CASE REPORT

Anxiety and Methylenetetrahydrofolate Reductase Mutation Treated With *S*-Adenosyl Methionine and Methylated B Vitamins

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Abstract

This case report highlights challenges faced in the clinical management of patients with methylenetetrahydrofolate reductase (MTHFR) gene mutations and the importance of precise dosage when recommending methylated B vitamins to compensate for deficiencies caused by the polymorphism or symptoms related to the polymorphism. It also underscores the importance of obtaining ongoing objective assessments of anxiety (eg, Patient Reported Outcomes Measurement Information System, or PROMIS) to help gauge patient response.

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A 32-year-old female patient with 2 primary concerns, hypothyroidism and anxiety, consulted a new physician who suspected that the patient might have a methylenetetrahydrofolate reductase (MTHFR) abnormality. Lab testing confirmed a compound heterozygous MTHFR gene mutation, and the patient was prescribed methylated folate and cobalamin. *S*-Adenosyl-methionine (SAMe) was added later for the management of anxiety. The cofactors methylcobalamin, methylfolate, and SAMe ensure adequate methylation in important biochemical pathways

Patient Information

Initial Medical Consultation: August, 2014

A 32-year-old Caucasian female with a history of hypothyroidism (and asthma) chose to visit a new doctor for evaluation of her thyroid medications. She was in graduate school and was experiencing academic-related stress and anxiety. In the past, she has used yoga, meditation, and dietary supplements to control her anxiety.

At her first visit, the patient was taking Thyroid (Erfa, Montréal, Quebec, Canada), 90 mg, 5 times per week and 115 mg, 2 times per week, for hypothyroidism. Laboratory testing revealed that she was hyperthyroid and her medication was adjusted to 90 mg of NP Thyroid (Acella Pharmaceuticals, Alpharetta, GA, USA) daily at her first visit. The patient was also advised to begin methylated B vitamins and a test was ordered to evaluate a possible MTHFR mutation. See Tables 1 and 2 for patient medications.

Follow-up Visit 1: September, 2014

After beginning the new methylated B vitamin with activated folate (Table 1), the patient returned to her physician complaining that she was experiencing increased anxiety. Laboratory results confirmed that this patient had a compound heterozygous MTHFR mutation (1 copy of the C677T mutation and 1 of the A1298C mutation). See Table 3 for thyroid laboratory evaluations for this patient.

Follow-up Visit 2: November, 2014

At the second visit, the patient continued to report increased anxiety and on one occasion had visited the hospital emergency room with anxiety-related chest pain that was successfully treated with Ativan (Wyeth-Ayerst Laboratories, Philadelphia, PA, USA). The physician suspected the methylated folate and cobalamin dosage might be contributing to the increased anxiety. Her methylated B-vitamin dose was lowered and changed to a methyl-B_{12}/L-5-MTHF lozenge form that would allow for better control of the dose of methylated B_{12} and folate. The patient on remained on Ativan PRN as needed (see Table 1).

Figure 1. Timeline With Medications and Doses

Age 16—Dx Hypothyroidism

Age 28—Begins new brand thyroid medication

- Erfa Thyroid (125 mg/d)

Age 30 (2012)—Per serum monitoring (low/normal T_3/T_4)

- Erfa Thyroid dose increase to 90 mg/d × 5 d and 120 mg/d × 2 d
  - Rx increase results in hyperthyroid symptoms, experienced as intermittent anxiety
- Discontinue Erfa Thyroid
- Begins NP Thyroid (Acella) 90 mg/d
  - Hyperthyroid symptoms alleviated

September 29, 2014

Pt PTC with CC acute anxiety
Dx GAD

November 7, 2014

- Discontinues Integrative Therapeutics Active B complex
  - *Follow up*: CC anxiety
    Suspected cause:
    Integrative Therapeutics Active B complex
- Begins new brand folate/B_{12} combination (Seeking Health):
  Lozenge form L-%-MTHF 400 µg QD
  B_{12} 500 µg QD
- Begins Ativan 0.5 to 1 mg PRN

February 9, 2015

- Reduce SAMe frequency:
  SAMe 400 mg BID 3×/wk, alternating with 200 mg BID 3 ×/wk weekends off
  - *Follow up*: Anxiety improved
    Updated prescription dose
- Maintenance:
  L-5-MTHF 500 µg QD (Douglas Labs)
  Liquid vitamin B_{12} 500 µg QD (Pure Encapsulations)

Age 2—Dx Asthma

Age 23—Thyroid Rx adjustment

- Levothroxine dose increase to 150 µg/d

Age 29 (Change in state of residence)

- Begins beclomethasone 80 mg inhaler BID (QVar)
- Begins B complex (Source Naturals, unmethylated formula):
  Folic acid 400 µg
  B_{12} 860 mg BID
- Erfa Thyroid dose decrease to 90 mg/d

August 5, 2014

Suspected MTHFR mutation per history of anxiety

- Begins active B vitamins (Integrative Therapeutics Active B complex)
  L-5-MTHF (methyletrahydrofolate) 8000 µg QD
  B_{12} (methylcobalamin) 1000 µg QD

October 21, 2014

MTHFR mutation confirmed (compound heterozygous):
+1 copy C677T mutation
+1 copy A1298C mutation

December 2, 2014

Anxiety improved since introduction of new lozenge product

January 12, 2015

Follow up: CC chronic anxiety
Suspected cause:
Vitamin combination
Dosages lowered independently of one another

- Discontinues Folate/B_{12} lozenge (Seeking Health)
- Begin L-5-MTHF 500 µg QD (Douglas Labs)
  Liquid vitamin B_{12} 500 µg QD (Pure Encapsulations)
- Begins SAMe (brand unknown) 400 mg BID

Abbreviations: Pt, patient; PTC, presents to clinic; CC, chief complaint; GAD, generalized anxiety disorder; QD, once per day; PRN, as needed; BID, twice per day.

Table 1. Medication and Dosage

Date	Supplement
Baseline	• 400 mg folic acid and 860 µg vitamin B_{12} • Included in a complete coenzymated sublingual B-complex supplement, PO, BID
August 05, 2014 (First Visit)	• 800 µg L-5-MTHF and 1000 µg methyl-B_{12}, PO, QD • Included in a complete B-complex supplement
November 07, 2014	• 400 µg L-5-MTHF and 500 µg methyl-B_{12}, PO, QD • Included in a lozenge and vitamin B complex, PO, QD
	• 0.5 to 1 mg Ativan tablet, PRN
January 12, 2015	• 500 µg L-5-MTHF, PO, QD • 500 µg methyl-B_{12}, PO, QD • Included in liquid B-vitamin complex supplement
	• Begin 400 mg SAMe, PO, BID
February 09, 2015	• Maintain January 12, 2015, B-vitamin protocol
	• Continue SAM-e 400 mg, PO, BID, Monday, Wednesday, Friday • Continue SAM-e 200 mg, PO, BID, Tuesday, Thursday • No SAMe on Saturday or Sunday

Abbreviations: PO, orally; BID, twice per day; QD, every day; PRN, as needed; SAMe, *S*-adenosyl methionine.

Table 2. Thyroid Medication Dosage

Date of Prescription	Dosage	Frequency
August 05, 2014	• 90 mg NP Thyroid	QD
April 22, 2015	• 90 mg NP Thyroid • 105 mg NP Thyroid	QD, 3 d/wk QD, 4 d/wk

Abbreviation: QD, every day.

Table 3. Thyroid Lab Results

Date of Test	TSH (RR: 0.5-4.7 U/L)	T_3 (RR: 2.1-5.3 U/L)	T_4 (RR: 0.8-2.0 U/L)
June 10, 2014	0.13	3.03	0.78
July 29, 2015	0.727	2.35	0.744
October 21, 2015	2.22	2.23	0.81
February 05, 2015	2.81	2.52	0.728
April 22, 2015	0.624	2.47	0.814

Abbreviations: TSH, thyroid-stimulating hormone; T_3, triiodothyronine; T_4, thyroxine.

Follow-up Visit 3: December, 2014

The patient noted improvement in her anxiety at this follow-up appointment on the new medication and reported on taking Ativan approximately once per week. A slight increase in the dosages of methylfolate and B_{12} was recommended with instruction to return if symptoms recurred.

Follow-up Visit 4: January, 2015

The patient reported that her anxiety appeared to be exacerbated when she attempted to raise the doses of the methylated B vitamins to more than one-half of a dose of the methyl-B_{12}/L-5-MTHF lozenge. Her medication was changed to a liquid B-complex containing a steady dose of methyl-B_{12} and a separate L-5-MTHF tablet that could be delivered individually to facilitate gradual dose adjustments

independent of one another (Table 1). The patient was also newly prescribed SAMe 400 mg twice daily.

Final Follow-up Visit 5: February, 2015

The anxiety level was markedly improved. Her SAMe dose was reduced and as of April 2015, the patient reported continued improvement in anxiety on her current B-vitamin protocol plus SAMe.

Discussion

This case outlines the challenges in treatment and the potential for improvements in the management of individuals with MTHFR gene mutations. Great awareness of the effects of B-vitamin supplementation in the context of varied heterozygous MTHFR mutations could be useful in clinical practice.

MTHFR mutations, for which at least 24 known genetic polymorphisms have been identified, are associated with metabolic dysfunction. They play a suspected role in several physiologic symptoms—including anxiety. The most common MTHFR mutation is the MTHFR C677T mutation. The frequency of the C677T polymorphism of MTHFR in the Caucasian population is 12% homozygous and up to 50% heterozygous.[1] Compound heterozygous MTHFR mutations are less well understood and are not generally believed to be clinically relevant.[3] Even though heterozygous mutations impair the regulation of homocysteine, adequate folate levels are believed to "cancel out" this defect.[2,3] The British Women's Heart and Health study and a meta-analysis found evidence for intermediate risk of depression (closely related to anxiety) for individuals with heterozygous mutations.[4,5] Another study indicates that a compound heterozygous patient may even encounter additional complications beyond that of a homozygous C677T patient.[6] These studies suggest potential clinical relevance beyond controlling homocysteine levels for heterozygous MTHFR individuals.

In a patient with MTHFR mutation(s), the active metabolite of folate, 5-methyltetrahydrofolate (5-MTHF), participates in the remethylation of homocysteine to create methionine at a reduced rate.[7] SAMe, the downstream metabolite of methionine, is involved in numerous biochemical methyl donation reactions, including reactions forming monoamine neurotransmitters. Without the participation of 5-MTHF in this process, SAMe and neurotransmitter levels decrease in the cerebrospinal fluid.[8] Adequate levels of SAMe and folate must be maintained for proper DNA, protein, and neurotransmitter production. It follows that SAMe plays an important role in the prevention of diseases related to altered genetic and neurotransmitter profiles including depression, anxiety, and MTHFR gene mutation. This suggests a role for SAMe in the treatment of anxiety in a patient with a compound heterozygous MTHFR gene mutation.

Anxiety affects approximately one-third of the US population and dietary supplementation with oral SAMe and B-vitamins represent one treatment option.[9,10] Though MTHFR gene mutations are associated with increased risk of a variety of common mental health conditions including depression and anxiety, B vitamins show promise in modulating these and other disease risks in those with homozygous MTHFR 677T mutations.[11,12,15] One of the best-studied nonpharmaceutical interventions for treating depression is SAMe, with one analysis reporting oral SAMe monotherapy to be associated with reduced depressive scores in 4 of 5 small randomized controlled trials reviewed.[13] SAMe has been shown to have a rapid effect evident as soon as 1 week.[14] B-vitamins are also implicated for adverse health outcomes, such as depression and anxiety, associated with homozygous MTHFR 677T mutations.[15] Further, a methylated B-vitamin complex has shown a positive effect on both depressive and anxiety symptoms,[16] presumably through similar mechanisms. It seems that appropriate levels of both B-vitamins and SAMe can help with mental health by helping normalize the varied MTHFR activity found within specific mutations.

Limitations

Standardized patient-reported response to SAMe and methylated B vitamins were not available. The absence of objective measures of anxiety for monitoring treatment response in this patient with time made the trial and error adjustment of methylated B-vitamins and SAMe problematic. Standardized patient reported outcome measurements such as PROMIS would have been helpful. This case report also illustrates a knowledge gap that exists regarding the complexity of compound heterozygous MTHFR mutations. These mutations are variable and require individualized treatment. Despite positive effects reported for SAMe and methylated B-vitamins in this patient, little is known about long-term treatment effects.

Conclusion

This case report highlights the importance of utilizing standardized measures of anxiety such as PROMIS®. This case also highlights taking extra care and precision when prescribing B-vitamins and SAMe with suspected or confirmed MTHFR mutation. Additional care should be taken to create an optimal B-vitamin and SAMe treatment plan for each patient based on both their unique biochemical requirement and their clinical response to treatment.

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