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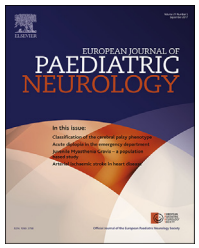

Case study

EEG with extreme delta brush in young female with methotrexate neurotoxicity supports NMDA receptor involvement

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ABSTRACT

Sub-acute neurotoxicity is a well-known complication to high-dose and intrathecal methotrexate (MTX) treatment of children with leukemia. Symptoms can be treated safely by dextromethorphan, a non-competitive antagonist to N-methyl-D-aspartic acid receptor (NMDAR). In a female with subacute MTX neurotoxicity, we observed an electroencephalographic (EEG) with extreme delta brush. Extreme delta brush is an EEG pattern previously described in patients with NMDAR autoimmune encephalitis. The observations suggest that the mechanism of this neurotoxicity may be mediated by the NMDAR. Furthermore, extreme EEG delta brush should suggest a diagnosis of MTX associated subacute neurotoxicity.

1. Introduction

Delta brush is an EEG phenomenon previously observed in patients with autoimmune N-methyl-D-aspartic acid (NMDA) receptor encephalitis and as a physiological finding in neonates. It has been thought to be a unique finding in this condition, when observed in older children and adults. In a recent study delta brush was observed in seven of 23 patients (30.3%) with NMDAR encephalitis.[1] In oncology, high-dose (HDM) and intrathecal treatment (i.t.) methotrexate (MTX) therapy can cause acute, subacute, and chronic neurotoxicity.[2,3] Subacute neurotoxicity, usually develops between two and fourteen days after HDM or i.t. MTX. Symptoms evolve gradually, including various degrees of headache,

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hemiparesis, bilateral weakness, dysphasia, confusion, affective disorders, and seizures.[4,5] MTX interferes with potentially neurotoxic aminoacid and neurotransmitter pathways causing accumulation of homocysteine and its metabolites with strong excitatory effect on NMDA receptors.[4] These changes can be partially reversed by dextromethorphan, a non-competitive antagonist to NMDA-receptors.[6] We here report an EEG with delta brush in a girl with HDM-associated subacute neurotoxicity, which was successfully reversed with dextromethorphan.

2. Case

A 13 year old girl with acute lymphoblastic leukemia (ALL) with no central nervous system involvement at diagnosis was treated according to Nordic/Baltic ALL2008 standard risk protocol and was in remission after four weeks of induction therapy. At treatment day 36 she received her first HDM 5.0 g/m^2 including 12 mg i.t. MTX followed by folinic acid rescue from hour 42 until serum MTX was below 200 nmol/l, obtained at hour 66. Five days after initiation of HDM she became confused and disorientated with latency of speech and weakness of limbs. She exhibited fluctuating symptoms for several days progressing to tonic-clonic seizures and coma. She received symptomatic treatment at the pediatric intensive care unit. Magnetic resonance imaging (MRI) showed hyperintensity in the corpus callosum on T2 and fluid attenuated inversion recovery sequences. Cerebrospinal fluid (CSF) examinations showed normal white cell count, glucose and protein, and herpes-, entero- and varizella-zostervirus DNA was not detected. Homocysteine in CSF analysis normal. Standard EEG on day three from first neurotoxic symptom revealed no signs of status epilepticus as suspected clinically, but was characterized by pronounced frontal 1–2 Hz activity with overlying 13–16 Hz activity, which could be classified as "delta brush" pattern (Fig. 1).

MTX-induced subacute neurotoxicity was suspected. Teophyllin infusion 5 mg/kg, an established treatment for acute MTX neurotoxicity, was given three days from first neurotoxic symptoms, but without any effect. The following day she started treatment with dextromethorphan 2.0 mg/kg/day, and symptoms improved within 24 h. EEG was repeated 9 days after first neurotoxic symptom, when she had improved clinically and was characterized by diffuse theta activity and muscle artifacts, but showed no evidence of delta brush.

Subsequently, she uneventfully received her planned seven additional courses of MTX; dextromethorphan 2.0 mg/kg/day was given in three divided doses from three days before until one week after HDM.

3. Discussion

Little has been published on EEG findings in patients with MTX neurotoxicity. A few studies describe EEG with non-specific changes such as generalized or regional slowing, whereas other patients seem to have an unaffected EEG, emphasizing the need for systematic EEG studies in case of MTX neurotoxicity.

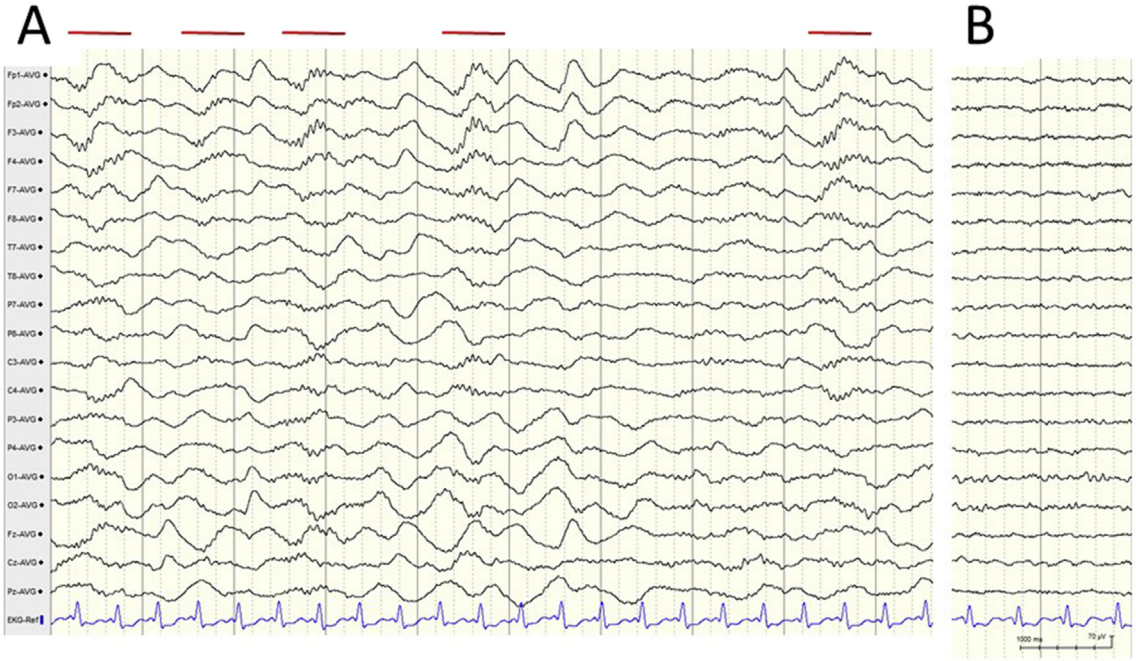

Fig. 1 – Electroencephalogram (EEG) of the patient presented. Panel A: Five appearance of delta brush marked with red bars on day three from first neurotoxic symptom. Panel B: Low amplitude theta activity on day nine from first neurotoxic symptom. The EEG of the two panels are similar: paper speed 30 mm/s, low cut filter 1.0 Hz, high cut filter 40 Hz, gain 150 uV/cm. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

EEG with delta brush, which was observed in the present case of MTX subacute neurotoxicity has previously been described in patients with NMDA receptor (NMDAR) encephalitis.[1] This is an autoimmune encephalitis characterized by a prodromal phase with flu-like symptoms followed by hyperkinetic movement disorder, expressive aphasia, seizure and behavioral changes.[7] NMDAR antibodies are found in the blood and CSF of the patients [7]; treatment with immunosuppressants can lead to full or partial recovery within months.[7]

The observation of EEG changes with delta brush pattern in the two conditions, where NMDA receptors are likely to be involved, may indicate that this EEG pattern is pathognomonic for pathology of the NMDA receptor.

The symptoms of subacute MTX encephalopathy usually resolve spontaneously within two weeks. However, clear guidelines for treatment of MTX-related neurotoxicity and approach to prevent recurrence are lacking, and treatment is mostly symptomatic. Dextromethorphan is an ingredient in many over-the-counter cough suppressants and acts as a non-competitive antagonist to NMDA-receptors. In the present case dextromethorphan reversed the symptoms of subacute neurotoxicity in accordance with previous studies.[6]

Prior studies support that many patients can be safely rechallenged with HDM or i.t. MTX, although some experience recurrences.[5,6] We have successfully used dextromethorphan as a prophylactic agent against MTX neurotoxicity,[6] however, it is not possible to extrapolate a causative association based on this case report and prospective randomized controlled studies are needed in order to determine the effect of dextromethorphan in these patients.

There are no reports of dextromethorphan use in NMDA receptor encephalitis, but with the favorable adverse effect profile of this drug, this option could be explored in future studies.

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Conflict of interest

None of the authors have any conflict of interest.

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