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MTHFR C677T POLYMORPHISM IS ASSOCIATED WITH METHOTREXATE-INDUCED MYELOPATHY RISK

Myelopathy is a rare complication of methotrexate (MTX) therapy.¹ A polymorphism (C677T) in the folate enzyme methylenetetrahydrofolate reductase (MTHFR) gene is associated with MTX hematologic and hepatic toxicity.² We describe 3 cases of severe MTX myelopathy associated with the MTHFR C677T polymorphism.

Case reports. *Case 1.* A 49-year-old man with a CNS relapse of acute myeloid leukemia (AML) received intrathecal (IT) MTX and cytarabine. He developed lower extremity numbness and urinary retention 6 weeks later. Serial lumbar punctures found elevated total (46 mg/dL) and myelin basic protein (MBP) (468 ng/dL). With continued IT MTX, he developed flaccid quadriplegia, a T10 sensory level, and areflexia that worsened following allogeneic stem cell transplant and radiation. MRI revealed T2 dorsal and lateral column hyperintensity from T2 to T12 (figure). Despite subcutaneous and oral cyanocobalamin and steroids, MRI 1 month later showed extension of the T2 hyperintensity into the medulla. MTHFR testing revealed C677T homozygosity. Autopsy demonstrated subacute multifocal necrosis of gray and white matter with neutrophilic invasion of the spinal cord and numerous eosinophilic α motor neurons. There was no preferential vasculature involvement or residual AML.

Case 2. A 58-year-old woman with rheumatoid arthritis was treated with oral MTX (20 mg weekly). After 5 years, she developed Lhermitte sign, asymmetric leg weakness, and ascending sensory loss. Examination revealed flaccid paraplegia, preserved reflexes, and a T8 sensory level. MRI demonstrated dorsal and lateral column T2 hyperintensity from T1 to T12 (figure). CSF was normal aside from elevated MBP (140.5 ng/dL). MTHFR testing revealed C677T homozygosity. Despite IV and oral folinic acid (leucovorin) and steroids, she developed spasticity and was lost to follow-up.

Case 3. A 52-year-old woman with HIV-associated Burkitt lymphoma was initially treated with chemotherapy including IT MTX. Following a relapse 5 months later, she received the modified Magrath regimen

including IV and supplemental IT MTX. During treatment she developed proximal leg weakness and ataxia, followed by flaccid paraplegia and incontinence. CSF analysis showed a pleocytosis (92 nucleated cells/mm³, 70% lymphocytes), likely from the subclinical aseptic meningitis commonly observed with IT MTX.³ Total protein and MBP were elevated (52 mg/dL and 14.8 ng/dL). MRI demonstrated T2 dorsal column hyperintensity from T6 to T12 (figure). MTHFR testing revealed C677T heterozygosity. Three months after methyl-transfer pathway repletion (S-adenosyl methionine [SAM], IV folinate, IV cyanocobalamin, oral methionine, and leucovorin), leg strength improved to 3/5, sensory findings resolved proximal to the ankles, and MRI was normal.

Discussion. We describe 3 patients with MTHFR C677T polymorphism who developed debilitating myelopathy following MTX therapy, consistent with prior descriptions of MTX myelopathy including dorsal and lateral column T2 hyperintensity, elevation of MBP (suggestive of but not diagnostic for demyelination), and vacuolar degeneration with or without spinal cord white matter necrosis.^{4–6} These findings suggest this polymorphism may be associated with increased risk of MTX myelopathy.

The C677T polymorphism has been associated with increased hematologic, hepatic, and mucosal toxicity following MTX administration, although an association with MTX myelopathy has not been firmly established.² Two MTHFR polymorphisms (C677T and A1298C) cause reduced enzyme activity.⁷ Forty percent of the population are C677T heterozygotes, while only about 9% are homozygotes, leading to a 40% and 70% reduction in enzyme activity, respectively.^{1,2} The odds that the polymorphisms in this case series are due to random chance is 1:346, making an association likely.

MTX myelopathy causes preferential but not exclusive injury to white matter tracts, similar to subacute combined degeneration associated with cobalamin deficiency. While the precise mechanism is unknown, there are several reasons that the MTHFR C677T polymorphism may increase risk. MTX directly damages endothelial spinal capillaries, leading to ischemic white matter injury and increased blood–brain barrier permeability.^{2,5} MTX also inhibits tetrahydrofolate

(A) Case 1: thoracic axial image shows dorsal and lateral column hyperintensity and sagittal image shows dorsal column hyperintensity. (B) Case 2: thoracic axial image shows dorsal and lateral column hyperintensity and sagittal image shows dorsal column hyperintensity. (C) Case 3: thoracic axial and sagittal images show dorsal column hyperintensity.

synthesis. Downstream, MTHFR converts bioactive tetrahydrofolate, 5,10-methylenetetrahydrofolate to 5,10-methyltetrahydrofolate, a precursor to S-adenosylmethionine, an essential substrate in the transmethylation and maintenance of myelin.^{2,4-7}

There is no standard treatment for MTX myelopathy but some studies propose SAM, folate, and cyanocobalamin supplementation.⁶ In this series, only patient 3, who received multiple metabolites,

achieved moderate recovery. The disparate outcomes in these patients likely reflect varying time to treatment, metabolite supplementation, underlying disease, previous neurotoxic treatments, and IT vs long-term oral (case 2) MTX therapy.

This series describes a possible link between MTX myelopathy and the MTHFR C677T polymorphism. Clinicians should have a high index of suspicion in patients receiving MTX who develop signs of unexplained myelopathy. MTHFR C677T testing is commercially available and may help stratify MTX myelopathy risk. Early treatment with SAM, methionine, leucovorin, and cyanocobalamin should be considered.

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