Neurotoxicity of intrathecal methotrexate: value of DWI in early detection

Poster No.:	C-0883
Congress:	ECR 2014
Type:	Scientific Exhibit
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Keywords:	Neuroradiology brain, MR-Diffusion/Perfusion, Diagnostic procedure, Acute
DOI:	10.1594/ecr2014/C-0883

Aims and objectives

Methotrexate is one of the most common causes of chemotherapy related neurotoxicity in patients with hematologic malignancies. The purpose of this study was to evaluate the role of the diffusion-weighted MR imaging (DWI) in the early detection of the acute methotrexate white matter neurotoxicity.

Methods and materials

Diffusion weighted images became part of the standard protocol for all patients at the Children's Cancer Hospital - Egypt. To assess its utility in evaluating patients with acute neurotoxicity during chemotherapy, we performed a retrospective review of patients with hematopoietic malignancy presented with neurological deficits after intrathecal methotrexate administration during the period from June 2008 through August 2012. The cases were collected by searching the division of pediatrics oncology data base and PACS system in the diagnostic imaging department. We identified 10 patients with clinical evidence of neurotoxicity. There were 5 cases of acute lymphocytic leukemia (ALL), 3 cases of acute myeloid leukemia (AML) and 2 cases of lymphoma. Symptoms included headache, seizures 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.

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. In addition, there was no other obvious etiology for the neurologic event (eg, tumor, hemorrhage or hypertension). The imaging sequences consisted of sagittal spin-echo T1, axial turbo spin-echo (TSE) T2, axial T1WI and axial Fluid Attenuation Inversion recovery (FLAIR), and DWI with Apparent Diffusion Coefficient (ADC) map.

Results

The clinical characteristics of the ten patients and description of neurotoxic events are listed in Tables 1. There were three females and seven males with age range from three to 17 years.

There were five cases of ALL, three cases of AML and two cases of lymphoma. Symptoms included right-sided facial droop and slurred speech in one case headache in

two cases, seizures in three cases and altered mental status in four cases. The MRI was done in the same day of the clinical onset in one patient, after one day in five patients and after couple of days in the other four patients.

In all ten patients, the initial MR imaging scan showed abnormal restricted diffusion in the Centrum semiovale . No abnormality on the FLAIR sequence in five cases, equivocal in three cases and show bright signal only in two cases (Table 1). In five of ten initial studies, the abnormal diffusion was symmetrical in both centrum semiovale (Fig.1), in four cases the abnormal signal was more on the left centrum semiovale (Fig 3&4) , unilateral affection was noted in only one case (Fig. 5&6). The splenium of the corpus callosum was affected in one case in addition to centrum semiovale affection (Fig 1&2). All patients had follow-up MR imaging, and in all cases there was resolution of the diffusion abnormality and interval development of abnormal signal intensity on FLAIR imaging and T2WI.

Images for this section:

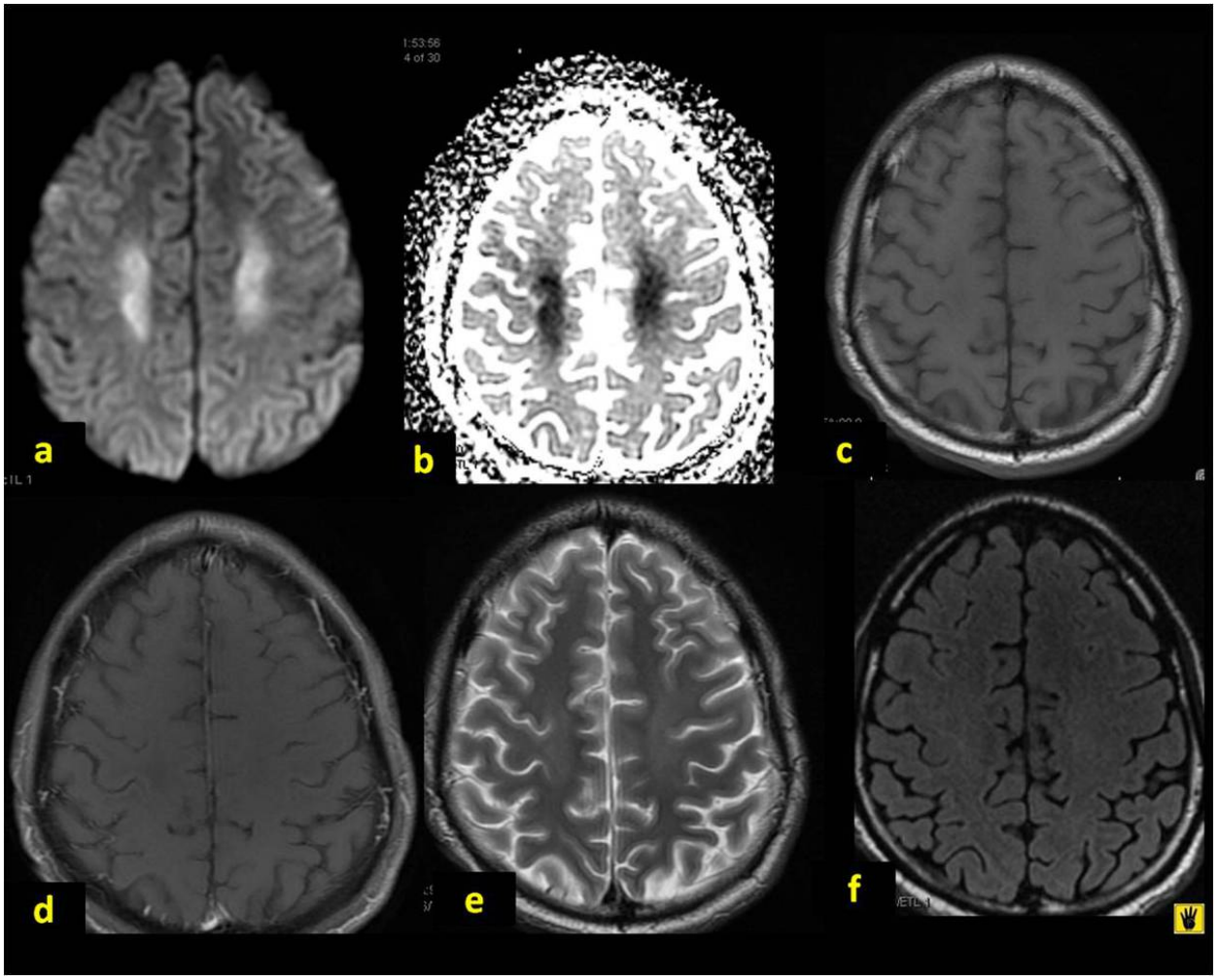

Fig. 1: 5 year old female patient with lymphoma under methotrexate therapy presented with acute right sided facial droop and slurred speech. MRI done one day after the neurological event. Bilateral symmetrical centrum semiovale areas of restricted diffusion (a) and reduced ADC value. These areas are isointense on T1WI, T2WI and FLAIR (c, e, f) with no significant enhancement (d).

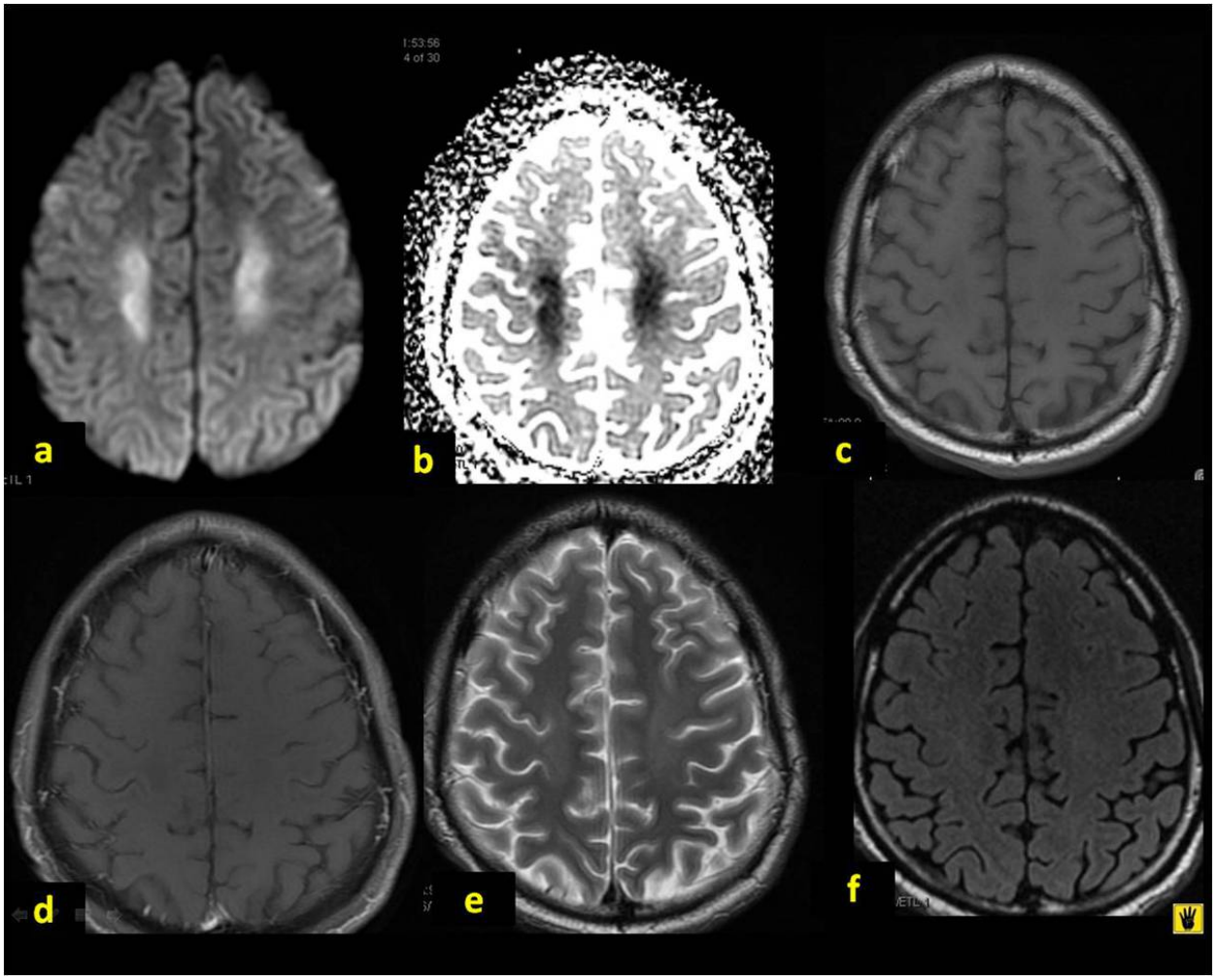

Fig. 2: same patient of Fig.1 .the spelnium of corpus callosum also showed area of restricted diffusion, reduced ADC , such abnormality was not appreciated on T1, T2 & FLAIR. no significant enhancement in post contrast study.

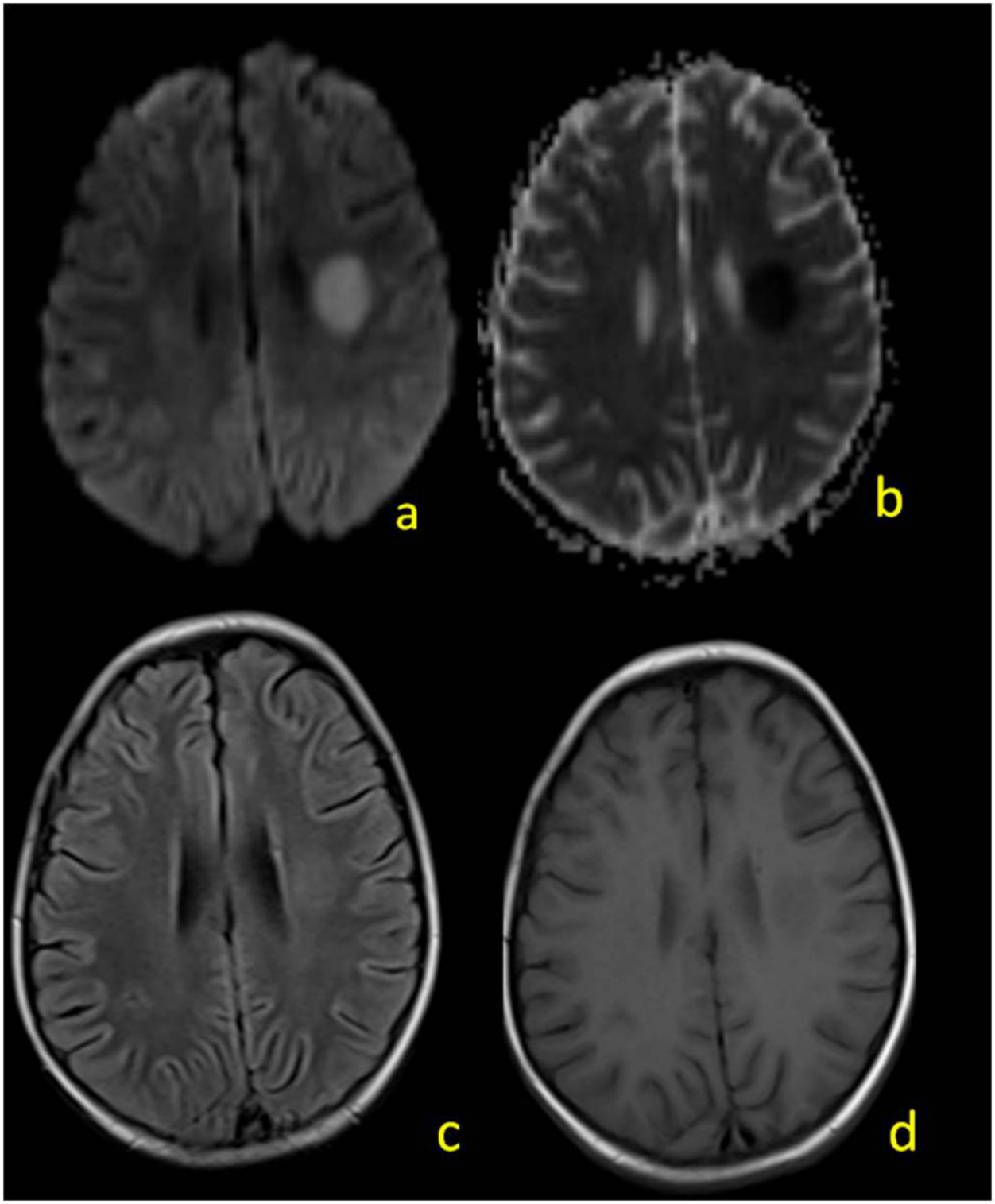

Fig. 3: 5 year old male patient with AML presented 11 days following intrathecal methotrexate with severe headache, initial MRI study show areas of restricted diffusion with reduced ADC value at the left centrum semiovale (Fig. a&b). No definite abnormalities could be detected at the FLAIR and T1WI images.(Fig. c&d).

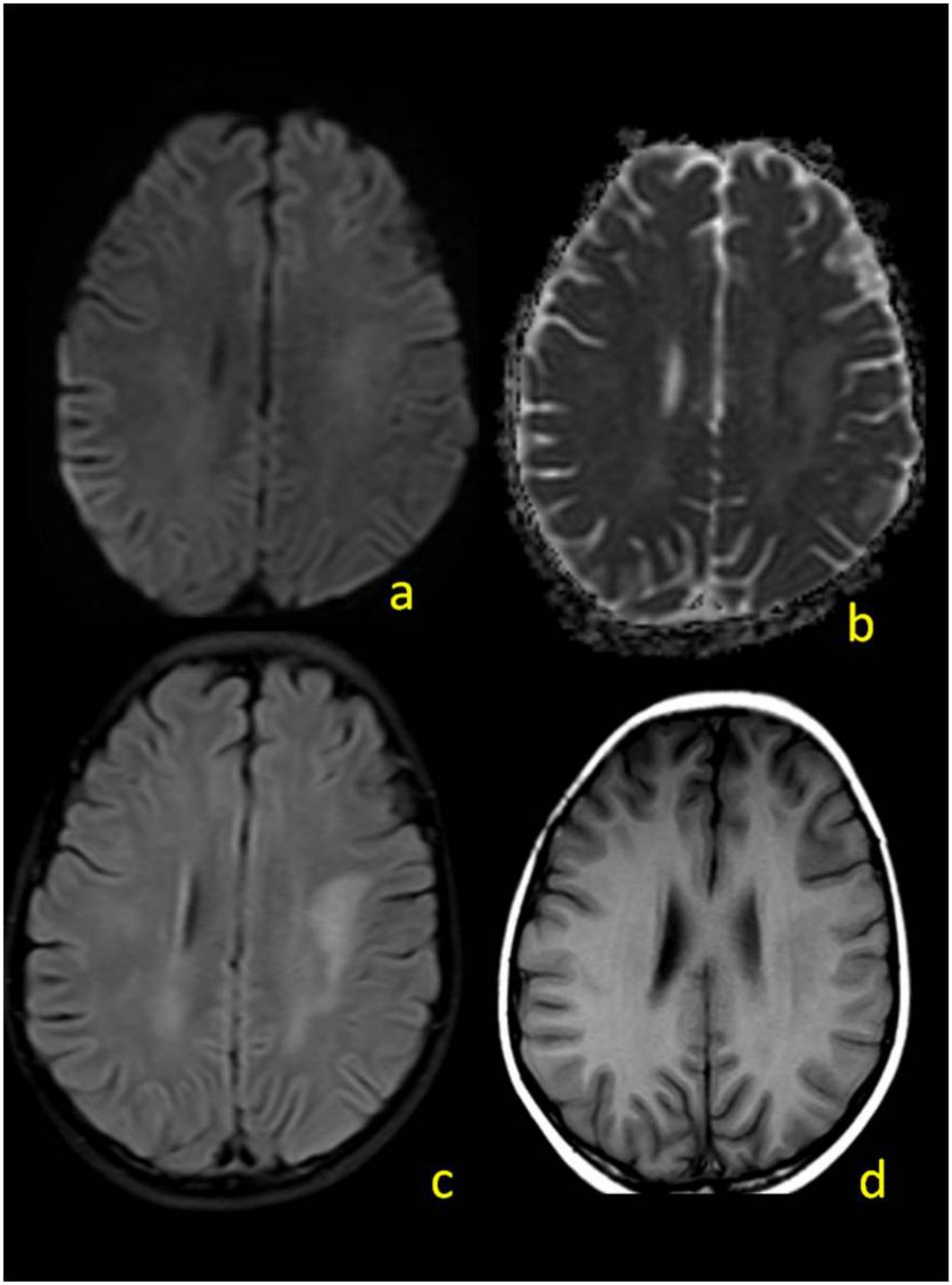
a
b
c
d

Fig. 4: Follow up study for the same patient of (fig. 3) done 10 days later show near total resolution of the restricted diffusion and slight elevation of the ADC value (Fig. a& b) . FLAIR images (Fig. c) show areas of bright signal in the left centrum semiovale, this area is almost isointense on T1WI (Fig. d).

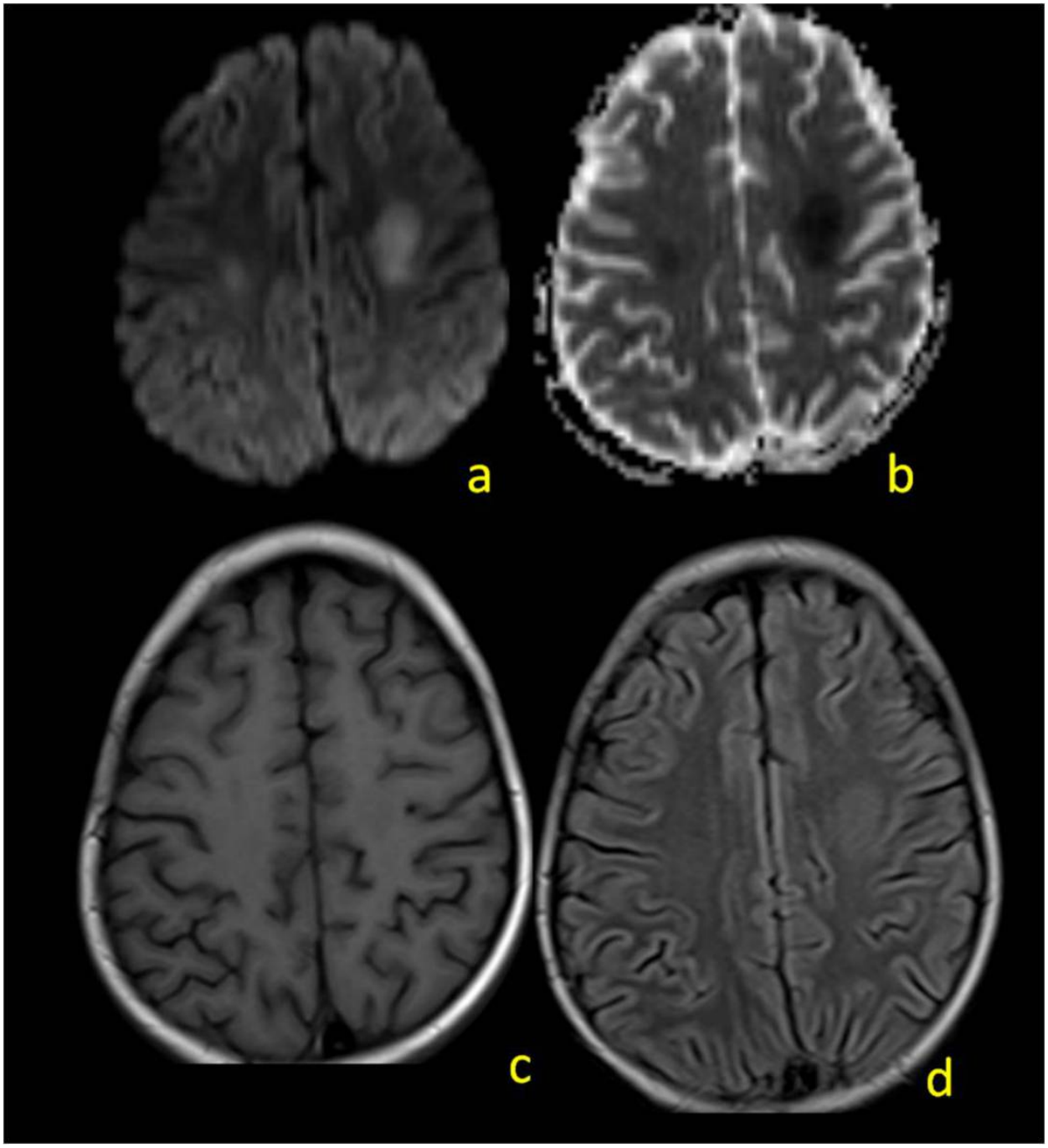

Fig. 5: 12 years old female patient with AML presented with altered mental status , initial MRI showed bilateral asymmetrical areas of restricted diffusion in the Centrum semiovale , more evident in the left side. These areas shows dark signal reduced ADC

value. No definite abnormality could be detected on T1WI (c). The FLAIR signal is equivocal. (d)

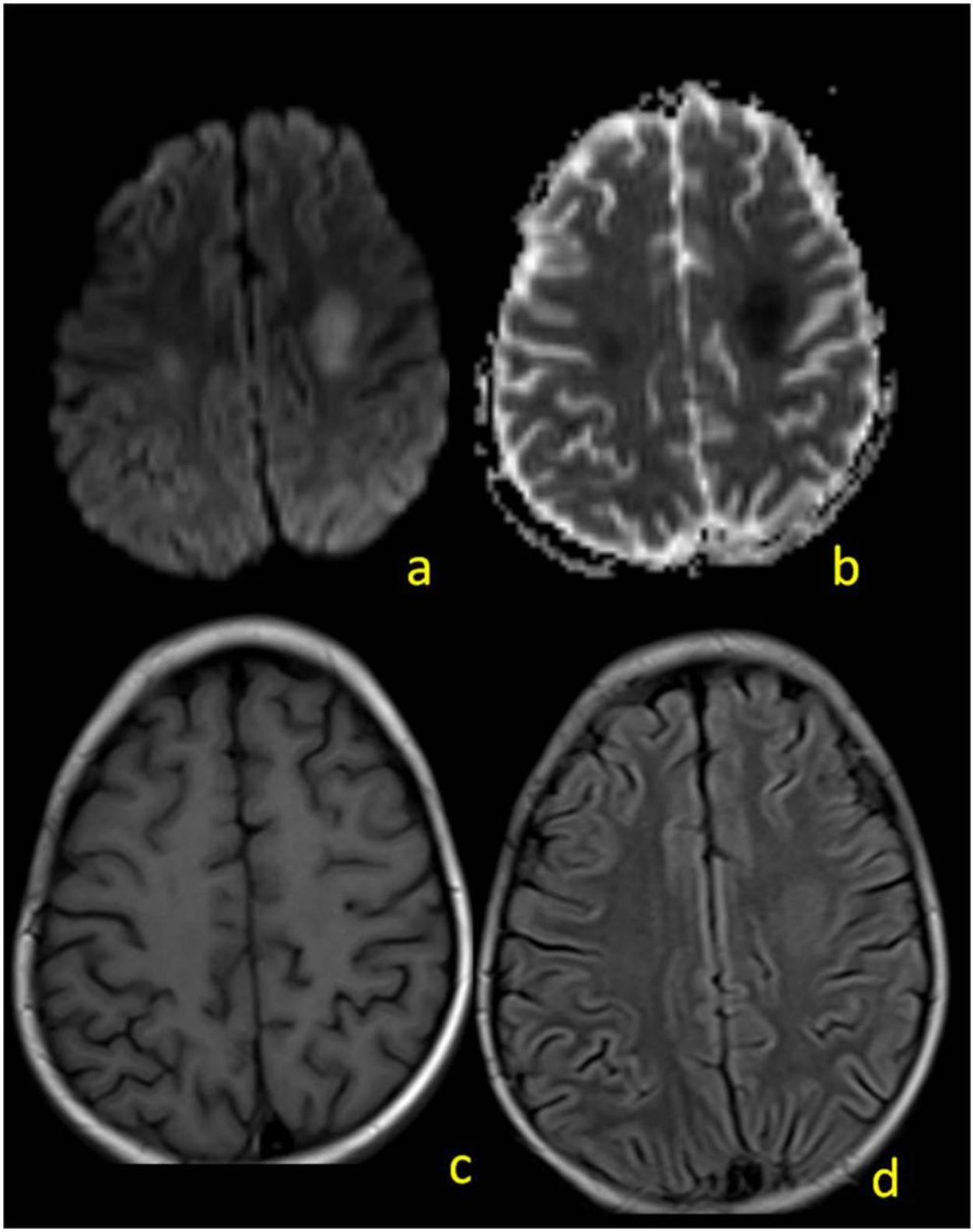

Fig. 6: 10 days later after Fig 5: the dark signal in ADC map was totally disappeared (a), DWI shows slight bright residue (b). The bright signal is now more appreciable (c), T1WI is still negative.

No	Age	sex	diagnosis	neurotoxic events	Time between Event and Initial MRI (days).	Location of signal abnormities	Dwi	FLAIR	Follow up
1	7	M	lymphoma	altered mental status	0	Bilateral symmetrical Centrum semiovale	Restricted	Negative	Progressed
2	2	F	ALL	seizure	1	Bilateral asymmetrical Centrum semiovale	Restricted	Equivocal	Partially Resoluted
3	4	F	ALL	altered mental status	2	Bilateral asymmetrical Centrum semiovale	Restricted	Negative	Progressed
4	5	F	lymphoma	Right sided facial droop, slurred speech	1	Bilateral symmetrical Centrum semiovale and splenium	Restricted	Equivocal	Progressed
5	15	M	AML	seizure	2	Bilateral asymmetrical Centrum semiovale	Restricted	Bright	Progressed
6	6	F	ALL	headache	1	Bilateral symmetrical Centrum semiovale	Restricted	Negative	Progressed
7	8	F	AML	altered mental status	2	Bilateral asymmetrical Centrum semiovale.	Restricted	Bright	Resoluted
8	17	F	ALL	seizure	1	Bilateral asymmetrical Centrum semiovale	Restricted	Negative	Progressed
9	10	F	ALL	altered mental status	2	Bilateral symmetrical Centrum semiovale	Restricted	Equivocal	Progressed
10	5	M	AML	headache	1	unilateral Centrum semiovale	Restricted	Negative	Resoluted

Fig. 7: Table (1):- Demographic, clinical and radiological data of our patients .

Conclusion

Intrathecal methotrexate is an essential component of chemotherapy for many malignancies mainly the hematological malignancies. It is effective in preventing recurrences of central nervous system leukemia. Although the hematologic and mucocutaneous toxicities are dose limiting, its neurotoxicity is especially worrisome because it may be more severe and irreversible, especially in cases undergoing cranial irradiation [1].

The exact pathogenesis of methotrexate neurotoxicity is unclear. Wide number of theories for is showed in the literature. The animal studies suggest that methotrexate may have a direct toxic effect on axons, secondary to inhabitation of the folic acid metabolism. Quinn et al. found elevated levels of homocysteine and neurotransmitters in patients exposed to methotrexate and they presumed that elevated homocysteine and its excitatory amino acid metabolites mediate, in part, methotrexate-associate neurotoxicity [2].

Many risk factors for methotrexate-induced neurotoxicity are recorded in the literature include high-dose treatment, intrathecal treatment , young age, and association with cranial radiation [3].

The degree of the methotrexate neuro-toxicity is multifactorial, dependent upon the specific clinical situation including dose, route of administration and other neurotoxic medications [4].

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, acute stroke like symptoms are also encountered [5].

The typical presentation of the methotrexate associated leukencephalopathy on MR imaging, is T2 and FLAIR hyperintensities signal located in the periventricular white matter, especially in the centrum semiovale [7-9]. In addition the splenium of corpus callosum may also involved [6]. In our study all patients show bilateral symmetrical, asymmetrical or unilateral centrum semiovale lesions, in one patient the spelnium of the corpus callosum was involved.

Diffusion-weighted MR imaging (DWI) is a rapid non invasive MRI technique used in imaging CNS abnormalities such as infarction, infection, or tumor and is a sensitive way of detecting cytotoxic edema. 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 almost reversed in all cases in the follow up studies when abnormal FLAIR signal was evident.

DWI is extremely sensitive in 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 includes patients with sustained seizure activity, in 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, methotrexate-induced cellular swelling is not necessarily irreversible [7].

The DWI findings in our patients did not support a vascular or ischemic theory of pathogenesis as it was reversible finding. The reduced ADC value, restricted diffusion resolved on follow up imaging, also there was no tissue loss. 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 [8].

To sum up the intrathecal methotrexate can result in reversible neurotoxicity in the form of white matter injury. DWI is accurate in the early detection of such changes, therefore it provides a rapid, noninvasive readily available accurate tool by which neurotoxicity can be early detected and treated. 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.

Personal information

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