## A Case of Low-Dose Oral Methotrexate–Induced Reversible Neurotoxicity

Methotrexate (MTX) has poor central nervous system penetration as an oral agent. Although commonly seen with intrathecal dosing, there are only few reports of oral MTX−induced cerebral toxicity, all describing leukoencephalopathy. We report the first case of oral MTX causing reversible cerebral diffusion-weighted imaging (DWI) hyperintensities without leukoencephalopathy. We have attempted to describe the mechanism of this transient MTX-induced neurotoxicity on the basis of a search of available literature.

A 61-year-old woman with a history of systemic lupus erythematosus and rheumatoid arthritis presented with word-finding difficulty, headache, and left-sided weakness for 2 days. Her home medications included hydroxychloroquine, 400 mg daily; folic acid; and oral MTX (15 mg/week; cumulative dose, 7800 mg during 10 years). Clinical examination, CT of the head, and electroencephalographic findings were normal. Laboratory studies disclosed the following values: rheumatoid factor, 63.3 IU/mL; antinuclear antibody titer, 1:640; and homocysteine, 16.4 mmol/L. Findings of MR imaging of the brain were abnormal (Figs 1*A*, -*B*). MTX was discontinued subsequently. Findings of repeat MR imaging performed 5 weeks after the cessation of oral MTX were normal. All of the patient's symptoms had resolved at this time.

To the best of our knowledge, this is the first reported case demonstrating isolated reversible cerebral DWI changes in the absence of leukoencephalopathy due to low-dose oral MTX. There are 6 previous reports of oral MTX−related cerebral toxicity, all describing leukoencephalopathy. Only 1 case report[1] described restricted diffusion of protons in a patient who eventually developed disseminated necrotizing leukoencephalopathy. The MR imaging findings of our patient suggest cytotoxic edema, most likely due to a metabolic insult causing myelin sheath edema. Possible mechanisms of MTX-induced neurotoxicity are elevated homocysteine levels and their excitatory amino acid neurotransmitter metabolites as homocysteic acid and-cysteine sulfinic acid[2]; elevated intracellular adenosine levels[3]; and impairment of biopterin metabolism, leading to decreased availability of monoamine neurotransmitters.[4] DWI/apparent diffusion coefficient (ADC) changes in our patient did not adhere to a vascular territory, excluding the possibility of stroke. Acute demyelination and posterior leukoencephalopathy are not very likely the etiology because they typically cause increased ADC signal intensity. The reversibility of the DWI signal intensity after withholding MTX suggests none of the patient's other medications or her diseases were the cause of her lesions.

Complete resolution of MR imaging changes in our patient suggests that oral MTX−induced neurotoxicity can be reversible with early intervention. Timely recognition might help prevent disseminated necrotizing leukoencephalopathy, which is a reported complication of oral MTX therapy.

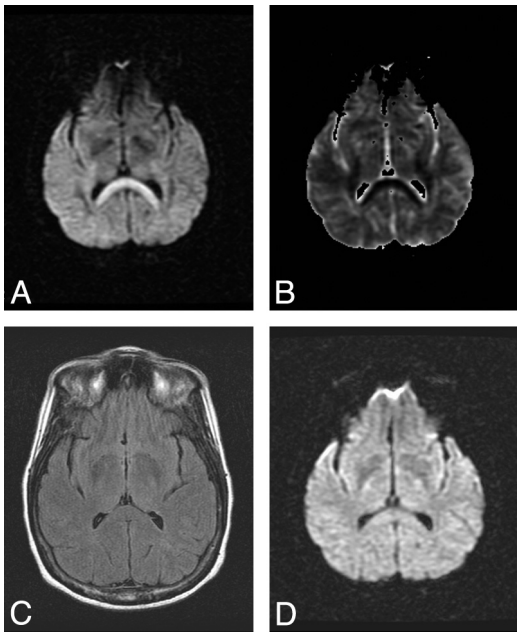


**Fig 1.** MR images of the brain show DWI hyperintensity in the splenium of the corpus callosum (*A*) and bilateral parietal lobes with corresponding low signal intensity in the ADC map (*B*). *C,* T2-weighted fluid-attenuated inversion recovery (FLAIR) findings are unremarkable. *D,* Repeat MR imaging shows complete resolution of prior DWI changes. The T2 FLAIR image (*C*) is unchanged.

### References


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