Methotrexate Induced Acute Encephalopathy-Occurrence on Re-challenge and Response to Aminophylline

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Abstract Methotrexate-induced acute encephalopathy is a serious complication of a common chemotherapy agent used in lymphoblastic leukemia. As this drug is considered vital for therapeutic success of leukemia therapy it is often rechallenged in these patients. A patient of acute lymphoblastic leukemia developed mild, transient hemiparesis after the 2nd dose of high dose methotrexate (5 g/m^2) during the consolidation phase of the BFM-95 protocol. When we repeated the drug in the 3rd cycle he developed severe life threatening quadriplegia and cranial nerve palsies. The toxicity was reversed after treatment with Aminophylline. The relevant literature is reviewed.

Keywords Methotrexate · Encephalopathy · Aminophylline · Acute lymphoblastic leukemia

Introduction

Methotrexate induced encephalopathy occurs in 0.8–15 % of patients treated with high dose methotrexate (HDMtx) [1–5]. Mostly manifesting as a mild and transient neurological dysfunction, rarely it can be severe and life-threatening [4, 5]. Similarly, majority of the patients tolerate re-challenge but it can recur with a variable reported incidence ranging from 10 to 56 % [1, 2, 4, 6]. Here we describe a patient who developed rapidly progressing life

threatening encephalopathy upon re-challenging HDMtx which responded to Aminophylline.

Case Report

A 24 year-old male presenting with fever and superior vena cava syndrome was diagnosed as having T cell acute lymphoblastic leukemia (Hemoglobin 10 g/dL, leucocytes 75,300/cmm with 90 % T-lymphoblasts, thrombocytes 1,04,000/cmm, CT chest showing large mediastinal mass). There were no neurological deficits and the cerebrospinal fluid (CSF) was acellular. He was treated with the BFM-95 lymphoblastic leukemia protocol [1] and achieved remission by 28th day of induction. The consolidation phase (involving four courses of fortnightly HDMtx 5 g/m^2 over 24 h with leucovorin rescue, 6-mercaptopurine and intrathecal methotrexate) was started 2 months after initiating therapy. The first HDMtx course was uneventful. On 10th day of the second course, he presented with history of right hemiparesis with grade 4/5 power. CSF was acellular and the magnetic resonance Imaging (MRI) of the brain was normal. He had full, spontaneous neurological recovery within 24 h and transient methotrexate induced encephalopathy was considered. He received 3rd course of HDMtx as scheduled without any dose modifications and leucovorin rescue as per protocol. His serum methotrexate levels were $<0.1 \text{ mmol/L}$ at 72 h and leucovorin was stopped. The patient was discharged with advice on close follow up.

On the 8th day he was re-admitted with right hemiparesis. Over 24 h, there was rapid worsening of weakness (0/5 power) with involvement of all limbs and axial muscles. He also developed bilateral facial palsy, jaw weakness, dysphagia, generalized hypertonia and upgoing plantars. Normal speech was difficult but he was able to

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communicate with eye movements. CSF was acellular with normal protein and sugar levels. MRI brain (done 48 h after onset) showed restricted diffusion and diffuse subcortical white matter changes in the bilateral parieto-occipital lobes (Fig. 1a, b). He was started on dexamethasone and leucovorin. By day 12, there was increasing pharyngeal palsy and worsening respiratory efforts. Intravenous aminophylline 100 mg 6th hourly was initiated on day 12 of the cycle (4 days after onset of neurological weakness). Within 24 h he showed signs of recovery with appearance of flicker of movements. Over the next 72 h, there was near complete recovery of the cranial nerve palsies-verbal communication and oral intake was possible. Limb power improved to 3/5 by 5th day of Aminophylline. We had to stop aminophylline after 5 days due to persistent tachycardia and agitation. However, improvement continued and physiotherapy was commenced once the hypertension resolved. By the end of 1 month he became ambulant

and ALL protocol could be re-initiated. The one remaining HDMtx was omitted. Repeat MRI done 6 weeks later showed persistent abnormalities on T2 weighted images but the diffusion had normalized (Fig. 1c, d). Four months after the event he walks well but has persistent mild weakness of lower limbs. Re-imaging of the brain is planned at 6 months.

Discussion

Encephalopathy can occur with intrathecal as well as intravenous methotrexate [1, 4, 6]. The exact pathogenesis is unclear-making it difficult to predict its occurrence in a given patient. Proposed pathogenetic mechanisms include altered methionine and homocysteine levels, increase in sulfur containing excitatory amino acids, elevated adenosine, and reduced altered tetrahydrobiopterin—all these

Fig. 1 MRI done 48 h after the onset of hemiparesis (10th day of methotrexate) shows restricted diffusion of water (diffusion weighted images, **a**) and demyelinating lesions (FLAIR image, **b**) in the white matter. Repeat imaging done 6 weeks later shows normalization of diffusion weighted images (**c**) while the lesions persist on the FLAIR sequences (**d**)

may affect multiple neuronal pathways [7]. Cumulative systemic MTX exposure, a high methotrexate: leucovorin ratio, and simultaneous use of IT and i.v. MTX, age > 10 years etc. have been implicated [1, 8]. Prior episodes probably constitute a risk, although safety of re-challenge has also been described [4–6]. In the above report, the paretic episode in the 2nd cycle was a grave warning—however we proceeded with the 3rd course. The high risk lymphoblastic leukemia, transient nature of the previous episode with complete recovery and previous reports indicating safety of rechallenging methotrexate (including our own experience with 8 cases) [6]—these were the reasons which prompted us to repeat the drug.

The clinical features of this condition are variable ranging from transient headache and neurological deficits to life threatening paralysis and extrapyramidal symptomatology [3–5]. Dysphasia is well described while the ability to communicate by non-verbal means may be preserved [4]. Our patient had quadriparesis, multiple cranial nerve palsies and dysphasia; however he could still respond to questions by eye movements and blinking of the eyelids.

There is no definite treatment for this condition. Steroids (possibly to reduce cerebral edema) and high doses of leucovorin have been recommended but are of unclear value [9, 10]. Our patient derived no benefit from dexamethasone and leucovorin. Raised adenosine levels have been implicated in methotrexate encephalopathy which can be pharmacologically antagonized by aminophylline [4, 9, 11]. We did not have access to adenosine levels, but empiric aminophylline yielded immediate response. We could not find definite recommendations regarding the dose or duration of aminophylline. As he showed response, we planned to continue till full recovery but had to stop due to toxicity. The possibility of spontaneous recovery from methotrexate encephalopathy must always be considered and it is difficult to attribute success to a particular therapeutic intervention. However, in the above instance there was progressive deterioration with prompt reversal within hours of starting aminophylline which strongly suggested that it had a beneficial effect.

Diffusion weighted MRI has been described as the most sensitive modality for identifying brain damage in this condition [4]. T2-weighted and Fluid attenuated inversion recovery (FLAIR) imaging show abnormalities but these take time to appear. Moreover, these images may continue to show residual abnormalities long after the resolution of neurological deficits [4, 12, 13]. Residual lesions detected on MRI do not preclude clinical recovery as in our case and the long term implications of these persistent imaging

abnormalities lesions are not known. Extreme caution is advisable when considering re-challenging methotrexate in patients who develop encephalopathy. Aminophylline is a useful agent for treatment of this condition.

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