COLLEGE of AMERICAN PATHOLOGISTS

5,10-Methylenetetrahydrofolate Reductase (MTHFR)

SYNOPSIS AND RELEVANCE

5,10-Methylenetetrahydrofolate Reductase (MTHFR) may be misapplied as a screening test for risk of thromboembolism, coronary artery disease or recurrent pregnancy loss. Testing for theses indications is no longer recommended and may lead to diagnostic misinformation.

Limited indications for MTHFR include prerequisite testing for hypersensitivity to anti-folate (eg, methotrexate) therapy, identification of patients with depression who may benefit from folate supplementation or evaluation of unexplained hyperhomocysteinemia in adults as well as congenital metabolic disorder in infant if recommended by genetic counselor.

INSIGHTS

Due to the potential for clinical misapplication MTHFR testing, development of consensus guidelines for testing indications should be sought among medical staff and stakeholders. Specifically, the following conditions should be considered as not meeting evidence-based practice:

- Screening for risk of neural tube defects in pregnancy.
- Evaluation of risk for recurrent pregnancy loss.
- Risk assessment for coronary artery disease.
- Evaluation of single or recurrent thrombotic event(s).
- Hypercoagulability risk assessment.
- Repeat MTHFR order for the same genotypes when the test was already performed.

MTHFR genotyping may be indicated for the following:

- Predicting toxicity of anti-folate medications (methotrexate).
- Evaluation of adults with persistent hyperhomocysteinemia.
- Identification of patients with depression who may benefit from folate supplementation.

BACKGROUND

There are two common MTHFR variants that are known to decrease MTHFR enzyme activity: the “thermolabile” variant, referred to as C677T, and the A1298C variant. Only Individuals who are homozygous for the former variant commonly demonstrate hyperhomocysteinemia, which is typically mild but may be enhanced in the setting of low serum folate levels. This variant is most common in Hispanics (25%) and 10-15% of North American Caucasians.[1]

While hyperhomocysteinemia is a known risk factor for venous thrombosis and is associated with other cardiovascular diseases (eg coronary artery disease), the clinical significance of MTHFR genetic variation alone is uncertain.[2] Furthermore, in the United States, grain products are fortified with folic acid, which may further reduce the potential impact of MTHFR variants.[3,4] In addition, results from recent studies, and meta-analyses have been unable to confirm earlier reports of MTHFR variants with various other conditions such as stroke, aneurysm, peripheral artery disease, migraine, hypertension, recurrent pregnancy loss, male infertility, risk for neural tube defects in offspring, several types of malignancy, neuropsychiatric diseases including depression, and chemotherapy-related toxicity.

Currently, MTHFR testing is not recommended in the work-up of thrombophilia or recurrent pregnancy loss by the American College of Medical Genetics and Genomics, the American College of Obstetricians and Gynecologists, the British Committee for Standards in Haematology, the British Society for Haematology, the American College of Chest Surgeons, the Royal College of Pathologists of Australasia, or the College of American Pathologists.[2] Providers caring for patients who have undergone MTHFR testing should ensure that patients have received appropriate work-up for their symptoms to avoid a misdiagnosis due to incorrectly attributing symptoms to the presence of MTHFR variants.

At present the only evidence-based indications for MTHFR variant testing are for: 1) predicting toxicity of anti-folate medications, 2) evaluation of adults with depression who may benefit from folate supplementation, 3) evaluation of the cause of patients with persistent hyperhomocysteinemia, or 4) infants with rare in-born errors of metabolism associated with severe elevations in homocysteine.

REFERENCES

1. Eldibany MM, Caprini JA. Hyperhomocysteinemia and thrombosis: an overview. *Arch Pathol Lab Med.* 2007;131:872-884. doi: https://doi.org/10.5858/2007-131-872-HATAO
2. Hickey SE, Curry CJ, Toriello HV. ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing. *Genet Med.* 2013;15:153-156. doi:10.1038/gim.2012.165