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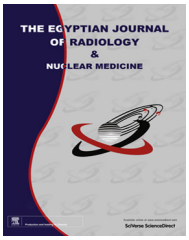

ORIGINAL ARTICLE

Child with acute methotrexate related neurotoxicity: Can diffusion weighted MRI help??

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KEYWORDS

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Abstract *Background:* Methotrexate is widely used chemotherapy especially in pediatric hematological malignancy. It may associate with acute neurotoxicity. We evaluate the role of the diffusion-weighted imaging (DWI) in the early detection of the acute methotrexate neurotoxicity.
Methods: Seventeen pediatric patients receiving high-dose methotrexate with clinical manifestation of neurotoxicity (seizures, headache, aphasia, hemiparesis or altered mental status) were included in our study. MRI was obtained in all cases within 48 h of onset of symptoms. DWI was done as a part of the routine MRI study.
Results: In all patients, initial MRI showed abnormal restricted diffusion in the centrum semiovale. FLAIR is positive in 9 cases showing bright signal. All patients had follow-up MR (within two weeks); in all cases there was resolution of the diffusion abnormality and interval development of abnormal signal intensity on FLAIR and T2WI.
Conclusion: Methotrexate can result in reversible neurotoxicity in the form of white matter injury. DWI may be used in early detection of such changes; therefore, it provides a rapid, noninvasive readily available tool by which neurotoxicity can be early detected and treated. It has the potential to alert the oncologist to this event and provide a technique by which neurotoxicity can be monitored.

1. Introduction

Methotrexate (MTX) is an essential chemotherapeutic agent for the treatment of neoplastic diseases (1). It is an essential chemotherapeutic drug for acute lymphoblastic leukemia (ALL) (2). MTX not only prevents central nervous system (CNS) recurrence but also prevents hematologic relapse (3). MTX crosses the blood–brain barrier; therefore, it can be administered intravenously or intrathecally for the treatment of CNS leukemic infiltration (1).

Methotrexate is one of the most common causes of neurotoxicity in patients with ALL and it usually affects periventricular deep white matter region (3). Methotrexate toxicity is often associated with damage to the white matter, termed "leukoencephalopathy" (LEP) (4,5). The reported incidence of MTX related neurotoxicity for patients with ALL is between 9% and 53% (6).

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Table 1 Demographic, clinical and radiological data of our patients.

No	Age	Sex	Diagnosis	Neurotoxic events	Time between IT MTX and vent (days)	Time between event and Initial MRI (days)	Location of signal abnormities	DWI	FLAIR
1	7	M	NHL	Altered mental status	8	0	Bilateral symmetrical Centrum semiovale	Restricted	Negative
2	2	F	ALL	Seizure	7	1	Bilateral asymmetrical Centrum semiovale	Restricted	Equivocal
3	4	F	ALL	Seizure	6	2	Bilateral symmetrical Centrum semiovale	Restricted	Negative
4	5	F	NHL	Left-sided facial droop, slurred speech	8	1	Bilateral symmetrical Centrum semiovale and splenium	Restricted	Equivocal
5	15	M	AML	Seizure	7	2	Bilateral asymmetrical Centrum semiovale	Restricted	Positive
6	6	F	ALL	Headache	6	1	Bilateral symmetrical Centrum semiovale	Restricted	Negative
7	5	M	AML	Altered mental status	8	2	Bilateral symmetrical Centrum semiovale.	Restricted	Bright
8	17	F	ALL	Seizure	8	1	Bilateral asymmetrical Centrum semiovale	Restricted	Negative
9	10	F	ALL	Seizure	10	2	Bilateral symmetrical Centrum semiovale	Restricted	Equivocal
10	5	M	AML	Headache	6	1	Unilateral Centrum semiovale	Restricted	Negative
11	2	F	AML	Left-sided facial droop, slurred speech	7	1	Bilateral asymmetrical Centrum semiovale	Restricted	Equivocal
12	5	F	ALL	Seizure	9	0	Bilateral asymmetrical Centrum semiovale	Restricted	Negative
13	3	M	AML	Headache	8	1	Bilateral symmetrical Centrum semiovale	Restricted	Equivocal
14	7	M	ALL	Seizure	11	2	Bilateral asymmetrical Centrum semiovale	Restricted	Positive
15	9	F	AML	Left-sided facial droop, slurred speech	7	0	Unilateral Centrum semiovale	Restricted	Negative
16	11	F	NHL	Seizure	10	0	Bilateral symmetrical Centrum semiovale	Restricted	Negative
17	4	M	ALL	Seizure	9	0	Bilateral asymmetrical Centrum semiovale	Restricted	Equivocal

Methotrexate-induced 'acute toxic leukoencephalopathy' includes various clinical manifestations: convulsion, transient ischemic attacks, encephalopathy, movement disorders and myelopathy (1). The risk factors for methotrexate related toxicity include young age, high-dose, intra-thecal route and association with cranial radiation (7).

On MRI, the hallmark of MTX related leukoencephalopathy is T2WI hyperintensities, typically located in the periventricular white matter, mainly in the centrum semiovale (7). Patients often recover from methotrexate-induced neurotoxicity after proper management (8).

Diffusion-weighted imaging (DWI) has become essential in imaging brain abnormalities and can detect early manifestation of toxicity secondary to methotrexate in hematological malignancy pediatric patients (1).

Our aim in this study was to illuminate the role of DWI in early detection, therefore the prompt management of the acute MTX neurotoxicity.

2. Patients and methods

Diffusion weighted images became a part of the standard protocol for all patients at our hospital. After the institutional board approval, we performed a retrospective review of patients with hematopoietic malignancy presented with neurological deficits after intrathecal methotrexate administration during the period from June 2010 through August 2014. The cases were collected by searching the division of pediatric oncology database and PACS system in the diagnostic imaging department.

Seventeen patients with clinical evidence of neurotoxicity were included. There were 8 cases of acute lymphocytic leukemia (ALL), 6 cases of acute myeloid leukemia (AML) and 3 cases of non-Hodgkin lymphoma (NHL). Symptoms included headache, seizures, aphasia, hemiparesis or altered mental status. The medical records were reviewed with attention to treatment protocol, time of onset of the neurologic events, recovery from the event, and neuroimaging.

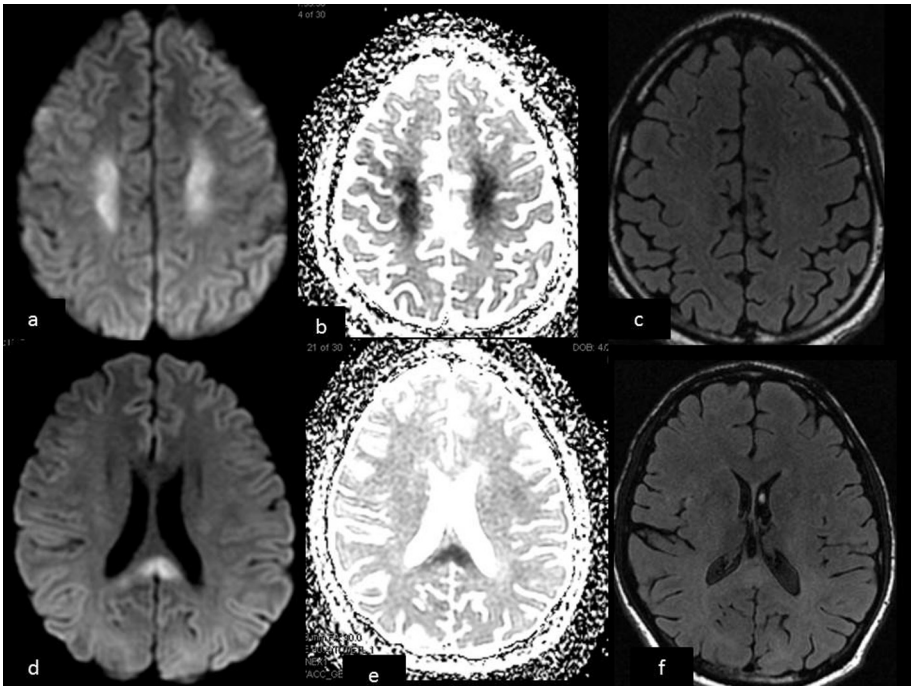

Fig. 1 5 year old female patient with ALL under methotrexate therapy presented with acute right sided facial droop and slurred speech. MRI done one day after the neurological event. Bilateral symmetrical Centrum semiovale areas of restricted diffusion (a) and reduced ADC value (b). The splenium of corpus callosum also showed area of restricted diffusion, reduced ADC (d and e), such abnormality these areas are isointense on FLAIR (c and f).

MR images were obtained with 1.5T scanners (Siemens SP, Erlangen, Germany). The patients had neurologic events whose clinical presentation and course were consistent with possible methotrexate toxicity. The medical records were reviewed with attention to treatment protocol, time of onset of the neurologic events, recovery from the event, and neuroimaging. In addition, there was no other obvious etiology for the neurologic event (e.g. tumor, hemorrhage or hypertension).

The imaging sequences consisted of sagittal spin-echo T1, axial turbo spin-echo (TSE) T2, axial T1WI, axial Fluid Attenuation Inversion recovery (FLAIR), and DWI with Apparent Diffusion Coefficient (ADC) map.

We described the radiological and clinical characteristics of the MTX related neurotoxicity in children with hematological malignancy.

3. Results

The clinical data of the patients and description of neurotoxic events are listed in Table 1. There were ten females and seven males with age range from three to 17 years. There were 8 cases of ALL, 6 cases of AML and 3 cases of lymphoma.

Symptoms included seizures in ten cases, right-sided facial droop and slurred speech in three cases, headache in two cases and altered mental status in two cases.

The MRI was done in the same day of the clinical onset in five patients, after one day in seven patients and after couple of days in the other five patients.

The MRI studies were evaluated by two independent radiologists, and in all patients, the initial MR scan showed abnormal restricted diffusion in the centrum semiovale. We considered FLIAR images were positive or negative when the two observed agreed. When they disagreed we conserved FLAIR findings "equivocal". The FLAIR sequence has no abnormality in nine cases, equivocal in six cases and shows bright signal only in two cases (Table 1).

In eight of seventeen initial studies, the abnormal diffusion was symmetrical in both centrum semiovale (Fig. 1); in seven cases the abnormal signal was more on the left centrum semiovale (Fig. 2), and unilateral affection was noted in only two cases (Fig. 3). The splenium of the corpus callosum was affected in one case in addition to centrum semiovale affection (Fig. 1).

All patients had follow-up MR imaging (after two weeks). There was resolution of the diffusion abnormality with interval development of abnormal signal intensity on FLAIR and T2WI noted in all patient (Fig. 2).

4. Discussion

Hematological malignancy is the commonest malignancy in the pediatric age group. Oral, intravenous, or intrathecal MTX is widely used for the treatment of pediatric cancer. The toxicity of MTX is myelosuppression, hepatotoxicity, nephrotoxicity, mucositis and neurotoxicity with acute or chronic encephalopathy. Acute encephalopathy usually develops within 5–14 days after high-dose MTX, which includes headache, nausea, emesis, lethargy, altered mental status, blurred vision, aphasia, hemiparesis, and seizure (9).

Till now the exact pathogenesis of methotrexate neurotoxicity is unclear. There are many theories showed in the

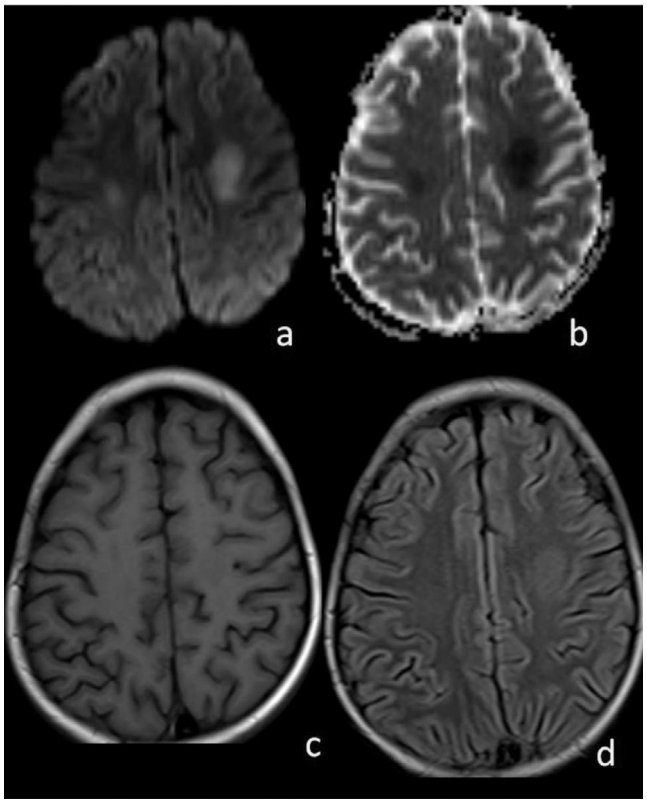

Fig. 2 12 year old female patient with AML presented with altered mental status, after 8 days of high dose methotrexate, initial MRI showed bilateral asymmetrical areas of restricted diffusion in the centrum semiovale, more evident in the left side. These areas show dark signal reduced ADC value. No definite abnormality could be detected on T1WI (c). The FLAIR signal is equivocal (d).

literature. Some animal studies suggest that methotrexate may have a direct toxic effect on axons, secondary to inhabitation of the folic acid metabolism. In the study done by Quinn et al. they found elevated levels of homocysteine and neurotransmitters in patients exposed to methotrexate so they presumed that elevated homocysteine and its excitatory amino acid metabolites mediate, in part, methotrexate-associated neurotoxicity (10).

The degree of the methotrexate neuro-toxicity is multifactorial, depending upon the specific clinical situation including dose, route of administration and other neurotoxic medications (7,11).

Rollin et al. found the neurological manifestation associated with the methotrexate neurotoxicity is fairly common, with recent estimates of the incidence of transient motor paralysis or seizures ranging up to 10% of patients receiving this therapy. The commonest neurological manifestation associated with methotrexate toxicity is seizures and altered mental status and acute stroke like symptoms are also encountered (12).

The typical presentation of the methotrexate associated leukoencephalopathy on MR imaging, is T2 and FLAIR hyperintensity signals located in the periventricular white matter, especially in the centrum semiovale (3). In addition the splenium of corpus callosum may also be involved (2).

In our study all patients show bilateral symmetrical, asymmetrical or unilateral centrum semiovale lesions, and in one patient the splenium of the corpus callosum was involved.

Diffusion-weighted imaging (DWI) is a rapid noninvasive MRI technique used in imaging of brain abnormalities. In our patients, the initial MRI scan showed abnormal restricted diffusion in the centrum semiovale in all cases whereas the FLAIR was positive only in two cases and equivocal in other three cases. Such restricted diffusion in the white matter was

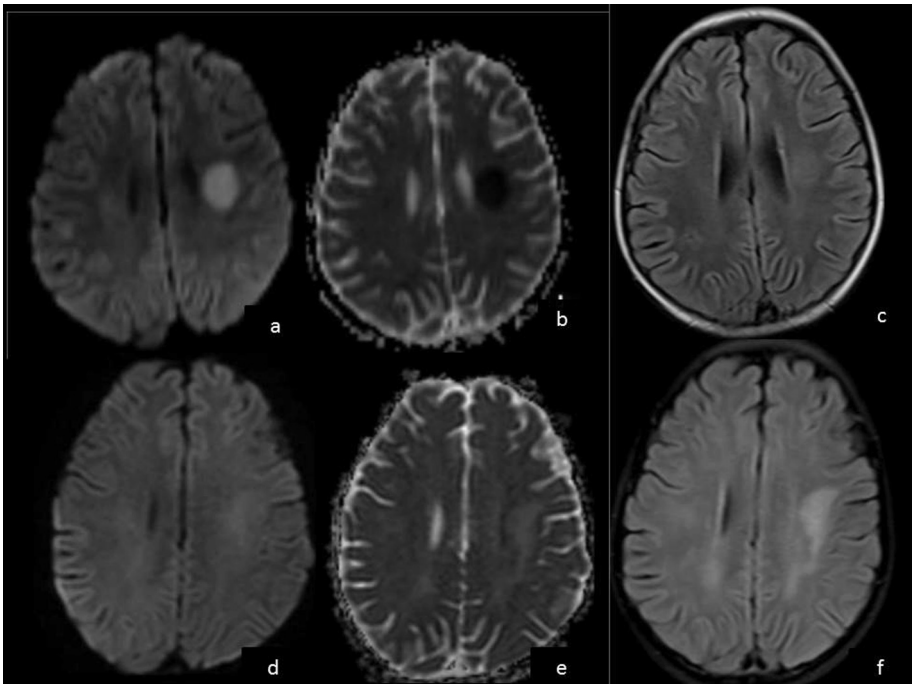

Fig. 3 5 year old male patient with AML presented 11 days following intrathecal methotrexate with severe headache, initial MRI study shows areas of restricted diffusion with reduced ADC value at the left Centrum semiovale (a and b). No definite abnormalities could be detected at the FLAIR (c). Follow-up done 10 days later shows near total resolution of the restricted diffusion and slight elevation of the ADC value (d and e). FLAIR images (f) show areas of bright signal in the left centrum semiovale.

almost reversed in all cases in the follow-up studies when abnormal FLAIR signal was evident.

DWI is extremely sensitive in the detection of cytotoxic edema, i.e. hyperacute ischemia. DWI abnormalities are usually indicative of irreversible cytotoxic injury. Yet very few cases of reversible DWI abnormalities have been reported which include patients with sustained seizure activity and patients with thromboembolic events who underwent rapid thrombolytic therapy. The restricted diffusion encountered in the cases of methotrexate neurotoxicity may be consistent with the proposed mechanisms of a direct neurotoxic effect of methotrexate on the cell. Yet the reversibility of the MR abnormalities as well as the resolution of symptoms in our patients suggests that this acute MTX related cellular swelling is not necessarily irreversible (3).

Our results are consistent more with the theory attributed the toxicity to a transient metabolic encephalopathy leading to cytotoxic edema in cerebral white matter. Such transient neurological syndrome associated with reversible DWI abnormalities due to intramyelinic edema has been described in acute exacerbations of leukodystrophy and in post-ictal events (13).

5. Conclusion

The high dose methotrexate can result in reversible neurotoxicity in the form of white matter injury. DWI is accurate in early detection of such changes; therefore, it provides a rapid, noninvasive, readily available, accurate tool by which neurotoxicity can be early detected and treated. Cytotoxic edema best explains our patient's clinical and radiographic findings. The reorganization of such pattern of chemotherapeutic induced neurotoxicity is important to avoid unnecessary workup and invasive procedures in such patients. It has the potential to alert the oncologist to this event and provide a technique by which neurotoxicity can be monitored.

Conflict of interest

The authors declare that there are no conflict of interests.

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