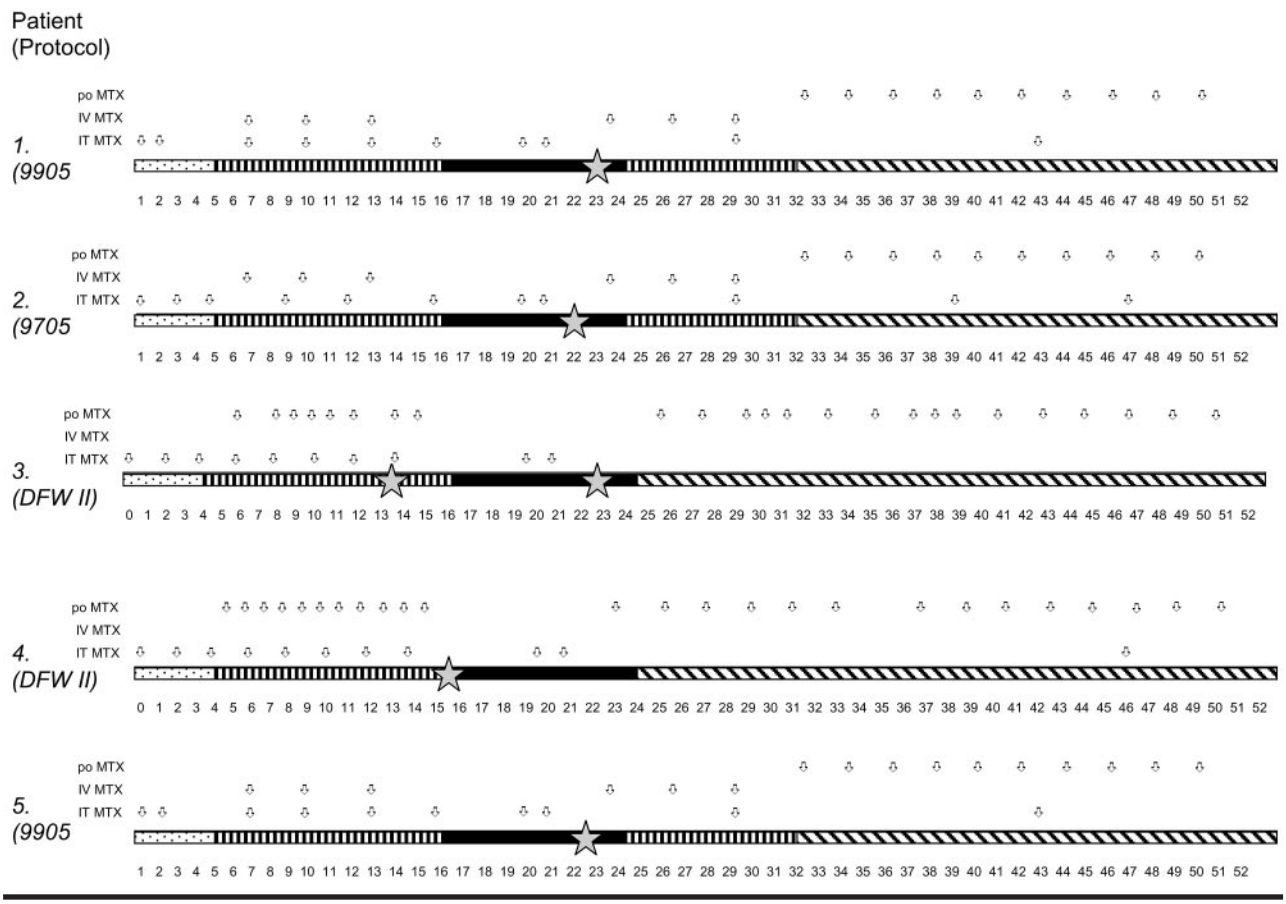
TABLE 1: Route and frequency of MTX



IT indicates intrathecal; *IV*, intravenous; *po*, oral; ☆, time of neurologic event.

usually obtained for non-clinical investigational purposes, in which case informed consent was obtained. Patients ranged in age from 12 to 15 years, and their high-risk pre-B cell ALL had been diagnosed at our institution.

Three patients were classified as having CNS I disease with no CSF lymphoblasts, and two, CNS II with <5 WBCs with lymphoblasts in the CSF. Two patients were being treated according to the Pediatric Oncology Group (POG) protocol 9905: One was enrolled in POG protocol 9705, and two were enrolled in our in-house protocol DFW2 (3). During induction, which lasted for 4 weeks, the patients received dexamethasone, vincristine, asparaginase, and intrathecal therapy that included MTX. Two patients also received daunorubicin. Intrathecal MTX, oral 6-mercaptopurine (6-MP), and vincristine–dexamethasone pulses. Consolidation therapy at weeks 5–15 included intravenous MTX with leucovorin rescue in three patients. The other two patients received divided-dose oral MTX with leucovorin rescue, intrathecal MTX, cytocine arabinoside (Ara-C), hydrocortisone, and oral 6-MP. Four patients received delayed intensification, which began at week 16 with vincristine, dexamethasone, asparaginase, daunorubicin, and intrathecal MTX followed by cyclophosphamide, Ara-C, thioguanine, and intrathecal MTX.

MR imaging was done within 17–23 hours of the onset of strokelike symptoms by using a 1.5-T system. Sequences included the following: pre-enhancement and post-enhancement imaging, T1-weighted spin-echo imaging in the sagittal and axial planes, axial fluid-attenuated inversion recovery (FLAIR; TR/TE/TI, 8000/20/2300) imaging, axial or coronal T2-weighted gradient-echo (TR/TE, 700/50; flip angle, 20°) imaging, axial or coronal T2-weighted turbo spin-echo imaging, and composite isotropic DW imaging ($b = 0$ and 1000 s/mm^2) with the use of apparent diffusion coefficient (ADC) maps in three patients. Axial 3D time-of-flight MR angiography was also acquired from the skull base through the Sylvian fissures.

Medical records were reviewed for the mode of MTX administration; the temporal relationship to MTX administration; the type, duration, and severity of strokelike symptoms; and the long-term neurologic outcomes.

Results

Review of the medical records showed that four of the five patients had no other medical problems, while the fifth patient had steroid-induced insulin-dependent diabetes mellitus (IDDM) that appeared early in induction. Four patients had a single strokelike episode that did not recur with subsequent MTX administration, while the patient with IDDM had a second strokelike event. The six strokelike events in five patients occurred 13, 15, 22, 22, 22, and 23 weeks into therapy. Four patients were in the consolidation limb of chemotherapy, and one was in the delayed-intensification limb (Fig 1).

The earliest strokelike event occurred in the patient with steroid-induced IDDM, while the next-earliest event occurred 2 weeks later in a patient with no other medical problems. Both patients were being treated according to in-house protocol DFW2. This

TABLE 2: MR findings in acute MTX neurotoxicity

Patient/Age	Symptoms	Site of Restricted Diffusion	Interval to Next MR Study	T2 Abnormalities on Next MR Study	Clinical Follow-Up (mo)
1/15/F	Aphasia, bilateral arm weakness R < L	Bilateral posterior centrum semiovale	13 mo	Minimal involvement of R cenetrum semiovale	25
2/14/M	Aphasia, L upper-extremity weakness	Bilateral posterior centrum semiovale	6 wk	Asymmetric involvement of centrum semiovale R > L	9
3/15/F					
Initial	Aphasia, R-sided weakness	Bilateral posterior centrum semiovale	8 wk	Bilateral centrum semiovale	42
Recurrence	Recurrence of aphasia, L hemiparesis, and focal seizure 8 wk later	R parietal cortex and white matter	28 mo	Progressive involvement of centrum semiovale, normal cortex	
4/14/M	Aphasia, fluctuating bilateral hemiparesis, L facial droop	Bilateral asymmetric anterior centrum semiovale	39 mo	Minimal scattered involvement of bilateral centrum semiovale	49
5/12/F	Aphasia, R-sided weakness, mild R facial droop	L precentral subcortical white matter	13 mo	Minimal scattered involvement of bilateral centrum semiovale	23

protocol entailed intrathecal MTX administration during consolidation that was more frequent than that of the other chemotherapeutic protocols (Table 1). The strokelike events were temporally related to intrathecal MTX therapy. Four events occurred within 6–11 days after two sequential, weekly intrathecal administrations of MTX. One event occurred after seven biweekly intrathecal doses of MTX, and one was after eight biweekly doses. There was no temporal relationship to intravenous or oral MTX administration. Three patients had a single strokelike event that resolved completely within 36 hours, while one had recurrent, transient, unilateral upper-extremity numbness 6 days after the initial presentation with acute neurotoxicity. The patients with a single strokelike episode continued with chemotherapy, as dictated by protocol. Subsequent intrathecal MTX was not associated with recurrence or exacerbation of the strokelike symptoms in four patients. The patient with steroid-induced IDDM experienced a recurrent strokelike event after two weekly doses of intrathecal MTX, which was discontinued after the second event. The patient subsequently underwent prophylactic cranial irradiation. No patient had any observable effect on cognition or school performance, as they or their families reported, and no patient had any observable residual neurologic deficits or seizures. All patients remained in complete remission.

At initial presentation, FLAIR images showed mild, diffuse cerebral atrophy in five patients. Four had no regions of abnormal T2 signal intensity, while the patient with IDDM had mildly increased T2 signal intensity in the callosal splenium. T2-weighted gradient-echo images and 3D MR angiograms were consistently normal. No pathologic enhancement was observed in any patient.

Aphasia was noted in every strokelike event. In four of six events, DW images showed restricted diffusion in the deep cerebral white matter that was frontoparietal in three events and frontal in one (Table 2). Bilateral frontoparietal diffusion abnormalities were associated with bilateral upper-extremity weakness, right-sided hemiparesis, and left-sided hemiparesis in one patient each. One patient also had a mild facial droop.

Follow-up MR imaging was done at 13 months in two patients, and at 6 weeks, 8 weeks, and 39 months in one patient each. Four of 5 patients had normal neurological findings at the time of the next MR study. One patient had minimal abnormal T2 signal intensity in the right posterior centrum semiovale that corresponded in location to the diffusion abnormality but was considerably smaller, while the diffusion abnormality in the contralateral cerebral white matter had no corresponding area of abnormal T2 signal intensity (Fig 1). The second patient had had fairly symmetric diffusion abnormalities in the cerebral white matter. Follow-up MR imaging showed asymmetric abnormal T2 signal intensity in the white matter (Fig 2). The third patient underwent repeat MR imaging 8 weeks later, when she presented with a second strokelike event. DW imaging showed re-

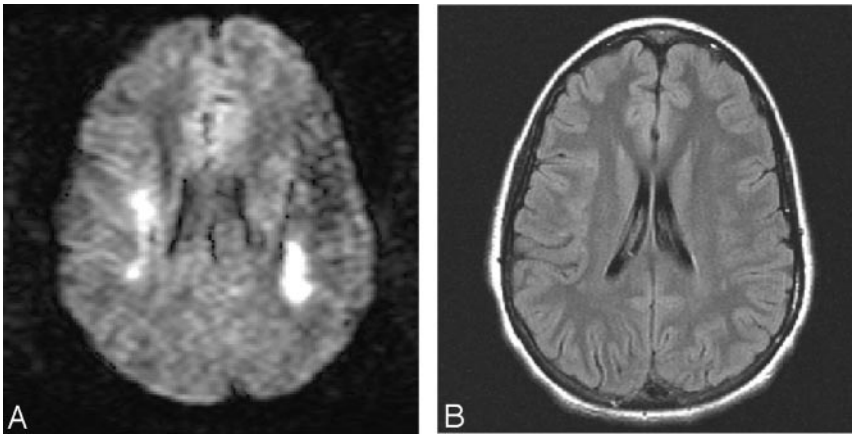


FIG 1. Patient 1 presented with nonfluent aphasia and bilateral upper-extremity weakness.

A, Axial DW image is limited by motion artifact. Areas of restricted diffusion in the centrum semiovale account for the arm weakness. Nonfluent aphasia may be subcortical.

B, Axial FLAIR image obtained 39 months later shows minimal abnormal T2 signal intensity consistent with demyelination. There are no residual neurologic deficits.

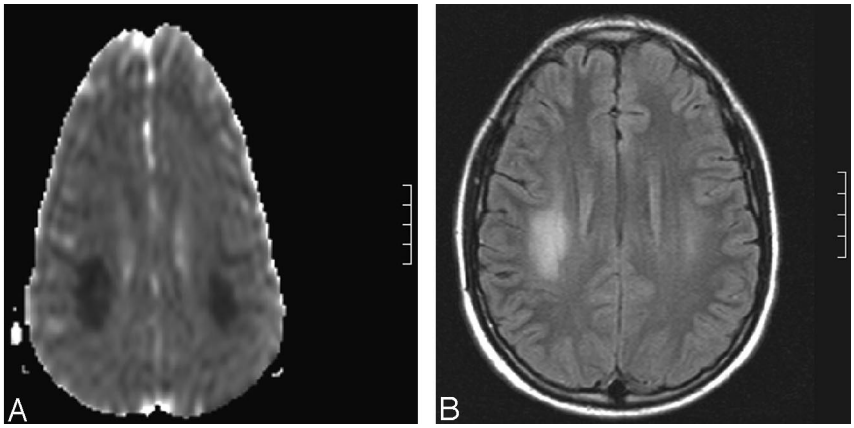


FIG 2. Patient 2 presented with nonfluent aphasia and left-sided hemiparesis and hemisensory loss.

A, Axial ADC map shows asymmetric areas of restricted diffusion in the centrum semiovale. Image distortion is due to orthodontia. Right-sided lesion is correlated with left-sided hemiparesis, whereas the left-sided white matter lesion was not accompanied by a motor deficit.

B, Axial FLAIR image obtained 8 weeks later shows large, confluent areas of presumed demyelination in the right centrum semiovale similar in size to the DW abnormality. Left cerebral white matter lesion that was clinically unapparent at presentation is smaller than the white matter lesion associated with neurologic deficit at presentation. Neurologic deficits had resolved.

stricted diffusion in the right parietal cortex and regional white matter that had not been present on the initial MR study. Strokelike symptoms during this event included left hemiparesis and focal seizure activity in addition to aphasia. The maximal blood pressure recorded was 145/90 mm Hg, while the patient's baseline blood pressure was 116/72 mm Hg. MR images showed no residual diffusion abnormalities in the centrum semiovale; extensive abnormal T2 signal intensity in the centrum semiovale corresponding to the diffusion abnormalities were seen on initial MR images. A subsequent MR imaging study in this patient done 28 months later, when she was asymptomatic, showed more-extensive abnormal T2 signal intensity in the deep cerebral white matter, while the area of restricted diffusion in the right parietal region showed no signal-intensity abnormalities (Fig 3).

One patient had asymmetric diffusion abnormalities in the bifrontal white matter at presentation. Symptoms included fluctuating bilateral hemiparesis and left facial palsy. A follow-up MR imaging study done at 39 months, when the patient was asymptomatic, showed minimal T2 signal intensity in the right frontal white matter that again corresponded to the diffusion abnormality in location but was smaller, while the left frontal white matter was essentially normal (Fig 4). The final patient had restricted diffusion in the left precentral subcortical white matter at presentation, with right hemiparesis, mild right facial palsy, and left-arm sensory deficits. A follow-up MR imaging study at 13 months showed patchy signal-intensity abnormalities in the bilateral white matter that did not correspond to the diffusion abnormality seen at presentation (Fig 5). The patient was neurologically intact at follow-up.

Four patients had no cerebral atrophy at follow-up, while the patient with IDDM who subsequently underwent cranial irradiation had mild, diffuse cerebral atrophy. The reversible, mild cerebral atrophy seen in four patients was presumed to be due to the high-dose exogenous steroids given during induction and consolidation.

Discussion

MTX is a cell cycle-specific agent that inhibits the enzyme dihydrofolate reductase, preventing the conversion of folic acid to tetrahydrofolic acid and inhibiting cell replication (3, 4). Both high-dose intravenous MTX and intrathecal MTX are associated with demyelination, white matter necrosis, loss of oligodendroglia, axonal swelling, microcystic encephalomalacia, and atrophy relatively selective for the deep cerebral white matter (5, 6). A diminished choline-to-creatine ratio has been reported in children with MTX-related neurotoxicity; this may be related to disturbances of myelin metabolism or inhibition of glucose metabolism, as seen on PET, induced by

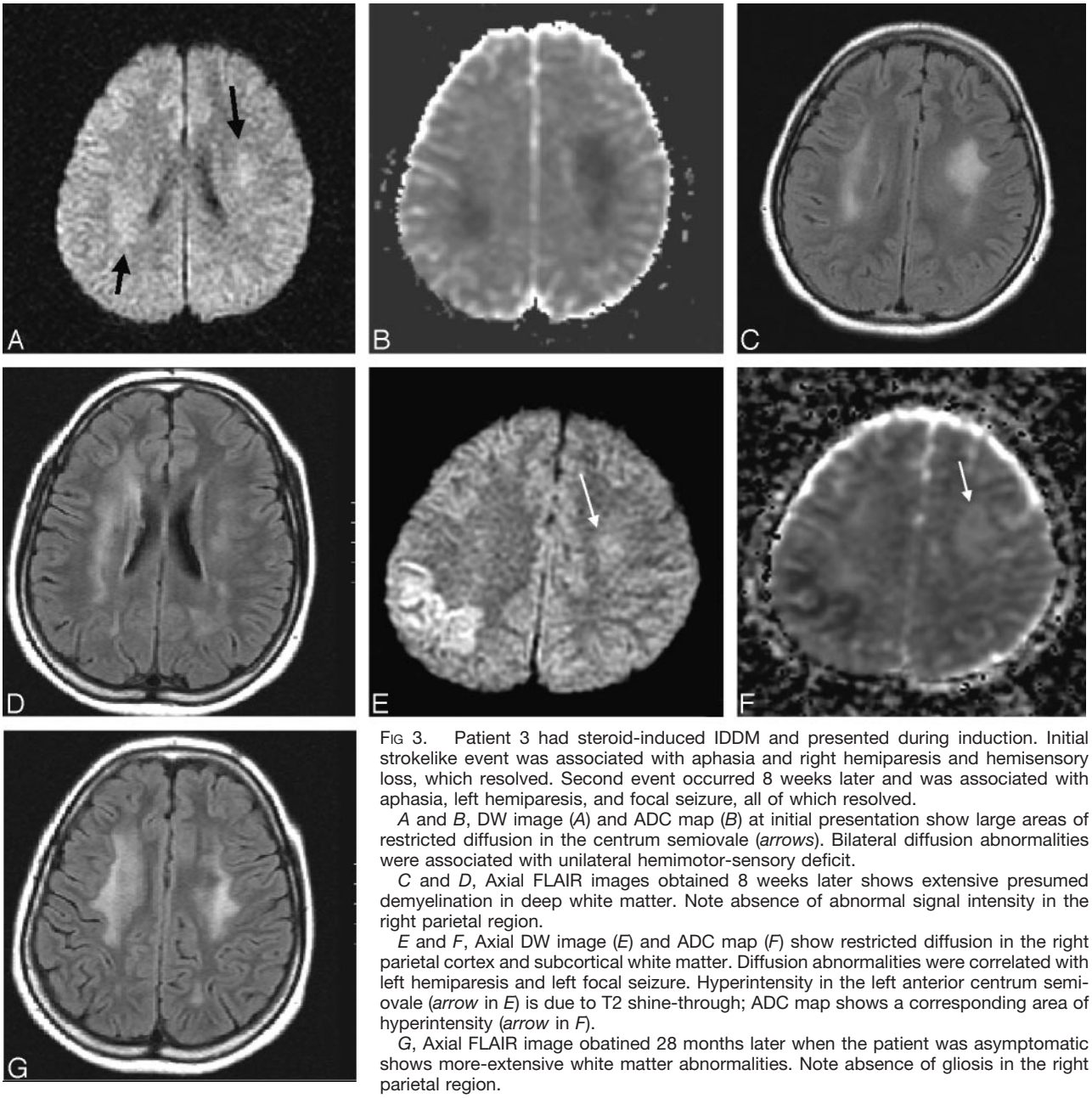


FIG 3. Patient 3 had steroid-induced IDDM and presented during induction. Initial strokelike event was associated with aphasia and right hemiparesis and hemisensory loss, which resolved. Second event occurred 8 weeks later and was associated with aphasia, left hemiparesis, and focal seizure, all of which resolved.

A and *B*, DW image (*A*) and ADC map (*B*) at initial presentation show large areas of restricted diffusion in the centrum semiovale (*arrows*). Bilateral diffusion abnormalities were associated with unilateral hemimotor-sensory deficit.

C and *D*, Axial FLAIR images obtained 8 weeks later shows extensive presumed demyelination in deep white matter. Note absence of abnormal signal intensity in the right parietal region.

E and *F*, Axial DW image (*E*) and ADC map (*F*) show restricted diffusion in the right parietal cortex and subcortical white matter. Diffusion abnormalities were correlated with left hemiparesis and left focal seizure. Hyperintensity in the left anterior centrum semiovale (*arrow* in *E*) is due to T2 shine-through; ADC map shows a corresponding area of hyperintensity (*arrow* in *F*).

G, Axial FLAIR image obatined 28 months later when the patient was asymptomatic shows more-extensive white matter abnormalities. Note absence of gliosis in the right parietal region.

MTX (7, 8). MTX also causes a relative excess of homocysteine, a byproduct of the folate deficiency, which is thought to induce small-vessel vasculopathy (9). The small-vessel disease presumably accounts for the decreased cerebral perfusion described in an animal model (10), the cortical perfusion defects documented in children with ALL previously treated with MTX (11), and the white matter diffusion abnormalities seen in patients receiving intrathecal MTX. However, a prospective study of homocysteine concentrations in CSF and plasma in children with ALL receiving high-dose intravenous MTX did not demonstrate a significant relationship between transiently elevated homocysteine concentrations after MTX treatment and the presence of symptoms of acute neurotoxicity (9).

DW imaging is sensitive to hyperacute cerebral ischemia (12, 13). Hyperacute cerebral ischemia results in diminished random water motion, which is seen on DW imaging as regions of high signal intensity and on ADC maps as diminished signal intensity (12). Animal studies in which the onset of cerebral ischemia was controlled have shown that restricted diffusion can be seen within minutes and hours, before conventional T2 images are abnormal (12). DW abnormalities are usually indicative of irreversible cytotoxic injury (14). However, lesions identifiable on DW imaging that are not associated with T2 abnormalities and that resolve have been reported in patients with sustained seizure activity and in some patients with thromboembolic events who underwent rapid thrombolytic therapy (12, 15). Acute neurotox-

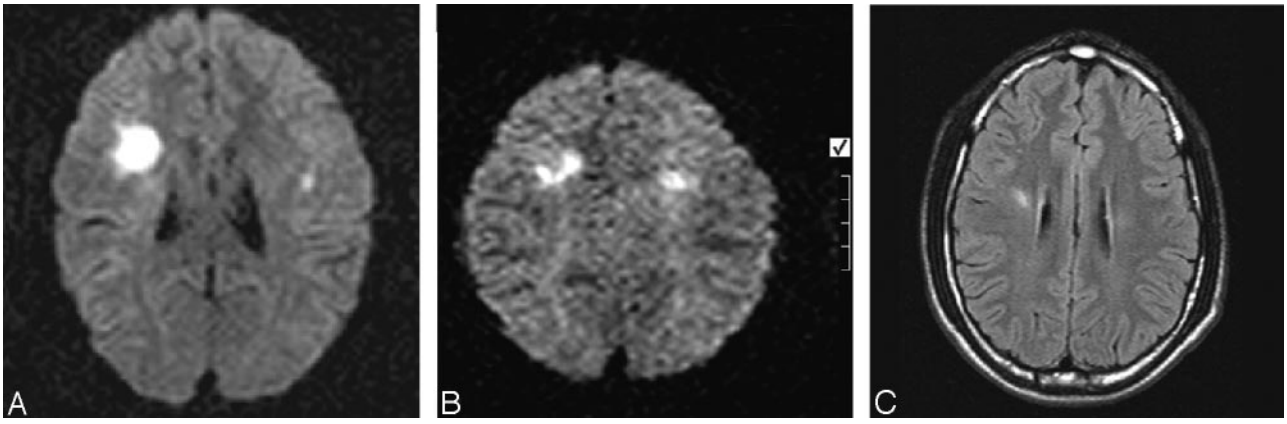


FIG 4. Patient 4 presented with nonfluent aphasia and alternating fluctuating hemiparesis and left facial droop.
A and *B*, Axial DW images show asymmetric regions of restricted diffusion in the anterior centrum semiovale that do not explain the motor neurologic deficits.
C, Follow-up MR image obtained 39 months later shows minimal scattered demyelination. The patient was neurologically intact.

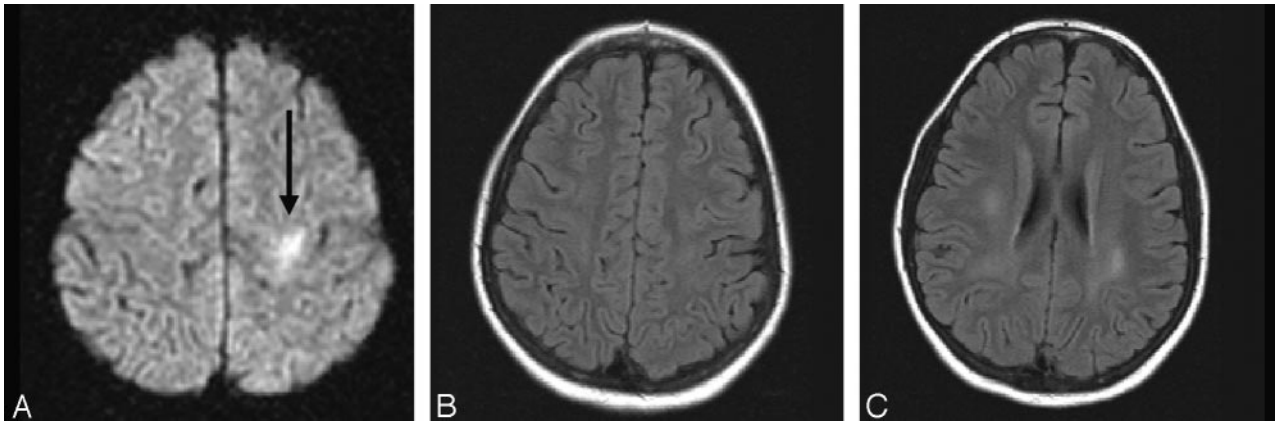


FIG 5. Patient 5 presented with nonfluent aphasia, mild right facial weakness, right hemiparesis, and left-arm sensory deficit.
A, DW image shows a small area of restricted diffusion with the left precentral region (*arrow*) that does not fully explain the neurologic deficits.
B, Axial FLAIR image obtained 13 months later shows no signal-intensity abnormality in the left precentral region.
C, Image shows small areas of presumed demyelination in the centrum semiovale. The patient was neurologically intact.

icity associated with intrathecal MTX is another clinical entity in which diffusion abnormalities are not necessarily associated with irreversible cell death.

The incidence of acute MTX neurotoxicity ranges from 3–10% (1, 2, 4) and varies with the dose and route of administration of MTX, the frequency with which MTX is given, and the use of leucovorin (1, 2, 4). The time from induction to the onset of acute neurotoxicity varies from 2 to 127 weeks (2). However, the temporal relationship between acute neurotoxicity and intrathecal administration of MTX is fairly predictable, as acute neurotoxicity is most often seen 10–11 days after intrathecal MTX administration (1, 2, 4). There is a poor correlation between white matter abnormalities as seen on conventional MR imaging in children with ALL and clinical neurologic deficits (16, 17). Conventional MR imaging has shown areas of T2 prolongation in 15–75% of the patients imaged during chemotherapy, usually within the deep cerebral white matter; these are not consistently associated with neurologic deficits (2). Transient T2 prolongation in the cerebellar white matter and cerebral cortex has also been described (17, 18). White matter lesions observed on conventional MR imaging are known to be temporary and reversible in some patients; however, as illustrated in our patients, progressive and persistent white matter changes may be seen in the absence of symptomatic neurotoxicity.

Ours is not the initial report of acute neurotoxicity studied with DW imaging. Sandoval et al (19) reported a 13-year-old female patient with acute MTX-induced neurotoxicity that occurred during the consolidation phase for pre–B cell ALL. She underwent DW imaging and follow-up MR imaging: Initial T2 images were normal, the DW images showed restricted diffusion within the white matter, and subsequent MR imaging showed white matter abnormalities that corresponded to the areas of restricted diffusion (19).

We report five additional patients, adolescents with acute neurotoxicity temporally related to intrathecal MTX that most often occurred 22–23 weeks into chemotherapy for pre–B cell ALL. DW imaging showed restricted diffusion limited to the white mat-

ter in five of six events and involving the cortex in one. The diffusion abnormalities were not consistently correlated with neurologic deficits. Bilateral frontoparietal diffusion abnormalities seen in three events were associated with bilateral upper-extremity weakness, right-sided hemiparesis, and left-sided hemiparesis in one event each, while one patient also had a mild facial droop. A unilateral subcortical diffusion abnormality observed in one patient was associated with contralateral hemiplegia and ipsilateral arm weakness. The nonfluent aphasia seen in all six strokelike events appears to have been loosely defined, as detailed bedside neurologic testing was not performed during the short-lived events. The transient nonfluent aphasia may have been subcortical aphasia, defined as lesion localization in the basal ganglia or deep white matter (20); the language characteristics of subcortical aphasia are reportedly atypical and may be difficult to characterize (20).

The strokelike symptoms resolved completely within 24–36 hours and were not associated with other signs of encephalopathy. However, no formal neurologic testing was done at follow-up, and subtle neurologic residua might have been missed on cursory examination. Follow-up MR imaging showed variable abnormal T2 signal intensity in the deep white matter, which was presumed to represent demyelination that did not consistently conform to the white matter that was previously abnormal on DW imaging. Therefore, diffusion abnormalities in acute MTX neurotoxicity appear to indicate cerebral dysfunction but not necessarily overt structural injury to the cerebrum, and the subsequent appearance of demyelination or gliosis cannot be predicted on the basis of the diffusion abnormalities.

Subsequent intrathecal MTX administration was not associated with recurrent acute neurotoxicity in four of the five patients. However, in the one patient with steroid-induced IDDM, subsequent intrathecal MTX therapy was associated with a recurrent strokelike event having a different distribution in that there was involvement of the parietal cortex and subcortical white matter with sparing of the deep white matter. The maximum blood pressure recorded in this patient was 145/90 mm Hg, while her baseline blood pressure was 116/75 mm Hg. Although the blood pressure elevation and the distribution of the diffusion abnormality were suggestive of posterior reversible encephalopathy syndrome (which has been reported in association with intrathecal MTX and multidrug treatment of pediatric ALL [21]), there were no corresponding T2 signal-intensity abnormalities to suggest this syndrome. The IDDM may have predisposed the patient to recurrent strokelike injury with subsequent intrathecal administration of MTX, or the cortical involvement seen during the second strokelike episode might have been another manifestation of MTX neurotoxicity.

The initial presentation of acute MTX neurotoxicity 20–22 weeks into therapy may be explained on the basis of the metabolic derangement in folate and homocysteine induced by cumulative effects of repeated administration of MTX. The cluster of patients in early to midadolescence is not readily explained. The absence of recurrent strokelike events in four of five patients despite repeated intrathecal MTX administration, given during the ongoing chemotherapy, may be explained by the less-frequent, subsequent intrathecal doses of MTX.

Conclusion

Restricted diffusion is not necessarily an ominous prognostic indicator in patients with acute MTX neurotoxicity and should not necessarily be considered an indication to omit intrathecal MTX during ongoing chemotherapy. Patients with suspected acute MTX neurotoxicity should be examined by using DW imaging in addition to other routine MR studies. Further investigation with MR spectroscopy and perfusion imaging is indicated.

Acknowledgments

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References

1. Winick NJ, Bowman WP, Kamen BA, et al. **Unexpected acute neurologic toxicity in the treatment of children with acute lymphoblastic leukemia.** *J Natl Cancer Inst* 1992;84:252–256
2. Mahoney DH, Shuster JJ, Nitschke R, et al. **Acute neurotoxicity in children with B-precursor acute lymphoid leukemia: an association between intermediate–dose intravenous methotrexate and intrathecal triple therapy: a Pediatric Oncology Group study.** *J Clin Oncol* 1998;16:1712–1722
3. Winick N, Shuster JJ, Bowman WP, et al. **Intensive oral methotrexate protects against lymphoid marrow relapse in childhood B-precursor acute lymphoblastic leukemia.** *J Clin Oncol* 1996;14:2803–2811
4. Rubnitz JE, Relling MV, Harrison, et al. **Transient leukoencephalopathy following high dose methotrexate treatment in childhood acute lymphocytic leukemia.** *Leukemia* 1998;12:1176–1181
5. Rubinstein LJ, Herman MM, Long TF, Wilbur JR. **Disseminated necrotizing leukoencephalopathy: a complication of treated central nervous system leukemia and lymphoma.** *Cancer* 1975;35:291–305
6. Ebner F, Ranner G, Slavc I, et al. **MR findings in methotrexate-induced CNS abnormalities.** *AJNR Am J Neuroradiol* 1989;10:959–964
7. Davidson A, Payne G, Leach MO, et al. **Proton magnetic resonance spectroscopy of the brain following high-dose methotrexate therapy for childhood cancer.** *Med Pediatr Oncol* 2000;35:28–34
8. Komatsu K, Takada G, Uemura K, Shisido F, Kanno I. **Decrease in cerebral metabolic rate of glucose after high dose methotrexate in childhood acute lymphocytic leukemia.** *Pediatric Neurol* 1990;6:303–306
9. Kishi S, Greiner J, Cheng C, et al. **Homocysteine, pharmacokinetics, and neurotoxicity in children with leukemia.** *J Clin Oncol* 2003;15:3084–3091
10. Mizuasawa S, Kondoh Y, Murakami M, et al. **Effect of methotrexate on local cerebral blood flow in conscious rats.** *Jpn J Pharmacol* 1988;48:499–501
11. Harila-Saari AH, Ahonen AKA, Vainionpaa LK, et al. **Brain perfusion after treatment of childhood acute lymphoblastic leukemia.** *J Nucl Med* 1977;38:82–88
12. Provenzale JM, Jahan R, Naidich TP, Fox AJ. **Assessment of the patient with hyperacute stroke: imaging and therapy.** *Radiology* 2003;229:347–359
13. Provenzale JM, Sorensen AG. **Diffusion-weighted MR imaging in acute stroke: theoretical considerations and clinical applications.** *AJR Am J Roentgenol* 1999;173:1459–1468
14. Rovira A, Rovira-Gols A, Pedraza S, et al. **Diffusion-weighted imaging in the acute phase of transient ischemic attacks.** *AJNR*

Am J Neuroradiol 2002;23:77–83
15. Yaffe K, Ferreiro D, Barkovich JA, Rowley H. **Reversible MRI abnormalities following seizures.** *Neurology* 1995;45:104–107
16. Paako E, Harila-Saari AH, Vainionpaa LK, Himanen S, Pyhtinen J, Lanning M. **White matter changes on MR during treatment in children with acute lymphoblastic leukemia: correlation with neuropsychological findings.** *Med Pediatr Oncol* 2000;35:456–461
17. Paako E, Vainionpaa LK, Pyhtinen J, Lanning M. **Minor changes on cranial MRI during treatment in children with acute lymphocytic leukemia.** *Neuroradiology* 1996;38:264–268
18. Chen C-Y, Zimmerman RA, Faro S, Bilaniuk LT, Chou TY, Malloy PT. **Childhood leukemia: central nervous system abnormalities during and after treatment.** *AJNR Am J Neuroradiol* 1996;17:295–310
19. Sandoval C, Kutscher M, Jayabose S, Tenner M. **Neurotoxicity of intrathecal methotrexate: MR imaging findings.** *AJNR Am J Neuroradiol* 2003;24:1887–1890
20. Kirshner HS. **Language disorders.** In: Bradley WG, Daroff RB, Fenichel GM, Marsden CD, eds. *Neurology in Clinical Practice.* 2nd ed. Boston: Butterworth-Heinemann; 1996:140–141
21. Shin RK, Stern JW, Janss AJ, et al. **Reversible posterior leukoencephalopathy during the treatment of acute lymphoblastic leukemia.** *Neurology* 2001;56:388–391