

## Reversible Leukoencephalopathy After Oral Methotrexate

To the Editor:

Central nervous system (CNS) white-matter changes have been reported after high-dose intrathecal or intravenous methotrexate (MTX) chemotherapy<sup>1,2</sup>. We describe reversible brain lesions following the use of oral MTX.

A 59-year-old woman developed leukoencephalopathy strictly localized in the cerebellum after treatment with oral MTX 25 mg/week for 4 years. She was diagnosed with rheumatoid arthritis (RA) 10 years earlier and initially did well, receiving sulfasalazine 1000 mg twice a day and diclofenac 75 mg twice a day. After a flare of RA disease 4 years ago, sulfasalazine was stopped and MTX 25 mg oral once a week was initiated. While she took MTX, no signs of arthritis were present. The last 6 months she complained of fatigue and subtle coordination disturbances during tennis and skiing and was referred to the neurology outpatient clinic. She reported having fallen from her bicycle several times recently and also had slurred speech for several minutes after drinking 2 glasses of wine. She complained of mood swings and increased agitation at times. In addition to MTX 25 mg once a week, she used folic acid 2.5 mg/day and diclofenac 75 mg twice a day. General and neurological examinations were normal. Magnetic resonance imaging (MRI) of the brain showed symmetrical lesions in the central white matter of the cerebellar hemispheres with an isolated discrete lesion bilateral in the middle cerebellar peduncle. These lesions were hyperintense on T2-weighted and fluid-attenuated inversion recovery sequences (Figure 1A, 1B), showed diffusion restriction on diffu-

sion-weighted imaging and apparent diffusion coefficient map (Figure 1C, 1D), and no disruption of the blood-brain barrier on postgadolinium T1-weighted images. Kidney function was normal and blood tests on anti-neural antibodies were negative. Cerebrospinal fluid (CSF) analysis showed no pleiocytosis and normal levels of protein and IgG, with oligoclonal bands absent. MTX concentration in the CSF (5 days after last intake) was 4.0 nmol/l. Reference values are nonexistent for MTX CSF levels; however, blood levels after intravenous treatment with MTX have been reported around 60 nmol/l at 72 h after administration.

The diagnosis was established as delayed MTX-induced leukoencephalopathy localized to the cerebellum; MTX was discontinued and folic acid was increased to 5 mg/day. Symptoms diminished within several weeks. Repeat MRI after 2 months showed considerable decline of the cerebellar lesions, while after 8 months MRI showed near complete resolution of the abnormalities, with only small lesions remaining in both cerebellar peduncles (Figure 1E, 1F). Initially no alternative treatment for RA was attempted, but after 4 months RA symptoms reoccurred and subcutaneous etanercept 50 mg once a week was started. The case was reported to the Netherlands Pharmacovigilance Centre.

MTX is lipid-insoluble and scarcely crosses the blood-brain barrier; CNS complications following oral MTX are very rare. In our patient no obvious reason explained the increased MTX levels. Kidney function was normal, no concurrent protein-binding medication was used, no comorbidities were present causing third-space phenomena, and no proton pump inhibitor or vitamin C was used. MTX acts as a folate antagonist, and there-

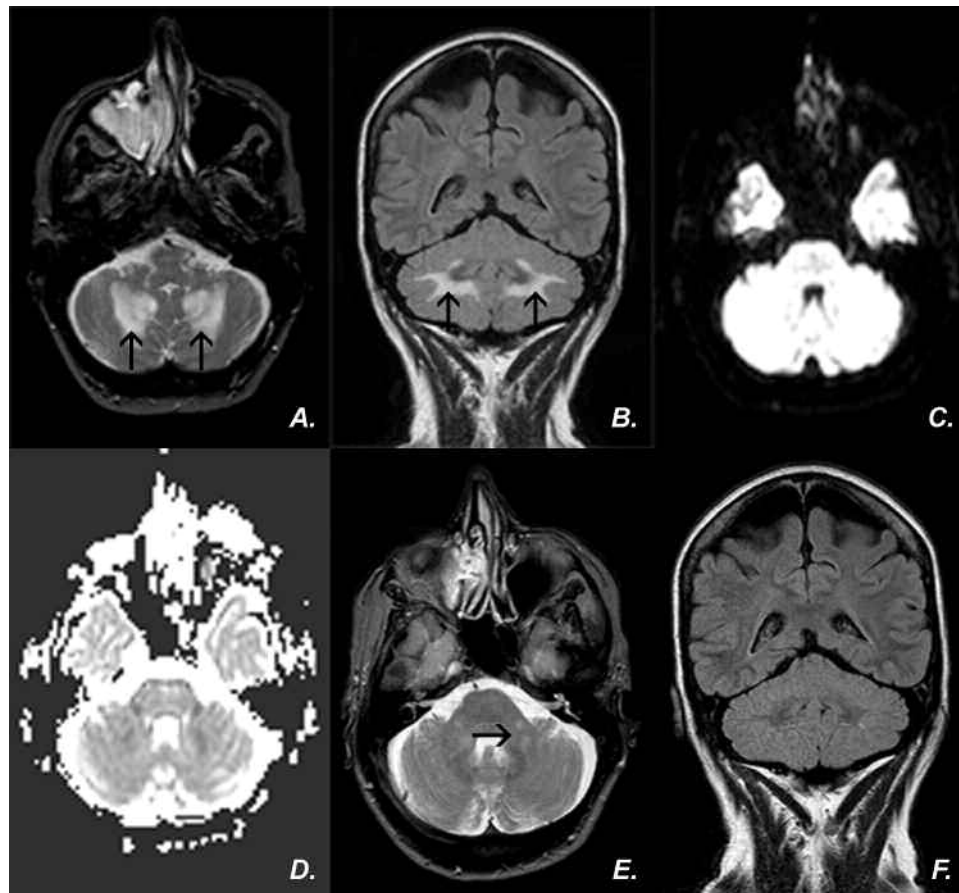


Figure 1. A to D. Magnetic resonance imaging of the brain at initial presentation [A, T2 spin-echo; B, fluid-attenuated inversion recovery sequences (FLAIR); C, diffusion-weighted imaging (DWI); D, apparent diffusion coefficient (ADC)] shows symmetrical lesions in the central white matter of the cerebellar hemispheres (arrows). Diffusion restriction is shown on DWI (C) and ADC (D). Panels E (T2 spin-echo) and F (FLAIR) at 8-month followup show nearly complete resolution, with small lesions remaining in both cerebellar peduncles (E, arrow).

fore folate is substituted in patients using MTX. In our patient folate was also substituted and the folic acid level was increased (> 45.3 nmol/l). Vitamin B12 (cobalamine), also necessary for the synthesis of methionine from homocysteine, was also normal (226 pmol/l).

The enzyme methylenetetrahydrofolate reductase (MTHFR) is necessary for folate metabolism; the related genes are *MTHFR 1298A>C* and *MTHFR 667C>T*. Genetic analysis revealed that haplotype C/C for both these genes was present, which leads to a mildly decreased metabolic capacity of the MTHFR enzyme. This probably leads to the inhibition of methionine that is necessary for normal CNS myelination<sup>3</sup>. The enzymes MRP2 and RFC are involved in transport of MTX into and out of cells; the related genes for these enzymes were found to be normal (heterozygous genotype): *ABCC2 (1251 G>A)*, *ABCC2 (A>G)*, and *RFC (81A>G)*. However, it has been shown that with the RFC A allele, which was present in our patient, MTX is taken up more efficiently, which can lead to increased MTX levels<sup>4</sup>.

The white-matter changes were strictly localized to the cerebellum. This selective localization has also been reported in intoxication by phenytoin<sup>5</sup>, an antiepileptic drug shown to inhibit MTHFR activity<sup>6</sup>. The selective cerebellar localization can possibly be explained by selective involvement of Purkinje cell axons in the white matter, which are found only in the cerebellum. There are a few reports of patients having MTX-induced white-matter changes after oral treatment<sup>7,8,9</sup>. Yokoo, *et al* described a patient with fatal leukoencephalopathy with severe demyelination during low-dose oral MTX treatment for RA; however, MTX could not be detected in the CSF<sup>7</sup>. Raghavendra, *et al* described a patient with reversible leukoencephalopathy receiving low-dose oral MTX; the initial reversible leukoencephalopathy was followed by a disseminated necrotizing leukoencephalopathy<sup>8</sup>. Worthley and McNeil reported a man who developed a dementing illness with leukoencephalopathy while receiving low-dose oral MTX for RA<sup>9</sup>. However, after cessation of treatment, there was no improvement of MRI findings or mental status. We believe our patient is unique in that she developed a leukoencephalopathy during oral MTX treatment that was reversible, clinically as well as on MRI imaging, after discontinuation of MTX. The strict localization to the cerebellar white matter in our case has not been reported previously and suggests a specific pathogenesis. As well, we were able to detect MTX in CSF and found the specific polymorphisms that interfere with methionine synthase activity and transport of MTX into the cell.

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