Methylenetetrahydrofolate Reductase Screening in Treatment-Resistant Depression

CAPT Courtney E. Kandler, MD, USA, MC; and MAJ Sherrell T. Lam, MD, USA, MC

Therapeutic response to antidepressant drugs is often partial. Multiple trials of medications may be prescribed before a patient achieves remission of symptoms. Further, no universally accepted definition for treatment-resistant depression (TRD) has been established. The most commonly proposed definition (and the definition used in this article) is the failure to achieve remission with 2 or more adequate antidepressant treatments.[1]

About 20% to 30% of patients with depression are treatment resistant. The overall Canada-wide prevalence of TRD in primary care was 21.7%.[2] In the US, about 15.7 million adults have had at least 1 major depressive episode in the past year, and 10% to 15% of major depressive disorder (MDD) cases can be classified as treatment resistant.[3,4] In a retrospective, longitudinal cohort analysis in a Medicaid population, 25.9% of pharmacologically treated adults with MDD met criteria for TRD.[5] Similarly, TRD in this review was defined as starting a third treatment regimen after 2 adequate regimens of antidepressants.

Why is this important? Treatment resistance is often associated with high rates of disability and comorbidity. Given the significant prevalence and impact of TRD, research into better understanding and treating these patients is paramount. Pharmacogenetics has been proposed for tailoring therapy and theoretically circumventing treatment resistance to achieve better outcomes.

Methylenetetrahydrofolate reductase (*MTHFR*) is a gene that encodes an enzyme similarly called MTHFR. The enzyme converts 5,10-MTHF to 5-MTHF. 5-MTHF then donates a methyl group in the conversion of homocysteine to methionine. Decreased or absent expression of *MTHFR* leads to decreased levels of 5-MTHF, which then leads to high levels of homocysteine. This results in suboptimal production of monoamines, including serotonin, dopamine, and norepinephrine as well as subsequent abnormalities in neural and vascular pathways.[6]

Screening for *MTHFR* polymorphisms has been proposed in past years due to weak associations with conditions such as cardiac disease, poor pregnancy outcomes, and colorectal cancer.[7] Recently, an increasing number of studies suggest screening for *MTHFR* polymorphisms in patients with depression. This proposal is based on demonstrated links between abnormal folate metabolism and high levels of homocysteine and an increased risk for MDD and reduced antidepressant effectiveness.

In a meta-analysis by Wu and colleagues of 26 published studies, including 4,992 depression cases and 17,082 controls, *MTHFR* C677T polymorphism was associated with an increased risk of depression especially in Asian populations. This relationship was not observed in the elderly.[8] A more recent article reviewing 6 small studies from 2005 to 2016 suggested that the *MTHFR* A1298C polymorphism (via abnormal homocysteine metabolism and folate cycles) may play a role in identifying those at risk of developing MDD particularly women in white populations.[9]

As the proposed mechanism of treatment resistance associated with the *MTHFR* polymorphisms seems to be related to folate metabolism, L-methylfolate supplementation has been recommended. In a 60-day randomized trial of a selective serotonin reuptake inhibitor (SSRI) and L-methylfolate vs SSRI and placebo, patients prescribed an SSRI with L-methylfolate had a greater response rate (reduction of baseline symptoms by at least 50%) that was statistically significant ($P = .04$) vs patients taking the placebo.[10]

In primary care and specialty settings, screening patients with TRD for *MTHFR*

Courtney Kandler is a Resident in the Dual Internal Medicine-Psychiatry Residency Program, and **Sherrell Lam** is the Service Chief, Inpatient Psychiatry, both at Walter Reed National Military Medical Center in Bethesda, Maryland. Sherrell Lam also is an Assistant Professor, Psychiatry and Internal Medicine at the Uniformed Services University of Health Sciences in Bethesda.
Correspondence: Courtney Kandler (crtkandler21@gmail.com)

polymorphisms has been proposed. LabCorp (Burlington, NC) and Quest Diagnostics (Secaucus, NJ) have a DNA assay that detects C677T and A1298C mutations in the *MTHFR* gene, using whole blood samples; however, the cost is high. In the DC/Maryland/Virginia region, test cost varies from $390 if the patient requests it from the lab to $325 if requested through an institution that has an account with LabCorp. Although there are little data regarding false positive and false negative rates, 1 source suggested an analytic sensitivity and specificity of 99% for the tests.[11]

Once obtained, positive screening results may assist in directing next steps in terms of adjunctive or next-line therapies. Given the high price of the test and positive responses with L-methylfolate supplementation thus far, the question remains: Why not supplement patients with TRD with folate and forego screening? For these 2 reasons: The treatment dosage in the studies referenced is 15 mg of L-methylfolate. This dosage is often unavailable over-the-counter and can cost as much as $75 for 90 capsules. Additionally, the high dosage of methylfolate may increase the risk of colon cancer in certain subpopulations, such as those with precancerous lesions.[12]

Although the current data seem promising, further research is needed to explore the benefits of folate supplementation in larger study samples and perhaps other targeted treatment options for patients with TRD with *MTHFR* gene polymorphisms.

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

Disclaimer

References

1. McIntyre RS, Filteau MJ, Martin L, et al. Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach. *J Affect Disord*. 2014;156:1-7.
2. Rizvi SJ, Grima E, Tan M, et al. Treatment-resistant depression in primary care across Canada. *Can J Psychiatry.* 2014;59(7):349-357.
3. Stahl SM. Novel therapeutics for depression: L-methylfolate as a trimonoamine modulator and antidepressant-augmenting agent. *CNS Spectr.* 2007;12(10):739-744.
4. Little A. Treatment-resistant depression. *Am Fam Physician*. 2009;80(2):167-172.
5. Olfson M, Amos TB, Benson C, McRae J, Marcus SC. Prospective service use and health care costs of Medicaid beneficiaries with treatment resistant depression. *J Manag Care Spec Pharm.* 2018;24(3):226-236.
6. Bottiglieri T, Laundy M, Crellin R, Toone BK, Carney MW, Reynolds EH. Homocysteine, folate, methylation, and monoamine metabolism in depression. *J Neurol Neurosurg Psychiatry.* 2000;69(2):228-232.
7. Long S, Goldblatt J. MTHFR genetic testing: controversy and clinical implications. *Aust Fam Physician.* 2016;45(4):237-240.
8. Wu YL, Ding XX, Sun YH, et al. Association between MTHFR C677T polymorphism and depression: an updated meta-analysis of 26 studies. *Prog Neuropsychopharmacol Biol Psychiatry.* 2013;46:78-85.
9. Cho K, Amin ZM, An J, Rambaran KA, Johnson TB, Alzghari SK. Methylenetetrahydrogolate reductase A1298C polymorphism and major depressive disorder. *Cureus.* 2017;9(10):e1734.
10. Papakostas GI, Shelton RC, Zajecka JM, et al. L-methylfolate as adjunctive therapy for SSRI-resistant major depression: results of two randomized, double blind, parallel-sequential trials. *Am J Psychiatry.* 2012;169(12):1267-1274.
11. Hickey SE, Curry CJ, Toriello HV. ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing. *Genet Med.* 2013;15(2):153-156.
12. Baggott JE, Oster RA, Tamura T. Meta-analysis of cancer risk in folic acid supplementation trials. *Cancer Epidemiol.* 2012;36(1):78-81.