CASE REPORT

Alternating hemiparesis and orolingual apraxia as manifestations of methotrexate neurotoxicity in a paediatric case of acute lymphoblastic leukaemia

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Accepted 12 April 2016

SUMMARY

A 15-year-old girl with a recent diagnosis of acute lymphoblastic leukaemia was admitted to hospital with pancytopenia after having received high-dose intrathecal methotrexate 1 day prior. During the next week she had intermittent episodes of alternating hemiparesis associated with speech arrest lasting minutes to hours at a time. The episodes were not associated with altered level of consciousness or headache. MRI of the brain showed features consistent with methotrexate encephalopathy. This report discusses the typical clinical and radiological features of methotrexate neurotoxicity in addition to differential diagnoses and the proposed pathophysiological mechanisms.

BACKGROUND

Acute/subacute methotrexate neurotoxicity may present with transient, fluctuating and reversible neurological phenomena that may be mistaken for progression of underlying disease, stroke, venous sinus thrombosis, migraine or seizures. MRI may be extremely helpful in confirming the diagnosis by revealing classic changes targeting the centrum semiovale region.

CASE PRESENTATION

A 15-year-old right-handed girl with a recent diagnosis of acute lymphoblastic leukaemia (ALL) 8 weeks earlier was admitted to hospital with pancytopenia. She was receiving chemotherapy based on the UK-ALL 2011 Regimen B protocol.¹ During a transfusion of red cells, she developed throat tightness, a numb tongue, drooling and difficulty speaking. The transfusion was stopped, and the patient reviewed and immediately treated with intravenous steroids and antihistamines for presumed transfusion-reaction. She recovered over the next 30 min. Twenty-four hours later, she had a similar episode, not in association with transfusion, lasting 6 h with spontaneous resolution. Neurological examination by on-call paediatric staff at the time was normal. MRI of the brain performed 1 month earlier was normal and cerebrospinal fluid (CSF) sampled during intrathecal (IT) methotrexate administration 1 day prior to admission was normal with no evidence of leukaemic cells. The patient had received five previous doses, each 12 mg of methotrexate intrathecally, without incident.

Forty eight hours after admission, the patient developed stuttering symptoms of the right arm, followed by right leg weakness and difficulty opening her mouth. She had no headache. Urgent non-contrast CT scan of the brain was performed and was normal. The patient was reviewed by neurology. On examination, she was alert but distressed. She was unable to open her jaw fully and could not move her tongue. She had normal comprehension and was able to follow commands—communicating via texting on her phone, without making grammatical errors—but she was unable to speak. She had a mild right facial droop with 1/5 power of right arm and 3/5 power of right leg. Tone was reduced on the right. Reflexes were globally reduced as on previous examinations. Sensory appreciation of touch was normal. Plantar responses were downgoing bilaterally. She had a hemiparetic gait.

MRI of the brain, MR cerebral angiogram and MR venogram were performed later that day, 72 h postinitial symptom onset. Images revealed new fairly symmetric areas of restricted diffusion in the centrum semiovale bilaterally, demonstrated by low signal intensity abnormalities on apparent diffusion coefficient (ADC) mapping with corresponding areas of hyperintensity on T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences (figure 1). There was absence of mass effect, contrast enhancement, meningeal enhancement, venous sinus thrombosis and arterial thrombosis. EEG was also normal. Methotrexate neurotoxicity was suspected. The patient was managed with supportive care, physiotherapy, speech and language therapy and occupational therapy. Her right-sided weakness and speech gradually improved.

Five days later, she presented with new left hemiparesis without any speech deficit. Repeat MRI of the brain demonstrated a new focus of restricted diffusion in the right temporal lobe on ADC map (figure 2). The patient continued to receive supportive care and multidisciplinary input. After spending 2 weeks in hospital, she was discharged with residual mild right hemiparesis. A clinical decision was made by the haematology team to halt the administration of further doses of IT methotrexate although oral methotrexate was continued. The patient was recently reviewed in outpatient clinic 1 year postsymptom onset. She has mild increased tone in her right leg with otherwise normal examination and reports that the right leg gets tired easily with exercise.

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To cite: Yap SM, MacEneaney P, Ryan C, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-214677

Figure 1 MRI of the brain axial cuts showing normal T1-weighted sequence (A), bilateral symmetric hyperintense lesions in the centrum semiovale on T2-weighted ((B), red arrows) and fluid-attenuated inversion recovery ((C), yellow arrows) sequences with corresponding hypointensities on apparent diffusion coefficient map ((D), green arrows) and absence of enhancement on T1-weighted sequence with gadolinium (E).

DISCUSSION

Methotrexate neurotoxicity has a reported incidence of 3–11% in paediatric cases with ALL.² It is more commonly associated with IT rather than oral methotrexate.³ Increased risk of methotrexate neurotoxicity is associated with: age ≥ 10 years at diagnosis of ALL;⁴ high cumulative dosage of methotrexate; IT administration;⁵ use of low-dose leucovorin rescue² and cranial irradiation.⁶ Certain genetic polymorphisms may predispose to methotrexate neurotoxicity in ALL.⁷

Acute methotrexate neurotoxicity presents with transient, fluctuating neurological symptoms. Progression of underlying disease, stroke, venous sinus thrombosis, migraine, seizures and functional disorder are all reasonable differentials for consideration. MRI may be extremely helpful in confirmation of diagnosis. Our patient had been clinically stable and recent CSF evaluation was negative for leukaemic cells, making progression of disease unlikely. Her events had a gradual onset and fluctuating course, which would be atypical for stroke. Venous sinus

Figure 2 First set of MRI of the brain axial cuts 72 h postinitial symptom onset (A) showing hypointense lesions on apparent diffusion coefficient maps (top two) and hyperintense lesions on fluid-attenuated inversion recovery sequences (bottom two); followed by second set of images 5 days after time of first MRI, showing a new hypointense lesion in the right temporal lobe on apparent diffusion coefficient map (B, blue arrow) corresponding with new left hemiparesis clinically.

thrombosis was a possibility given her haematological diagnosis but unlikely given lack of headache. Normal MR of the venous system definitively excluded this. Migraine was a possibility but the absence of headache, photophobia, nausea and prior personal or family history of migraine made this less likely. Partial seizures were considered in the differential as awareness may be maintained with purely sensory or motor symptoms, but the events were not stereotyped. Functional disorder was considered briefly, as the patient was a vulnerable young person with a serious illness and symptoms were unusual, however, this was felt to be least likely and a diagnosis of exclusion. Once MRI was performed, this confirmed the diagnosis of methotrexate neurotoxicity.

The majority of reported cases to date developed symptoms 3–11 days after treatment.^{5 8–11} Our patient's symptoms of fluctuating orolingual apraxia and alternating hemiparesis are typical of methotrexate toxicity.^{9 10} Headache, somnolence, cognitive and behavioural difficulties, tremor, ataxia and seizures have also been described.¹² Most cases are transient and recover with supportive treatment, with death rarely reported.^{12 13}

The pathophysiology of methotrexate neurotoxicity is poorly understood. Transient signal abnormalities on diffusion weighted imaging (DWI) and ADC map suggest cytotoxic rather than vasogenic oedema. DWI abnormalities are transient and do not always result in structural injury to the brain, unlike, for example, stroke. Resolution of abnormalities and persistence of T2-weighted and FLAIR hyperintensities have both been reported, often without clinical neurological sequelae.^{5 8 10} The centrum semiovale is particularly susceptible to MRI changes.^{5 8 9 11} Both methotrexate-induced disruption of homocysteine and adenosine metabolism affecting vascular supply to neurons as well as disturbances in myelin metabolism have been implicated.^{8 9 12 14} Neuropathological cases of methotrexate-induced encephalopathy have demonstrated a mixture of findings including coagulative necrosis of white matter, axonal damage, glial cell loss, demyelination and a paucity of an inflammatory cellular response.¹⁵

In conclusion, methotrexate neurotoxicity is most commonly seen in young patients with haematological malignancies who receive IT methotrexate. It presents with fluctuating neurological symptoms that can alternate sides and be mistaken for other neurological diagnoses. Cases may present within 2 weeks of receiving IT methotrexate. Characteristic MRI findings on DWI, FLAIR and T2 sequences involving the centrum semiovale may aid diagnosis.

Contributors SMY performed the literature review, prepared the first draft and revised the manuscript. PM interpreted the radiological imaging and revised the manuscript. CR was involved in overall patient care and revised the manuscript. OOT performed the literature review, was involved in overall patient care and revised the manuscript.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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Learning points

- In patients on methotrexate who experience unusual neurological symptoms, neurotoxicity should be considered in the differential diagnosis, particularly for those on intrathecal methotrexate.
- Manifestations include fluctuating neurological symptoms such as orolingual apraxia and alternating hemiparesis.
- The majority of cases recover with supportive care only.
- Characteristic radiological features include transient restricted diffusion on MRI of the centrum semiovale.

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