Clinical and radiological characteristics of methotrexate-induced acute encephalopathy in pediatric patients with cancer

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Background: Little information is available about the diagnosis and management of acute methotrexate (MTX)-induced encephalopathy.

Methods: We reviewed clinical and magnetic resonance imaging (MRI) [including diffusion-weighted imaging (DWI)] characteristics of this complication in pediatric cancer patients treated from 2000 to 2006.

Results: Six of 754 (0.8%) patients with leukemia or lymphoma and 2 of 44 (4.5%) with bone sarcoma experienced acute encephalopathy within 2 weeks (median, 7.5 days) after receiving high-dose i.v. and/or intrathecal MTX. The signs and symptoms varied at presentation and during episodes: hemiparesis (eight patients, alternating from side to side in four), dysphasia (six), confusion/emotionality (six), headache (three), choreoathetosis (two), and seizure (two). All patients recovered after 1–7 days (median, 5.5 days). DWI revealed restricted diffusion in anatomic brain regions associated with the symptoms; changes on T2-weighted and fluid-attenuated inversion recovery (FLAIR) imaging were consistently less marked. After recovery, DWI findings were normal but T2 and/or FLAIR imaging usually showed residual abnormalities.

Conclusions: Acute MTX toxicity often manifests as fluctuating neurologic symptoms with alternating hemispheric involvement. Restricted diffusion on DWI is a reliable early sign of acute MTX encephalopathy and resolves as clinical status improves, despite the persistence of subtle abnormalities on MRI.

Key words: encephalopathy, leukemia, magnetic resonance imaging, methotrexate, neurotoxicity, osteosarcoma

introduction

Oral, i.v., or intrathecal (IT) methotrexate (MTX) are widely used for the treatment of pediatric cancer [1, 2]. High-dose MTX (HD MTX) with leucovorin rescue is used to treat osteosarcoma (8–12 g/m²) and acute lymphoblastic leukemia (ALL) (≤8 g/m²). The toxic effects of MTX are myelosuppression, mucositis, nephrotoxicity, hepatotoxicity, and neurotoxicity with acute or chronic encephalopathy [3–9]. Acute encephalopathy generally develops within 5–14 days after IT MTX or HD MTX and may include headache, nausea, emesis, lethargy, altered mental status, blurred vision, aphasia, hemiparesis, and seizure. Chronic encephalopathy develops slowly, may progress, and can permanently impair neurologic function. Transient acute encephalopathy has been clinically observed in 3%–15% of cancer patients after HD MTX [4, 7, 8]. Most patients can resume MTX therapy without permanent neurological sequelae, although 10%–56% may experience recurrence on rechallenge [4, 7, 8]. The pathophysiology of MTX-induced acute encephalopathy is largely unknown but does not appear to be related to MTX pharmacokinetics [4].

The optimal diagnosis and management of MTX-induced acute encephalopathy are not well established. We reviewed our pediatric cancer institution’s experience during the past 6 years, including neurologic symptoms and signs, brain magnetic resonance imaging (MRI), clinical course, and MTX pharmacokinetic data.

methods

patients and imaging

We searched the leukemia and solid tumor databases of St Jude Children’s Research Hospital to identify children who had a diagnosis of MTX-induced acute encephalopathy from January 2000 to August 2006, when MRI with diffusion-weighted imaging (DWI) was routinely used to evaluate neurological symptoms. We included only patients...
whose neurological abnormalities occurred within 2 weeks after MTX administration and had no other identifiable cause as determined by the neurologist. Clinical and management information was obtained from the medical records. All neurological evaluations were carried out by a single neurologist and all neuroimaging studies were retrospectively reviewed by a single neuroradiologist experienced in neurologic complications of cancer. The study was approved by our Institutional Review Board.

**Pharmacokinetics**
Pharmacokinetic data for all patients who received i.v. HD MTX were analyzed. Plasma concentration of MTX was measured before (to confirm absence of detectable MTX levels) and 6, 23, 42, and 72 h after the start of each 24-h continuous infusion of MTX and before and 4, 24, 48, and 72 h after the start of each 4-h infusion. The pharmacokinetic parameters were estimated with a maximum a priori Bayesian estimation algorithm with pediatric population priors as implemented in ADAPT II software [3, 10]. The MTX clearance rate was estimated as the volume of the central compartment times the elimination rate constant, and the area under the plasma concentration–time curve was estimated with concentration versus time data extrapolated from the estimated pharmacokinetic parameters.

**Results**
**Patients**
Of the patients who received any form of MTX from January 2000 to August 2006, 6 of 754 (0.8%) with leukemia or lymphoma and 2 of 44 (4.5%) with osteosarcoma or malignant fibrous histiocytoma met the study criteria (Table 1). Their median age at the time of encephalopathy was 14 years. None had central nervous system tumor involvement or recent intake of steroids. Seven patients had no history of neurological disorders; patient 7 had experienced headache due to a transient cerebrospinal fluid (CSF) leak after resection of a tumor of the vertebral body. Encephalopathy occurred after a median of three courses (range, 1–5 courses) of i.v. MTX or 3.5 courses (range, 2–8 courses) of IT MTX. Four children had received both i.v. HD MTX (4.4–5 g/m²) and IT MTX (12 mg), two had received i.v. HD MTX only (12 g/m²), and the remaining two had received IT MTX only (12 mg) within the previous 2 weeks. One patient who received IT MTX only (patient 2) had previously undergone 5 i.v. courses of HD MTX. No acute encephalopathy was observed after low-dose i.v. MTX or oral MTX.

**Neurological Symptoms**
Neurological symptoms and signs (Table 2) arose 2–9 days (median, 7.5 days) after MTX administration and resolved after 1–7 days (median, 5.5 days). These manifestations varied and often waxed and waned. Headache or nausea/vomiting was the initial symptom in three patients. All patients had stroke-like hemiparesis or bilateral weakness. Symptoms and signs progressed over a period of minutes to many hours. Four patients had alternating hemiparesis; as weakness resolved on one side, it developed on the other side. In patient 1, bilateral weakness evolved into hemiparesis. Six patients experienced expressive dysphasia and poor orofacial and lingual movement but had intact auditory comprehension and reading and writing ability. One patient with aphasia (patient 8) developed marked orolingual apraxia manifested as impaired swallowing (drooling) and an inability to open the mouth voluntarily. Six patients developed emotional lability ranging from inappropriate laughter to unprovoked crying, anxiety, and unresponsiveness. Two patients had choreoathetoid movements (bilateral flailing movements of arms and legs and intermittent writhing of the neck and trunk). Other manifestations were seizure (two patients), transient gait ataxia (one), and transient impaired vision (for 2 h) when the patient was disoriented (one).

**Management of Encephalopathy**
Four patients were treated with i.v. aminophylline and one with aminophylline and leucovorin. Seizures in patients 4 and 6 were treated with phenytoin and subsequently with gabapentin. Steroids were not used in any patient. The decision to resume MTX therapy was made by the treating physician after consideration of the severity of the encephalopathy, potential risks and benefits of resuming MTX, and patient/family preference. All four patients with ALL resumed MTX therapy; three received prophylactic leucovorin (with IT MTX) or aminophylline with subsequent HD MTX. Patient 3 developed severe headache after rechallenge with HD MTX, which was discontinued, and after IT MTX, which was continued uneventfully with leucovorin rescue. The remaining four cases (non-ALL) did not receive further HD MTX or IT MTX. Patient 5 had completed her planned HD MTX before the development of encephalopathy. None of the patients had apparent residual neurologic deficits.

**Imaging**
Five patients had computed tomography (CT) scans of the brain shortly after the onset of neurologic symptoms; no abnormalities were seen. All eight patients had MRI, a median of 3 days (range, 0–5 days) after the onset of symptoms. All patients had conventional MRI with DWI; seven had T1 gadolinium contrast studies and six had MR angiograms. The gadolinium contrast studies and angiograms were normal, but in seven patients DWI revealed restricted diffusion of water within the cerebral deep white matter, at anatomic sites associated with the observed motor impairment (Table 2 and Figure 1). All five patients with alternating hemiparesis or bilateral weakness showed bilateral restricted diffusion in the white matter. The patient with transient impaired vision (patient 3) had restricted diffusion in the deep white matter of both cerebral hemispheres (Figure 1); MRI findings were not consistent with posterior reversible encephalopathy syndrome and the patient did not have hypertension or seizure [11]. In the eighth patient (who had choreoathetosis), MRI 5 days after the onset of symptoms showed bilateral areas of increased diffusion in the putamina and caudate heads with a focus of T2 and fluid-attenuated inversion recovery (FLAIR) signal increase in the frontal periradial white matter. This frontal focus also showed increased diffusion on DWI. The other patient with choreoathetosis had bilateral weakness, and MRI showed restricted diffusion in the centrum semiovale, corona radiata,
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (years)</th>
<th>Race/sex</th>
<th>Primary diagnosis</th>
<th>No. prior HD MTX/IT MTX courses</th>
<th>Onset (days after MTX)</th>
<th>MTX route within 2 weeks of onset</th>
<th>Days to resolution</th>
<th>Treatment</th>
<th>Subsequent MTX therapy</th>
<th>Recurrence of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>W/M</td>
<td>Pre-B ALL</td>
<td>2/2</td>
<td>9</td>
<td>i.v./IT</td>
<td>1</td>
<td>Aminophylline</td>
<td>HD MTX as scheduled with aminophylline IT MTX as scheduled</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>W/M</td>
<td>Pre-B ALL</td>
<td>5/7</td>
<td>9</td>
<td>IT</td>
<td>6</td>
<td>Heparin</td>
<td>IT MTX as scheduled with LV</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>W/F</td>
<td>T-ALL</td>
<td>1/2</td>
<td>7</td>
<td>i.v./IT</td>
<td>5</td>
<td>None</td>
<td>HD MTX with aminophylline x1, then discontinued due to headache</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>18</td>
<td>W/M</td>
<td>T-ALL</td>
<td>1/4</td>
<td>5</td>
<td>i.v./IT</td>
<td>7</td>
<td>Phenytoin</td>
<td>IT MTX as scheduled with LV</td>
<td>No</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>W/F</td>
<td>Lymphoblastic lymphoma</td>
<td>4/8</td>
<td>8</td>
<td>i.v./IT</td>
<td>6</td>
<td>Aminophylline Lorazepam Clonazepam Diphenhydramine</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>W/F</td>
<td>AML M1</td>
<td>0/3</td>
<td>4</td>
<td>IT</td>
<td>4</td>
<td>Aminophylline Lorazepam Phenytoin Gabapentin</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>14</td>
<td>W/M</td>
<td>Osteosarcoma</td>
<td>5/0</td>
<td>8</td>
<td>i.v.</td>
<td>3</td>
<td>Aminophylline Lorazepam Leucovorin</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>18</td>
<td>O/F</td>
<td>MFH</td>
<td>3/0</td>
<td>2</td>
<td>i.v.</td>
<td>6</td>
<td>Aminophylline</td>
<td>None</td>
<td>No</td>
</tr>
</tbody>
</table>

MTX, methotrexate; HD MTX, high-dose methotrexate; IT, intrathecal; W, white; M, male; ALL, acute lymphoblastic leukemia; F, female; LV, leucovorin; AML, acute myeloid leukemia; O, other; MFH, malignant fibrous histiocytoma.
<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Headache</th>
<th>Hemiparesis</th>
<th>Bilateral weakness</th>
<th>Dysphasia</th>
<th>Confusion/ emotionality</th>
<th>Movement disorder</th>
<th>Anatomic locations of MRI abnormality (pattern)</th>
<th>Restricted diffusion on DWI/increased T2 and/or FLAIR signal (days after onset of symptoms)</th>
<th>Follow-up MRI findings (time after initial MRI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Bilateral cerebral white matter (focal)</td>
<td>Yes/yes (0 day)</td>
<td>Normal diffusion with persistent T2 and FLAIR signal increase (7 days)</td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Bilateral cerebral white matter (R &gt; L) (focal)</td>
<td>Yes/yes (4 days)</td>
<td>Increased diffusion within larger focal T2 and FLAIR abnormalities than initial imaging (8 months)</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Bilateral cerebral white matter (diffuse)</td>
<td>Yes/near normal (4 days)</td>
<td>Normal diffusion. Minimal residual T2 and FLAIR increase (5 months)</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Bilateral cerebral white matter (frontal lobes &gt; parietal lobes) (focal)</td>
<td>Yes/yes (3 days)</td>
<td>Increased diffusion with mild residual leukoencephalopathy on T2 and FLAIR (7 days)</td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Basal ganglia, caudate &gt; putamen (R &gt; L) and unilateral cerebral white matter (focal)</td>
<td>No (increased diffusion) /yes (5 days)</td>
<td>Increased diffusion. Residual small left perialtrial white matter signal on T2 and FLAIR (5 months)</td>
</tr>
<tr>
<td>6</td>
<td>No</td>
<td>Yes</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Bilateral cerebral white matter (focal)</td>
<td>Yes/yes (2 days)</td>
<td>All imaging normal (3 months)</td>
</tr>
<tr>
<td>7</td>
<td>No</td>
<td>Yes</td>
<td>Yes*</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unilateral cerebral white matter (focal)</td>
<td>Yes/yes (2 days)</td>
<td>Not done</td>
</tr>
<tr>
<td>8</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes*</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Bilateral cerebral white matter (focal)</td>
<td>Yes/yes (3 days)</td>
<td>Normal diffusion. A small focus of residual T2 and FLAIR signal in left deep white matter (13 months)</td>
</tr>
</tbody>
</table>

*Alternating hemiparesis.

MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; focal, nonconfluent abnormalities; diffuse, confluent abnormalities.
and internal capsules. In all cases, concurrent T2-weighted and FLAIR imaging showed no abnormalities or abnormalities less marked than those on DWI. Seven patients underwent follow-up MRI after 1 week to 13 months (median, 5 months). The restricted diffusion had resolved in all six patients who had follow-up DWI, although minor signal abnormalities persisted on T2 and/or FLAIR in five patients. The increased diffusion initially observed in one patient showed improvement, although a small left frontal periventricular white matter signal persisted on T2 and FLAIR.

**MTX pharmacokinetics**

Table 3 summarizes the pharmacokinetic data for the six patients who received i.v. HD MTX and provides historical comparison data from our institution [10, 12]. Four of the six patients required additional leucovorin due to delayed MTX clearance: three patients required two additional doses and one patient required seven doses. Only one patient (patient 8) had detectable plasma MTX at the onset of symptoms (headache, starting 2 days after MTX administration). MTX was undetectable in CSF in the three patients tested.

**discussion**

In our study group, neurologic events occurred after HD MTX (12 g/m²) alone (n = 2), after IT MTX alone (n = 2), and after combined HD MTX and IT MTX (n = 4), but not after low-dose MTX. Mahoney et al. [5] reported cumulative systemic MTX exposure, a high MTX : leucovorin ratio, and concurrent IT and i.v. MTX to be associated with acute neurotoxicity. Acute encephalopathy usually resolves within a week but may recur after MTX therapy is resumed [4, 7, 8]. In our study group, MTX was resumed only in the four ALL patients; three of these received prophylactic aminophylline or leucovorin, and only one had recurrence (headache after aminophylline prophylaxis).

The incidence of acute encephalopathy among patients who received MTX was 0.8% for leukemia/lymphoma and 4.5% for osteosarcoma or malignant fibrous histiocytoma. The higher incidence in the latter group may reflect the higher doses of MTX used to treat bone sarcoma. Dufourg et al. [13] recently reported that HD MTX doses of 1.5–8 g/m²

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**Table 3. Pharmacokinetics of i.v. high-dose MTX in six patients**

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>MTX route</th>
<th>MTX dose</th>
<th>MTX plasma C&lt;sub&gt;max&lt;/sub&gt; (µM)</th>
<th>MTX plasma concentration at 42 h (µM)</th>
<th>MTX clearance rate (ml/min/m²)</th>
<th>Population mean MTX clearance (ml/min/m²) in historical comparison group [10, 11]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>i.v./IT</td>
<td>4.4 g/m² i.v. over 24 h/12 mg IT bolus</td>
<td>63.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.92&lt;sup&gt;b&lt;/sup&gt;</td>
<td>99.1</td>
<td>107.8 ± 20.7</td>
</tr>
<tr>
<td>2</td>
<td>i.v./IT</td>
<td>5 g/m² i.v. over 24 h/12 mg IT bolus</td>
<td>59.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.03&lt;sup&gt;b&lt;/sup&gt;</td>
<td>119.7</td>
<td>107.8 ± 20.7</td>
</tr>
<tr>
<td>3</td>
<td>i.v./IT</td>
<td>5 g/m² i.v. over 24 h/12 mg IT bolus</td>
<td>78.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.62&lt;sup&gt;b&lt;/sup&gt;</td>
<td>90.1</td>
<td>107.8 ± 20.7</td>
</tr>
<tr>
<td>4</td>
<td>i.v./IT</td>
<td>5 g/m² i.v. over 24 h/12 mg IT bolus</td>
<td>72.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.80</td>
<td>94.9</td>
<td>107.8 ± 20.7</td>
</tr>
<tr>
<td>5</td>
<td>i.v./IT</td>
<td>12 g/m² over 4 h IT bolus</td>
<td>1239.9</td>
<td>0.13&lt;sup&gt;bc&lt;/sup&gt;</td>
<td>63.5</td>
<td>53.2 ± 10.1</td>
</tr>
<tr>
<td>6</td>
<td>i.v.</td>
<td>12 g/m² over 4 h</td>
<td>1811.0</td>
<td>0.26&lt;sup&gt;d&lt;/sup&gt;</td>
<td>40.1</td>
<td>53.2 ± 10.1</td>
</tr>
</tbody>
</table>

<sup>a</sup>MTX plasma steady-state concentration is reported for patients who received 24-h continuous i.v. MTX infusion.
<sup>b</sup>Patient required increased leucovorin rescue dosage due to delayed clearance.
<sup>c</sup>Plasma concentration measured at 48 h after start of MTX infusion.
<sup>d</sup>Plasma concentration measured at 51 h after start of MTX infusion. MTX, methotrexate; C<sub>max</sub>, maximum plasma concentration; IT, intrathecal.
and age >10 years were associated with acute encephalopathy in children with ALL. Age ≥10 years was also associated with transient encephalopathy in another study in pediatric ALL [4], although this effect remains unexplained. Seven of our eight patients were older than 10 years, and four of the six who were assessable had delayed systemic MTX excretion and required additional leucovorin. The tendency toward lower MTX clearance in adolescents may contribute to the age risk, although no significant relation between MTX pharmacokinetic parameters and encephalopathy has been detected [4].

Previously reported manifestations of acute MTX neurotoxicity include headache, confusion, disorientation, seizure, and focal neurologic deficits [4–9]. All of our patients experienced paresis, and four had alternating hemiparesis, indicating sequential involvement of both frontal lobes or connections. The symptoms evolved over minutes to many hours, progressing, resolving, and involving ipsilateral or contralateral brain areas. Six patients developed dysphasia but retained language comprehension and could read and write, consistent with cortical sparing shown by imaging studies, and patient 8 had marked orolingual apraxia. The gradual evolution and waxing and waning of symptoms were described by Walker et al. [7] and is similar to that associated with migraine. Although the pathophysiological mechanisms are unclear, slow waxing and waning of neurologic symptoms indicates progressive depolarization of neuronal and axonal membranes (as in migraine-associated cortical spreading depression) rather than vascular occlusion [14]. Generalized choreathetoid movements in two patients were associated with bilateral involvement of the basal ganglia in one and restricted diffusion in the frontal and parietal subcortical white matter in the other. Acute injury or disruption of the basal ganglia or their connections can reportedly cause such manifestations [15]. The occurrence of choreathesitis indicates that gray matter may be vulnerable to MTX acute toxicity.

The mechanism of MTX-induced acute encephalopathy remains unclear. MTX promotes release of adenosine from fibroblasts and endothelial cells [16, 17], and elevated adenosine has been demonstrated in CSF after MTX therapy. High adenosine levels dilate cerebral blood vessels, modify the release of pre- and postsynaptic neurotransmitters, and may slow the discharge rate of neurons. Thus, adenosine release may contribute to the pathophysiology of acute MTX neurotoxicity. Aminophylline displaces adenosine from its receptor sites [17]. Of six patients treated with aminophylline by Bernini et al. [17], four had complete resolution of MTX-induced neurotoxicity. Five of our eight patients received aminophylline, but its efficacy is difficult to ascertain. Winick et al. [18] reported that the incidence of encephalopathy was reduced from 19.5% to 0% by giving leucovorin 24 and 36 h after completion of low-dose oral MTX (four doses, 6 h apart) and IT MTX. Further study is warranted to determine whether a decreased MTX : leucovorin therapeutic ratio can reduce the incidence of MTX neurotoxicity.

Conventional CT scans, T1- or T2-weighted MR imaging, and angiography have failed to show consistent abnormalities that characterize MTX-induced neurotoxicity [4, 7, 8]. Recently, however, diffusion-weighted MRI has shown restricted diffusion of water in the brains of patients with ALL who experienced stroke-like events after IT MTX [19–21]. DWI derives its image contrast from the Brownian motion of water [22–24]. Restricted diffusion is hypothesized to represent the reduction of such motion along axons as a result of cytotoxic edema. Our patients had extensive bilateral evidence of restricted diffusion that cleared after resolution of their clinical symptoms. T2-weighted and FLAIR MRI continued to show residual focal abnormalities in six patients with no detectable neurological sequelae. Increased diffusion was observed in one patient, who was first imaged 5 days after the onset of symptoms, when restricted diffusion may have resolved. Although we did not identify neurological sequelae in our cases, the significance of minor residual T2 and FLAIR abnormalities in six patients is unknown. These patients did not receive detailed neurocognitive assessments; however, the clinical outcome of acute encephalopathy is favorable in general.

We believe that all patients who experience encephalopathy after MTX therapy should undergo DWI as part of a diagnostic MR examination. MTX-associated acute encephalopathy syndrome can be confidently diagnosed when DWI shows areas of restricted diffusion across multiple vascular beds and involving deep cerebral white matter, in the clinical context of waxing and waning neurological signs and symptoms. Follow-up DWI typically shows resolution of restricted diffusion.

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references