METHOTREXATE-INDUCED STROKE LIKE NEUROTOXICITY: CASE REPORT, EIGHT YEARS OF EXPERIENCE AND LITERATURE REVIEW.

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Abstract

Methotrexate (MTX) intrathecal and intravenous administration is associated with neurotoxicity. We report a 15-year old girl diagnosed with large cell B lymphoma. On eighteen-day after intrathecal MTX presented stroke-like symptoms. Magnetic resonance was informed as a possible stroke in the right frontal lobe. The patient does not meet the criteria for fibrinolysis. MTX neurotoxicity was suspected, and theophylline was initiated. She showed complete recovery after three days of treatment. After describing the case, we review MTX neurotoxicity cases from our centre from January 2010 to December 2018. Also, we added to this data the previously published cases in the literature.

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Methotrexate stroke like neurotoxicity

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ABSTRACT

Methotrexate (MTX) intrathecal and intravenous administration is associated with neurotoxicity. We report a 15-year old girl diagnosed with large cell B lymphoma. On eighteen-day after intrathecal MTX presented stroke-like symptoms. Magnetic resonance was informed as a possible stroke in the right frontal lobe. The patient does not meet the criteria for fibrinolysis. MTX neurotoxicity was suspected, and theophylline was initiated. She showed complete recovery after three days of treatment. After describing the case, we review MTX neurotoxicity cases from our centre from January 2010 to December 2018. Also, we added to this data the previously published cases in the literature.

Keywords: Methotrexate; neurotoxicity; stroke; theophylline.

Abbreviations

Acute lymphoblastic leukaemia	ALL
Central nervous system	CNS
COPADM	Cyclophosphamide, Oncovin (Vincristine) Prednisone, Adriamycin and Methotrexate
Magnetic resonance	MRI
Methotrexate	MTX
Pediatric intensive care unit	PICU

INTRODUCTION

Methotrexate (MTX) is a cornerstone treatment of children oncohematological diseases[1]. For acute lymphoblastic leukaemia (ALL) its intrathecal administration is essential to avoid central nervous system (CNS) recurrences. After its use associated or not with other chemotherapeutic agents the CNS recurrences has decreased from 25% to 5% [2].

Methotrexate, a folic acid antagonist, blocks the synthesis of the purine by inhibiting regulatory enzymes. Its administration is associated with multiple side effects: myelosuppression, mucositis, liver damage, kidney failure or neurotoxicity. This toxicity can lead to acute, subacute and chronic syndromes. The symptoms and the severity of them will depend on the route of administration, dose and association with other chemotherapies.

Regarding MTX neurotoxicity, it takes place in days or weeks after intrathecal or intravenous administration. It can be associated with hemiparesis, sensory deficit, aphasia, dysarthria, dysphagia or diplopia. There is no precise pathophysiological description, but a delay in MTX elimination could be related to it. Therefore, clinical suspicion is essential to avoid inappropriate approaches in a clinical event that may remind an ischemic episode.

We present a fifteen-year-old female with a large-cell B lymphoma diagnosis after the accidental discovery of a mediastinal mass. She had pleural and pericardial effusion, bilateral multiple pulmonary nodules, right lateral cervical and supraclavicular adenopathies, mesenteric and retroperitoneal, hepatic, pancreatic, renal and intestinal adenopathy conglomerate (stage IIIB). She received chemotherapeutic and radiotherapy according to the group B of high-risk protocol ("Inter B NHL RTX 2010"). She suffered delayed MTX elimination, acute renal failure, vincristine neurotoxicity and grade four myelosuppression.

On the eighteenth day of the second COPADM cycle (Vincristine, Cyclophosphamide, Prednisone, Adriamycin and Methotrexate), she presented left facial palsy and left upper limb weakness. The sensitivity was preserved. Two hours later, she showed left arm paralysis without other symptomatology. A magnetic resonance (MRI) was done and described as compatible with stroke (Figure 1). She was transferred to the pediatric intensive care unit (PICU). The patient did not meet fibrinolysis criteria, so it was maintained a conservative treatment. The cranial doppler was symmetrical. It was impossible to perform a lumbar puncture (low platelet count). Therapy with acyclovir was started. Two hours after PICU admission, the clinical deficiencies disappeared.

On the second day of PICU admission, the patient repeats the symptoms previously described adding a left lower limb paresis. Like the previous day, the clinic was fully solved in less than 12 hours. On the third day of admission, she started again with self-limited peribucal paresthesias without other neurological signs. In this context, and with the suspicion of a possible link to MTX, oral theophylline was started. This treatment was continued for three days. The patient showed complete recovery. Before PICU discharge, a new MRI did not show changes. The patient did not suffer other neurological symptoms.

As seen, we present a case of MTX neurotoxicity treated with supportive therapies and antiviral drugs. After clinical suspicion, theophylline was started. The clinical and imaging tests observed were similar to the described in cerebral ischemic events. The link between MTX and neurotoxicity was critical to avoid nor indicated therapies that could lead to severe complications.

The MTX is a folic acid antagonist that interrupts cell replication by inhibiting dihydrofolate reductase. It prevents the folic acid conversion to tetrahydrofolic acid. The pathophysiology that induces neurotoxicity is not entirely understood. A hypothesis is based on the elevation of homocysteine levels in the blood and cerebrospinal fluid. This conversion can be carried out by betaine-homocysteine methyltransferase, an enzyme found in the liver or the kidney but not in the CNS. So, the homocysteine accumulated in the CNS could generate vascular endothelium damage. Also, its metabolites may activate the NMDA receptors, which contribute to neurological symptoms.

We reviewed the MTX neurotoxicity cases in our centre between 2010 and 2018 (Table 1). We also made a literature review of previously published cases. According to the literature, the MTX neurotoxicity incidence is around 4%. The only risk factor described is age older than ten years old [1,3-5]. The interval from the MTX administration to the symptom varies from 3 to 29 days (Table 1)[1,6]. The occurrence of this event is linked to the chemotherapy intensification or consolidation phases[1,3,7]. Also, the concomitant administration of cytarabine and cyclophosphamide may facilitate it[1,7]. In our centre, one of the children was in the high-risk protocol for large-cell B lymphoma, and the other was in the consolidation phase (Table 1).

The symptoms, such as palsy, loss of strength or paresis, are described and observed in most cases. Also, psychomotor agitation or aggressiveness are described. Regarding the complimentary tests, MRI brain alterations are commonly observed. Focal images with restriction to diffusion are generally described[1,4,5,8]. Two main therapeutics approaches are described to treat MTX neurotoxicity. First, dextromethorphan, a non-competitive NMDA receptor antagonist. It has been indicated to improve the cognitive deficit[5,9,10]. In our experience, this drug has been prophylactically used with slight efficacy. Also, theophylline, an adenosine antagonist, can be used. This drug decreases the toxicity of vascular endothelium. However, digestive and cardiac side effects should be monitored. In the case reported, this drug was administered after 48 hours of symptoms. We do not know if the clinical improvement could be related to this drug or just to the MTX clearance.

In conclusion, neurotoxicity is a described but little known complication related to MTX. It should be considered in children with cancer and stroke-like symptoms or image findings. The treatment should be based on a supportive approach with drugs aimed to antagonise or minimise the effect of MTX metabolites on the endothelium. The evolution is usually towards a complete recovery without neurological sequelae.

Figure legend.

Figure 1. A. MRI in the acute onset of cerebral dysfunction demonstrated a focal area of hyperintensity in the right centrum semiovale with diffusion restriction (white arrow). **B.**48 hours after, MRI revealed no more lessions and showed more clearly a focal white matter hyperintensity with diffusion restriction (white arrow).

References

1. Watanabe K, Arakawa Y, Oguma E, et al. Characteristics of methotrexate-induced stroke-like neurotoxicity. *International journal of hematology.* 2018;108(6):630-636.

2. Millan NC, Pastrana A, Guitter MR, Zubizarreta PA, Monges MS, Felice MS. Acute and sub-acute neurological toxicity in children treated for acute lymphoblastic leukemia. *Leukemia research.* 2018;65:86-93.

3. Bhojwani D, Sabin ND, Pei D, et al. Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2014;32(9):949-959.

4. Cruz-Carreras MT, Chaftari P, Shamsnia A, Guha-Thakurta N, Gonzalez C. Methotrexate-induced leukoencephalopathy presenting as stroke in the emergency department. *Clinical case reports.*2017;5(10):1644-1648.

5. Rogers P, Pan WJ, Drachtman RA, Haines C. A Stroke Mimic: Methotrexate-induced Neurotoxicity in the Emergency Department.*The Journal of emergency medicine.* 2017;52(4):559-561.

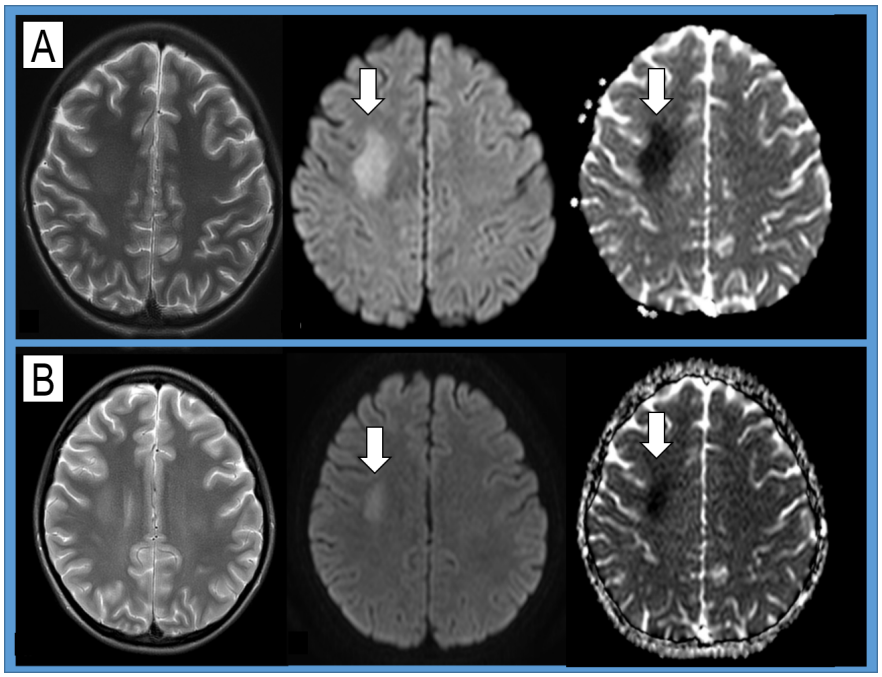
6. Iwatani K, Fujii N, Deguchi S, Tanimoto M. Subacute methotrexate-related leukoencephalopathy with stroke-like presentation.*International journal of hematology.* 2012;96(6):683-684.

7. Bond J, Hough R, Moppett J, Vora A, Mitchell C, Goulden N. 'Stroke-like syndrome' caused by intrathecal methotrexate in patients treated during the UKALL 2003 trial. *Leukemia.*2013;27(4):954-956.

8. Valle DA, Kakehasi FM, Melo RM, Siqueira CM, Soares TF, Rodrigues KE. Stroke-like encephalopathy following high-dose intravenous methotrexate in an adolescent with osteosarcoma: a case report. *Revista brasileira de hematologia e hemoterapia.* 2016;38(4):364-367.

9. Afshar M, Birnbaum D, Golden C. Review of dextromethorphan administration in 18 patients with subacute methotrexate central nervous system toxicity. *Pediatric neurology.* 2014;50(6):625-629.

10. Vijayanathan V, Gulinello M, Ali N, Cole PD. Persistent cognitive deficits, induced by intrathecal methotrexate, are associated with elevated CSF concentrations of excitotoxic glutamate analogs and can be reversed by an NMDA antagonist. *Behavioural brain research.*2011;225(2):491-497.



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