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EDİTÖRE MEKTUP / LETTER TO THE EDITOR

Methotrexate induced sizures in a girl with acute lymphoblastic leukemia

Akut lenfoblastik lösemi tanılı bir kızda metotreksat ile tetiklenen nöbetler

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To the Editor,

Methotrexate (MTX) is a frequently used chemotherapeutic agent in treatment of acute lymphoblastic leukemia (ALL). It can be used intravenously in high or moderate doses in induction and consolidation phases, via per oral route in maintenance therapy and in intrathecal treatment for central nervous system (CNS) prophylaxis. Although MTX is an essential drug in treatment of ALL it can cause acute, subacute, and long-term neurotoxicities. The mechanism of neurotoxicity is thought via disruption of CNS folate homeostasis or direct neuronal damage[1]. In the present report, a girl with ALL who had been treated with weekly methotreaxate and daily mercaptopurine in maintenance phase and who has experienced seizures after per oral administration of MTX is presented.

A 3-year-old girl with a diagnosis of pre-B ALL, randomized into high-risk group, was treated with a modified BFM-ALL chemotherapy protocol. She was in remission when the maintenance therapy was started with weekly methotreaxate (p.o.) and daily mercaptopurine (p.o.). The day after administration of per oral MTX the patient was brought to the hospital because of multiple petit mal fits. Neurologic examination and blood biochemistry were normal. Brain magnetic resonance imaging (MRI) and electroencephalography of the patient showed no abnormality (Figues 1,2). There was no CNS involvement in cerebrospinal fluid examination. Twentyfour hours after second administration of per oral MTX the patient again experienced multiple petit mal fits. Subsequent per oral MTX treatment was omitted and weekly intramuscular MTX (20 mg/m^2) was administered for the remaining part of the maintenance therapy without any complications. The treatment was ceased in October 2013 when the patient was in full remission. The patient did not undergo hematopoetic stem cell transplantation because no HLA compatible donor was found. She is stil regularly followed-up in our outpatient clinic with an interval of 3 months.

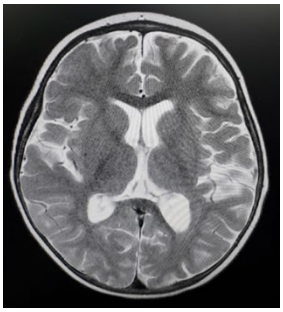

Figure 1. Contrasted brain axial MRI of the patient showing no abnormality

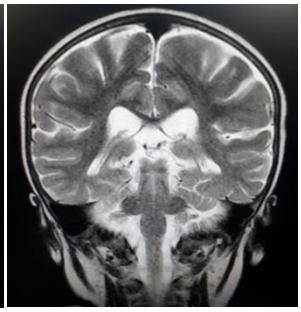

Figure 2. Contrasted brain coronal MRI of the patient showing no abnormality

After administration of multiagent chemotherapy schemes, the prognosis of pediatric ALL patients

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has dramatically improved. Among these drugs MTX is important both for systemic control of leukemia and for prophylaxis and treatment of sanctuary sites, including the CNS. Subacute MTX neurotoxicity typically occurs 2 to 14 days after prolonged low-dose oral, intrathecal, or high dose MTX and manifests with transient stroke-like symptoms, encephalopathy, seizures, and/or aphasia[2].

Interestingly, we did not observe any adverse reactions or signs or symptoms related with intravenous or intrathecal use of MTX prior to per oral administration. In literature, there are numerous cases presenting with findings corresponding to methotrexate encephalopathy[3-5]. Generally, the patients described in literature had epileptic seizures and calcifications in MRI examination. Seizures seen in the present case was petit mal attacks, typically emerging 24 hours after administration of per oral MTX, continuing a few minutes and recurred 2-3 times in a day. No calcifications was described in MRI. Although prior reports have demonstrated that many patients can be safely rechallenged with MTX, some have recurrences of neurotoxicity[6]. Unfortunately, second administration of per oral MTX resulted again in petit mal fits. But, weekly intramuscular administration of MTX was completed for the remaining part of the maintenance therapy without any complication.

Patients reported for MTX neurotoxicity or leukoencephalopathy had neurologic symptoms such as seizure, stroke, behavioral changes or aphasia occurred within 2 weeks of receiving intrathecal or intravenous MTX in literature. To our knowledge, this is the first case of ALL who developed MTX neurotoxicity in the form of petit mal seizures due to per oral administration of MTX and whose treatment was replaced by intramuscular MTX without any complications.

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