

DO MTHFR MUTATIONS KICK IN DURING FAMILIAL MEDITERRANEAN FEVER ATTACKS?

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To the editor,

A 26-year-old woman had been admitted to the hospital with abdominal pain, fever (39 °C) and vomiting one year ago. She had also had myalgias in the lower extremities bilaterally. The medical history had otherwise been noncontributory. Physical examination had revealed generalized abdominal tenderness in the lower quadrants. Gynecological examination had yielded sensitivity in the cervix uteri. Laboratory tests had been as follows; leukocytes: 12900/ μ L hemoglobin: 12.9 g/dL C-reactive protein: 5.96 mg/dL, fibrinogen: 417 mg/dL. Pelvic ultrasonography had been unremarkable except minimal fluid in Douglas pouch. She had been hospitalized with a suspect diagnosis of pelvic inflammatory disease and a combination of i.v. ofloxacin plus metronidazole treatment had been started. One day later, she had been discharged with oral antibiotics as her complaints had subsided significantly.

One month later, she had been hospitalized again with the same (above quoted) complaints. She had been commenced clindamycine and sulbactam/ampicillin therapy again for pelvic inflammatory disease. On the 3rd day of her hospital stay, abdominal computed tomography, performed for persistent abdominal tenderness, had been inconclusive other than free pelvic fluid. In the meantime, as the patient had been planning pregnancy, further laboratory tests had been also performed. Hyperhomocysteinemia (15.4 μ mol/l, N:5.5-10) and increased antithrombin III activity (128%, N:80-120) had been detected. Thereafter, she had been found to be heterozygous for methylene tetrahydrofolate reductase (MTHFR) and plasminogen activator inhibitor-1 (PAI-1) gene mutations. Accordingly, she had given up using oral contraceptive drugs.

After an asymptomatic period for one year, she

was recently seen for fever and abdominal pain. Since her gynecologic examination was normal, and in the light of her previous history, she was clinically diagnosed to have familial Mediterranean fever (FMF). Oral colchicine treatment (1.5 mg/day) was then started. On detailed questioning, she also recalled six similar episodes during the last eight years. Currently, she is free of any attacks under colchicine treatment. Genetic analysis for FMF was inconclusive.

In patients with MTHFR mutations, folate metabolism is affected in several ways. Specifically, the methylation cycle seems to be impaired; reduced enzyme activity and decreased remethylation of homocysteine to methionine lead to elevated total homocysteine and reduced *de novo* methyl group supply for transmethylation reactions. Moreover, altered Th1/Th2 balance resulting from inhibition of the remethylation cycle is speculated to cause abnormal cellular immune response in relevant patients.¹ There are various reports on the relationship between hyperhomocysteinemia and common rheumatic diseases (Th1 immune response).²⁻⁶ A similar causal relationship has also been shown in atopy (Th2 immune response).¹ On the other hand, to the best of our knowledge, any linkage between homocysteine metabolism and FMF, whereby Th1 polarization is already known,⁷ has not been reported in the pertinent literature.

Overall, far from being able to exclude only a coincidence, we draw attention to the possible contribution of MTHFR mutations to the inflammatory cascade in FMF. Last but not least, if our observation can be substantiated with further studies, evaluation for MTHFR mutations and perhaps folate supplementation may become necessary in selected patients.

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