

METHOTREXATE-INDUCED NEUROTOXICITY IN PAEDIATRIC MALIGNANCIES

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Abstract: Hematologic malignancies have a growing variety of therapeutic options, but many of these have both central and peripheral nervous system side effects, which may force the physician to discontinue or lower the dosage of the offending drug to prevent irreversible damage.

Neurotoxicity is a common side effect of chemotherapy. Peripheral neuropathy is frequent with many medicines, but other complications such as seizures and encephalopathy may require immediate intervention. Early detection of undesirable neurological side effects may lead to more effective treatments and dosage changes.

Furthermore, understanding typical toxicities may aid in distinguishing chemotherapy-related symptoms from cancer progression into the CNS. In this article, we discuss the potential side effects of Methotrexate use in childhood hematologic malignancies, with focus on the difficulty of the differential diagnosis of newly onset neurological symptoms in paediatric oncology patients and potential interventions.

Key words: Methotrexate, neurotoxicity, CNS progression, leukemia, lymphoma

1. Introduction

Over the last 50 years, significant advances were made in the diagnosis and treatment of pediatric oncology patients. New therapies are now used based on the risk stratification of each patient [1]. Cytostatic treatments made the prognosis

for these diseases more promising, with patients living longer and more often surviving [2]. The number of therapeutic options for hematologic malignancies continues to grow as time passes by [3], but unfortunately, given the aggressive therapies, other systems and organs are affected: cardiological (i.e. arrhythmia) [4],

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gastrointestinal (i.e. vomiting and mucositis) and psychological disorders (i.e. depression and cognitive impairment) may arise after or during treatment [2].

Methotrexate (MTX) is one of the main chemotherapy drugs used in treating malignant diseases [5]. It can be administered by systemic route in low doses (1g/m²) or high-doses (5g/m²) for treating the disease or intrathecal for treatment or prevention of neoplastic infiltration of the central nervous system [6]. Also known as antifolate, methotrexate can irreversibly inhibit the enzyme dihydrofolate reductase [7] resulting in low tetrahydrofolates which are essential in converting homocysteine to methionine [6]. The accumulation of homocysteine, an N-methyl-D-aspartate agonist can cause neuronal damage and apoptosis [8].

Toxicity of MTX can present as myelosuppression, hepatotoxicity, nephrotoxicity, mucositis and neurotoxicity with acute or chronic encephalopathy [5]. The balance between benefits and side effects is crucial in managing to get to the end of a cure [9].

Out of these complications, we will focus in this article on the neurological ones, which occur in a significant number of patients.

Neurotoxicity can be:

- Acute, within hours or days following administration of methotrexate, with somnolence, confusion, headache, nausea, vomiting, dizziness, encephalopathy [10] and aseptic meningitis characterized by headache, neck pain, nausea, fever, and photophobia; [11]
- subacute, after several days following the administration with seizures [10], stroke-like symptoms including

hemiparesis, sensory deficits, aphasia, dysarthria, dysphagia, and diplopia [12] or myelopathy presenting as limb weakness, back pain, and bladder dysfunction [11];

- chronic, which occurs months to years after therapy and may be manifested by cognitive dysfunction, behavioral abnormalities, spasticity [11] and encephalopathy.

Recognizing the involvement of the central nervous system in pediatric malignancies is very difficult due to the absence of a biopsy, the lesions not being accessible. That is why brain imaging became most important in the paraclinical evaluation of these patients [13]. Neurotoxicity associated with methotrexate administration can appear on MRI as local hyperintensity signals mainly in the white matter, especially periventricular on T2, FLAIR, and DWI [5]. After the initial phase, the MRI images progress to bilateral symmetric diffused foci [14]. Lumbar puncture tests tend to show no pathological modification and EEG testing can show a diffuse slowing in a small number of cases [3].

2. Case Report

2.1. Case no. 1

T. N., a 6-year-old male, with no significant personal or family history, is admitted to Brasov Children's Emergency Clinical Hospital for abdominal distention and leg pain with onset of about 5 days. For approximately 2 months he has had morning pain in the calves, which decreased in intensity during the day.

On admission the neurological exam and the CT scan of the brain were normal.

Surgery for peritoneal fluid harvest and mesenteric biopsy was performed. Cytological, biochemical, histopathological and immunohistochemical examination confirmed the diagnosis of non-Hodgkin's lymphoma, Burkitt abdominal type, stage III, therapeutic group R3 (AA, BB, CC, AA, BB).

The B-NHL BFM 2004 protocol was initiated, with the first administration of intravenous Methotrexate 5 g/m² and a lumbar puncture was performed with triple intrathecal therapy with administration of Methotrexate, Cytarabine and Hydrocortisone. A cerebrospinal fluid (CSF) examination was

also performed, which showed normal results.

Serum Methotrexate levels were analyzed and its deficient elimination from the body was evidenced. The level of Methotrexate was 2.1 µmol/L after 48 hours, above the normal value which is <0.4.

We performed genetic testing for thrombophilia, which showed a heterozygous mutation in the MTHFR (methylenetetrahydrofolate reductase) gene, which, according to some studies, could increase the risk of neurological toxicity after MTX therapy.

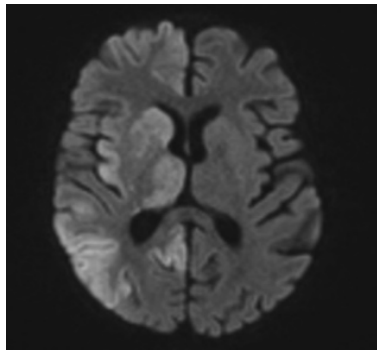


Fig. 1. T.N. first brain MRI scan

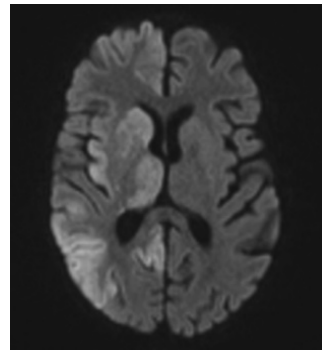


Fig. 2. T.N. first brain MRI scan

7 days after intrathecal MTX administration, the patient developed left hemibody focal motor seizures with postictal left Todd's Palsy. Treatment with Diazepam, Midazolam, Dexamethasone, and Mannitol was started. On the same day, he presented two more paroxysmal cerebral manifestations with left hemibody myoclonus and eyeball deviation movements. He was neurologically reassessed, cranial nerve examination revealing nystagmus on right lateral gaze, swallowing difficulties, hypersalivation, drowsiness, generalized hypotonia, and decreased reflexes in the

lower limbs. Levetiracetam treatment was started, due to persistent EEG abnormalities.

A brain MRI scan was performed, which showed diffuse hyperintense signal at the right frontal, parietal, temporal and occipital cortical substance, at the right caudate and thalamic nuclei and around the calcarine sulcus (figures 1, and 2).

Subsequent evolution was with clinical improvement, the patient became more reactive, swallowing difficulties slowly improved, he started to communicate and to take a few steps with support. However, he developed left central facial

paresis with an absence of the left nasolabial fold, drooping of the left buccal commissure and left palpebral ptosis.

Taking into account the post-chemotherapy side effects presented above, it is further decided to reduce the dose of iv Methotrexate and to withhold the administration of intrathecal methotrexate. We also started Aminophylline treatment.

One month after the initial neurological symptoms, a follow-up brain MRI exam was performed, which showed partial resolution of the hyperintense signal with its persistence in the right occipital lobe and caudal nucleus, bihemispheric atrophy and dilated ventricles secondary to the atrophy (figure 3).

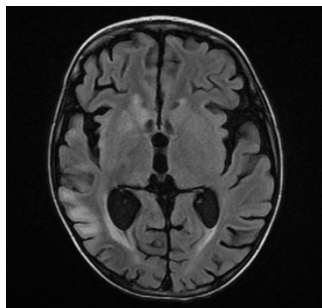


Fig. 3. T.N. second brain MRI scan

After the last chemotherapy course, 4 months after the initial neurological symptoms, another brain MRI scan was performed, which showed almost complete resolution of signal changes in the right cortex, the hyperintense signal being detectable only in the temporo-occipital lobe in T2 and FLAIR sequences with discrete diffusion restriction.

We considered that the constellation of symptoms presented above falls in the subacute category of the MTX toxicity,

manifested by stroke-like onset of focal neurologic deficits and seizures.

After finishing the chemotherapy courses, we performed a WHOLE BODY Pet CT scan, that showed no metabolically active lesions with oncological significance.

In the present, the patient's neurological exam is normal, he hasn't had any seizures, but he is still on Levetiracetam treatment, due to the persistence of EEG abnormalities.

2.2. Case no. 2

A.I., a 13-year-old male, without significant personal or family medical history, was admitted to Brasov Children's Emergency Clinical Hospital with fever, weight loss, poor appetite, headaches, myalgia and arthralgia, with onset in the last couple of weeks.

On admission, the patient's neurological exam, CT scan of the brain and cerebrospinal fluid examination were normal.

Based on anamnestic data, clinical examination and laboratory tests (peripheral blood smear, bone marrow cytology, immunophenotyping and cytogenetic examination), the diagnosis of CALLA positive B-precursor acute lymphoblastic leukemia was established, with medium risk, and the ALL-IC-BFM 2009 Protocol was initiated. Intrathecal methotrexate was administered on days 1, 12 and 33 of protocol IA, on days 45 and 59 of protocol IB, on days 8, 22, 36, 50 of the mM protocol and on days 38 and 45 of Protocol II.

He started the Maintenance Therapy, with the first MTX administration in week 4, then in week 8 and 12. During the 4th hospitalization for week 16 of the

Maintenance Protocol, a lumbar puncture with the administration of MTX was performed. A CSF exam was performed, which was normal, without the presence of leukemic blasts.

The following days, he started to complain of intense frontal headache and photophobia. The neurological exam showed slight neck stiffness, nausea and vomiting, hypotonia in the limbs and a positive Babinski sign. Cerebral depletive treatment with Mannitol and Dexamethasone was started.

Suspicion of early relapse was raised and objectified by the detection of 25% blastic infiltration in the bone marrow exam. The CSF, however, remained clear, without any leukemic blasts.

The ophthalmological exam showed papillary edema and the MRI scan of the brain showed diffuse bihemispheric intergirial hyperintensity of the cortical substance. (fig.4) Based on the MRI findings, we raised the suspicion of MTX toxicity as the cause of the patients symptoms and added Aminophylline to the treatment.

Subsequently, frontal headache worsened, with no response to analgesics, with extension of the pain to the maxilla and mandible, then to the cervical and thoracic spine. He also complained of photophobia, night sweats and bone pain in lower limbs with functional impotence.

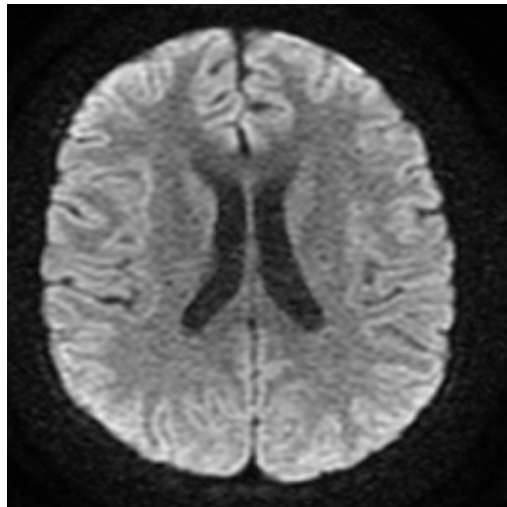


Fig. 4. A.I. brain MRI scan

We decided to perform another lumbar puncture to confirm the suspicion of relapse in the central nervous system (CNS), but we couldn't extract any CSF, probably due to CSF hypotension post administration of cerebral depletive treatment.

After a few days, he had a seizure with generalized hypertonia, eye deviation and opisthotonos, lasting about 5 minutes, with spontaneous recovery. Later that day he had another similar seizure, but he developed bradycardia, then went into cardio-respiratory arrest and died. At the request of the relatives, no

anatomopathological exam was performed.

In this case, the symptomatology suggests the diagnosis of aseptic meningitis, which is an acute MTX toxicity manifestation.

2.3. Case no. 3

T.N., a 14-year-old female, with a family history of thrombophilia and insignificant personal medical history, was admitted to Brasov Children's Emergency Clinical Hospital for joint pain, ecchymosis, petechiae, fatigability and fever. Affirmative, the symptoms started about 1 month before the admission with lower limb pain and fatigability. Her family physician recommended a topical analgesic, after which the symptoms temporarily improved. She later developed lower limb bruising in the absence of any trauma and her mother decided to bring her to our hospital.

On admission, the patient's neurological exam, CT scan of the brain and cerebrospinal fluid examination were normal, but the ophthalmological consult showed multiple intraretinal hemorrhages (Roth spots) in the posterior pole, in all quadrants, with no papillary edema.

Corroborating anamnestic data with clinical examination and paraclinical investigations (peripheral blood smear, bone marrow examination, immunophenotyping and cytogenetic examination), the diagnosis of intermediate-risk B-cell acute lymphoblastic leukemia, with CNS involvement was established and the ALL IC- BFM 2009 Protocol was started.

A thrombophilia screening was performed and we found a heterozygous mutation in the MTHFR gene.

Intrathecal methotrexate was administered on days 1, 12, 18, 27 and 33 of protocol IA, subsequently on days 45 and 59 of protocol IB, with a favorable response. She started the mM Protocol, which involves 4 administrations of intravenous methotrexate and 4 administrations of 12 mg of intrathecal Methotrexate on days 8, 22, 36 and 50.

Then we started the Protocol II, with intrathecal MTX administration on days 1 and 18. CSF exams were also performed and they were normal.

After day 18 of the Protocol II, she complained of pain in the right shoulder and muscle weakness of the lower limbs. A neurological exam was performed, which revealed a lower limb muscle strength deficit and absent DTR (deep tendon reflexes), which were attributed to postchemotherapy polyneuropathy.

We did another lumbar puncture on day 38, with intrathecal MTX administration. This time the CSF exam showed 59 elements/field (lymphocytes).

Her symptoms progressively worsened the following days, so we did an ophthalmological exam, which showed newly developed retinal leukemic infiltrates and papillary edema of the left eye. We also performed a brain MRI examination, which showed circumscribed lesions with isointensity in the left frontal, and bilateral posterior periventricular white matter and in the left basal ganglia, circled by hyperintense signal (figure 5).

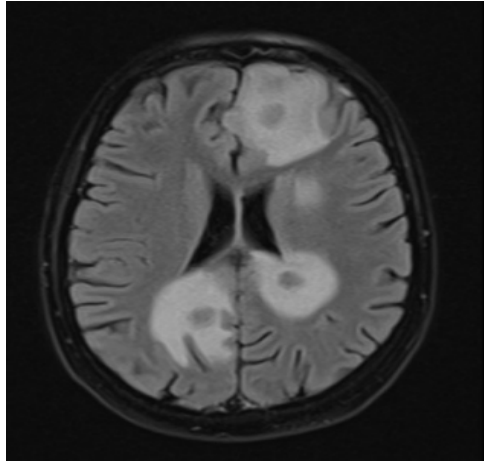


Fig. 5. T.N. First brain MRI scan

At this moment we considered a differential diagnosis of early CNS relapse and Methotrexate toxicity.

Aminophylline treatment was started. We also decided to continue Protocol II, day 45, and another lumbar puncture with intrathecal therapy was performed.

The neurological exam showed left eye hemianopsia and worsening of axial and limb muscle hypotonia so, 2 weeks after the previous MRI, we did another brain MRI exam that showed diffused restriction near the occipital corn of the left lateral

ventricle. The frontal and the right periventricular lesions described at the previous exam were reduced, but the lesion near the left basal ganglia increased in size and the left periventricular lesion got an irregular infiltration. The diagnosis of Methotrexate-induced neurotoxicity was suggested by the resolution of the lesions from the frontal lobe and the periventricular white substance, but the evolution of the other lesions may confirm the diagnosis of CNS relapse (figures 6-7).

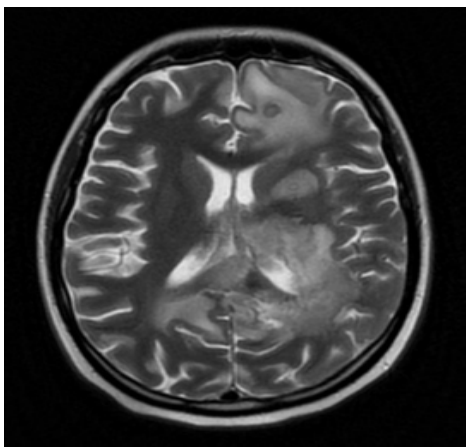


Fig. 6. T.N. second brain MRI scan

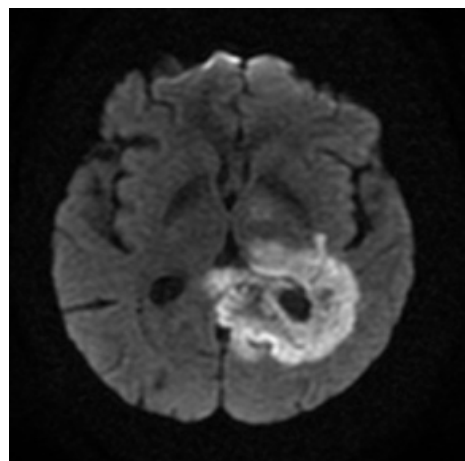


Fig. 7. T.N. second brain MRI scan

We decided to initiate the relapse protocol - ALL-IC-REL 2016, but despite the treatment, her condition progressively deteriorated, the neurological exam showed a motor deficit in the right upper and lower limbs, intense headache and drowsiness.

In evolution, the patient developed status epilepticus, with right body myoclonus, masticatory movements, jerkings of the right upper limb, hardly responsive to antiepileptic treatment and required ICU admission. Due to the impossibility of resuming the cytostatic protocol for CNS relapse and exceeding therapeutic resources for the underlying disease, it was decided to continue with palliative treatment until the patient's death.

3. Discussions

After myelosuppression, neurotoxicity is the second most frequent side effect induced by chemotherapy [3].

The differential diagnosis is the most challenging task after the onset of neurological symptoms. A wide range of other conditions, including CNS infiltration, cerebral infarction, intracranial hemorrhage and CNS infections, can cause focal neurological deficits in patients with hematologic malignancies. Also, paraneoplastic syndromes may cause neurological symptoms, but this only happens in less than 1% of patients [3]. Using a brain MRI scan we can identify parenchymal and leptomeningeal metastasis and using a PET-CT we can distinguish between tumors and inflammation. A lumbar puncture can also be helpful in the diagnosis of leptomeningeal disease and CNS infection [11].

Several factors can contribute to a higher risk of toxicity after MTX treatment. Patients who have mutations in the MTHFR gene, which encodes a key enzyme in the metabolism of folate, may be more susceptible to toxicity. This was the case with our first and third patient [15].

Studies also showed that the association with other drugs will increase the risk of neurologic disturbances. Concomitant administration of cytarabine and cyclophosphamide may induce MTX-neurotoxicity as Bond et al. reported in their study [15]. All of our patients have received concomitant treatment with cytarabine.

More frequent side effects have been reported in higher total cumulative MTX dosage. In our cases, the side effects developed after the 14th administration in our second patient, respectively after the 13th administration in our 3rd patient. Higher doses of MTX are also thought to be responsible for neurological symptoms [16] as can be seen in our first patient, who received a 5g/m² MTX dose.

In addition, studies show that patients who receive concomitant systemic and intrathecal MTX, which is the case in all of our patients, have a higher risk of developing treatment-induced neurotoxicity.

Some medications can help prevent and treat neurotoxicity after MTX treatment, but few studies prove their efficacy. Firstly, folinic acid should be given concomitant with the MTX administration. Studies showed that giving folinic acid in the first 24-36 hours after initiating MTX therapy can prevent neurotoxicity [17]. Secondly, after the onset of the neurological symptoms, Dextromethorphan, an N-methyl-D-

aspartate receptor antagonist, and aminophylline, an adenosine receptor antagonist, have been helpful in the management of MTX-neurotoxicity [1], [11], [18].

4. Conclusions

As the survival rate of children with hematologic malignancies improves, it's essential that the treatments we use don't decrease their quality of life. With greater knowledge of neurotoxicity, there is hope for finding novel medications with less neurotoxic side effects and even potential therapies to reverse or prevent them. The purpose of our study is to raise awareness of the potential neurological side effects of methotrexate use so they can be rapidly recognized and treated.

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