

Patient with Major Depressive Disorder Responds to L-Methylfolate Post-Genetic Testing

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Abstract

The current case describes a 69 year old Caucasian male with a long history of untreated depressive symptoms. At age 68, the patient was started on a treatment regime for depression, but remission was not achieved. Genetic testing was performed to determine if this patient's genetic background could help explain his resistance and suggest a more effective treatment strategy. The results of the genetic test showed variations in four pharmacodynamic-related genes, including MTHFR. These results supported the use of several medications in the current regime and indicated the addition of L-methylfolate which led to complete remission of depression symptoms.

Keywords: Pharmacogenetics; Genetic testing; Treatment resistant depression; Treatment guidance; Major depressive disorder

Introduction

Depression is the leading cause of disability world-wide, affecting approximately 350 million people [1]. Several studies have found that about 70% of patients with depression treated with first-line therapies show some level of response; however, 30% of patients remain refractory to treatments leading to poor quality of life and impairment in overall functioning [2]. There are numerous factors that contribute to treatment resistance including depression severity, number of psychiatric and medical comorbidities, environmental factors such as family conflict, maternal depression, history of physical or sexual abuse, as well as genetic vulnerabilities [2]. It has long been recognized that there is substantial variation of psychiatric treatment response [3]. Understanding an individual's genetic background can help to predict drug response and potential risk for adverse health events [4].

Case Report

A 69-year old Caucasian male presented to a psychiatric nurse practitioner with sadness, negative and perseverative thinking, and sleep difficulties. He reported sleep onset insomnia and frequent awakenings. The patient complained of fatigue, low energy, and lack of interest in activities. He reported a decreased ability to concentrate and complained of ongoing procrastination in his activities and interference with his longstanding hobbies. The patient has been married for 36 years, has two children, and is semi-retired, working part time as a manufacturer's sales representative. The patient reported feeling depressed "for years" but was not treated until age 68. The patient's medical history is significant for myocardial infarction with stents placed at age 42. There is no known family psychiatric history, however, two of his three children, daughter age 32 and son age 28, have been diagnosed with Major Depressive Disorder (MDD). The patient reports no known drug allergies.

The patient's psychiatric history included a diagnosis of MDD at age 68 by his primary care physician. He was initiated on first-line depression therapies including Duloxetine 60 mg twice daily, Bupropion 300 mg daily and Trazodone 25 mg at bedtime. Trazodone resulted in improvement in sleep continuity. Duloxetine was subsequently discontinued due to lack of efficacy. Venlafaxine 225 mg daily was initiated and Bupropion was increased to 450 mg daily to address ongoing depression. The benefit from Bupropion was limited to improved concentration. He was an avid reader and reported that after initiating Bupropion, he was able to read again. The patient reported Venlafaxine had reduced depression symptoms by 50%, but he still struggled with ongoing amotivation and apathy. Genetic testing was performed using the Genecept™ Assay to guide additional treatment decisions and to determine why this patient had not fully responded to the previous treatment regime.

There are two broad classes of genetic variations that could lead to variations in treatment response: pharmacodynamic variations and pharmacokinetic variations. Pharmacodynamic gene variations occur in various target proteins which influence the type of response a patient will have to certain medications or treatments [3]. Pharmacokinetic gene variations alter enzymes responsible for drug metabolism which affects medication concentrations in the body and can alter treatment response [3]. Genetic testing revealed the patient to have variants in four pharmacodynamic genes. He was identified to be a carrier for a 43 base pair deletion in the serotonin transporter (SLC6A4) and for a variant in methylenetetrahydrofolate reductase (MTHFR). He was also found to be homozygous for a serotonin subtype 2-C receptor (5HT2C) variation and the Val allele of catechol-o-methyltransferase (COMT).

Discussion

The first clinically significant variation identified was in SLC6A4. This gene encodes for the serotonin transporter protein which removes serotonin from the synapse and returns it to presynaptic cells [5]. Variants in the 5' region of SLC6A4 alter expression of the SLC6A4 protein affecting transport and extracellular concentrations of

serotonin [6]. Several large meta-analyses have shown that the S (short) allele correlates with slow, poor response and greater risk of side effects to selective serotonin reuptake inhibitors (SSRI) medications [7,8]. Genotyping revealed the patient to be a carrier for the short allele and thus at an increased risk for failure and/or intolerance with SSRI medications. The addition of an SSRI to the treatment regime of a patient with these variants may lead to SSRI intolerance and in some instances the occurrence of severe adverse reactions including serotonin syndrome [6]. SLC6A4 variants have also been associated with early medication discontinuation which is likely due to the increased number of side effects associated with SSRI treatment [6]. As SLC6A4 is believed to be the primary therapeutic target for SSRIs [9], non-SSRI medications that target other neurotransmitter pathways for antidepressant effect may prove to be useful treatment options [10]. Genetic testing for this particular variant could become a reliable way to identify patients at risk for developing intolerance and adverse effects from SSRI treatment.

The next clinically significant variant was found in COMT. The genetic test results revealed him to be homozygous for the Val allele. Retrospective studies show that the Val/Val genotype reflects elevated enzymatic activity of COMT resulting from increased transcription [11]. Dopamine transporters are largely responsible for removal of dopamine in much of the brain; however clearance in the prefrontal cortex is achieved primarily via enzymatic metabolism by COMT [12]. Norepinephrine and Dopamine play pivotal roles in the prefrontal cortex including involvement in working memory and cognitive function [13]. Specifically, this polymorphism leads to altered dopamine levels which influence cognitive processes for various tasks that are dependent upon dopamine signaling in the prefrontal cortex [14]. Dopamine also plays a role in motivational behaviors and several studies have shown that depletion of dopamine can alter the response to an endeavor which requires energy expenditure [15]. The patient's poor concentration and amotivation may be related to his COMT Val/Val genotype. This variation may also explain why the patient was unable to maintain his long time reading hobby. An agent that increases circulating dopamine levels, such as Bupropion, may theoretically assist in balancing the effects of this variation.

The third clinically significant variant was identified in 5HT2C. This gene encodes for a serotonin receptor subtype which is a site of antagonism by various neuroleptics. Serotonin acting at this receptor signals satiety [16]; thus 5HT2C antagonism has been shown in clinical studies to lead to increased food intake, hyperlipidemia, glucose intolerance and obesity [17,18]. In patients taking atypical antipsychotics, the -759C/T polymorphism confers risk for weight gain and metabolic syndrome, with the T allele showing protective effects for these adverse events [18-20]. The patient is homozygous for the C (high risk) allele. If an atypical antipsychotic were chosen for a patient with this variation, additional vigilance for strategies with lower weight gain may be warranted.

The final clinically significant variant identified in this patient is in MTHFR. Methylfolate is formed from folic acid through a series of reactions with the final step utilizing MTHFR for enzymatic conversion [21]. After completion of these reactions, methylfolate becomes available to the brain to be used in the synthesis of monoamine neurotransmitters (norepinephrine, dopamine, and serotonin) which are associated with mood regulation [21]. Disruption in any step in the pathway leading to the methylfolate production can result in deficiencies of methylfolate [21], and possibly deficiency in the synthesis of serotonin, norepinephrine, and dopamine in the brain

[22]. Specifically, the risk allele of the MTHFR variant analyzed in this patient leads to reduced thermodynamic stability and enzymatic activity of MTHFR, and ultimately an inability to complete the enzymatic conversion, and therefore a deficiency of methylfolate [21]. The relationship between methylfolate deficiency and monoamine metabolism is established but is not entirely understood [22]. Deficiencies in methylfolate, along with other nutrients important for neuronal function, can lead to poor memory or cognitive dysfunction [23]. This variation, while not diagnostic, has been modestly correlated with depression, bipolar disorder, and schizophrenia [24,25]. Preliminary studies suggest that supplementation with L-Methylfolate may be beneficial in Major Depressive Disorder [24], and therefore the patient may potentially benefit from supplementation with a methylfolate based intervention.

Conclusions

Genetic testing was able to provide a unique insight to help explain the patient's previous treatment failures and resistance. The presence of the SLC6A4 variation supported the use of Venlafaxine, which has additional targets in the norepinephrine system outside of the serotonin system. The patient was previously prescribed another serotonin-norepinephrine reuptake inhibitor (SNRI), Duloxetine, which was found to be ineffective. Duloxetine more potently blocks the serotonin transporter and norepinephrine transporter compared to Venlafaxine [26], and the more potent effect of Duloxetine on SLC6A4 may be the reason for treatment failure. The presence of the high activity COMT allele provided an explanation for the patient's ongoing amotivation and concentration issues, which may explain the reduction in cognitive side effects and improvement of motivation with Bupropion, an agent which has dopamine agonist properties. Trazodone was continued after genetic testing for its positive effects on sleep continuity. Lastly, the patient was initiated on 15 mg L-Methylfolate in response to the presence of an MTHFR variant and ongoing depression.

After these changes were instituted, the patient reported full remission of depressive symptoms and improved concentration. Fatigue and sleep disturbances have subsided, and the patient reports being able to fully enjoy his reading hobby again. Eleven months after the addition of L-methylfolate to the patient's regimen, he continues to report full remission, with no depression symptoms and is fully functional and active with work and hobbies.

Conflicts of Interest

Therese Jaeckle is listed as a preferred provider on Genomind's website, the company which provided genetic testing.

References

1. Marcus M, Yasamy MT, van Ommeren M, Chisholm D, Saxena S (2012) Depression A Global Public Health Concern. World Health Organization Department of Mental Health and Substance Abuse.
2. Al-Harbi KS (2012) Treatment-resistant depression: therapeutic trends, challenges, and future directions. *Patient Preference and Adherence* 6: 369-388.
3. Mrazek DA (2010) Psychiatric pharmacogenomic testing in clinical practice. *Dialogues Clin Neurosci* 12: 69-76.
4. Vegter S, Boersma C, Rozenbaum M, Wilffert B, Navis G, et al. (2008) Pharmacoeconomic evaluations of pharmacogenetic and genomic screening programmes: a systematic review on content and adherence to guidelines. *Pharmacoeconomics* 26: 569-587.

5. Schloss P, Williams DC (1998) The serotonin transporter: a primary target for antidepressant drugs. *Journal of Psychopharmacology* 12: 115-121.
6. Murphy DL, Moya PR (2011) Human serotonin transporter gene (SLC6A4) variants: their contributions to understanding pharmacogenomic and other functional GxG and GxE differences in health and disease. *Current Opinion in Pharmacology* 11: 3-10.
7. Porcelli S, Fabbri C, Serretti A (2012) Meta-analysis of serotonin transporter gene promoter polymorphism (5-HTTLPR) association with antidepressant efficacy. *European Journal of Neuropsychopharmacology* 22: 239-258.
8. Kato M, Serretti A (2010) Review and meta-analysis of antidepressant pharmacogenetic findings in major depressive disorder. *Molecular Psychiatry* 15: 473-500.
9. Yoshida K, Takahashi H, Higuchi H, Kamata M, Ito K, et al. (2004) Prediction of antidepressant response to milnacipran by norepinephrine transporter gene polymorphisms. *American Journal of Psychiatry* 161: 1575-1580.
10. Kung S, Li X (2010) The Clinical Use of Pharmacogenomic Testing in Treatment-Resistant Depression. *Primary Psychiatry* 17: 46-51.
11. Baune BT, Hohoff C, Berger K, Neumann A, Mortensen S, et al. (2008) Association of the COMT val158met variant with antidepressant treatment response in major depression. *Neuropsychopharmacology* 33: 924-932.
12. Yavich L, Forsberg MM, Karayiorgou M, Gogos JA, Männistö PT (2007) Site-specific role of catechol-O-methyltransferase in dopamine overflow within prefrontal cortex and dorsal striatum. *Journal of the Society for Neuroscience* 27: 10196-10209.
13. Gamo NJ, Arnsten AF (2011) Molecular modulation of prefrontal cortex: rational development of treatments for psychiatric disorders. *Behavioral Neuroscience* 125: 282-296.
14. Frank MJ, Fossella JA (2011) Neurogenetics and pharmacology of learning, motivation, and cognition. *Neuropsychopharmacology* 36: 133-152.
15. Tsai SJ, Gau YT, Hong CJ, Liou YJ, Yu YW, et al. (2009) Sexually dimorphic effect of catechol-O-methyltransferase val158met polymorphism on clinical response to fluoxetine in major depressive patients. *Journal of Affective Disorders* 113: 183-187.
16. Halford JC, Harrold JA (2009) 5-HT(2C) receptor agonists and the control of appetite. *Handbook of Experimental Pharmacology* 209: 349-356.
17. Bonhaus DW, Weinhardt KK, Taylor M, DeSouza A, McNeeley PM, et al. (1997) RS-102221: a novel high affinity and selective, 5-HT_{2C} receptor antagonist. *Neuropharmacology* 36: 621-629.
18. Reynolds GP, Zhang ZJ, Zhang XB (2002) Association of antipsychotic drug-induced weight gain with a 5-HT_{2C} receptor gene polymorphism. *Lancet* 359: 2086-2087.
19. Miller DD, Ellingrod VL, Hilman TL, Buckley PF, Arndt S (2005) Clozapine-induced weight gain associated with the 5HT_{2C} receptor -759C/T polymorphism. *American Journal of Medical Genetics Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics*. 133B: 97-100.
20. Buckland PR, Hoogendoorn B, Guy CA, Smith SK, Coleman SL, et al. (2005) Low gene expression conferred by association of an allele of the 5-HT_{2C} receptor gene with antipsychotic-induced weight gain. *The American Journal of Psychiatry* 162: 613-615.
21. Farah A (2000) The role of L-methylfolate in depressive disorders. *CNS Spectrums* 14(1 Suppl 2): 2-7.
22. Bottiglieri T, Laundry M, Crellin R, Toone BK, Carney MW, et al. (2000) Homocysteine, folate, methylation, and monoamine metabolism in depression. *Journal of Neurology, Neurosurgery, and Psychiatry* 69: 228-232.
23. Qureshi NA, Al-Bedah AM (2013) Mood disorders and complementary and alternative medicine: a literature review. *Neuropsychiatric Disease and Treatment* 9: 639-658.
24. Lewis SJ, Lawlor DA, Davey Smith G, Araya R, Timpson N, et al (2006) The thermolabile variant of MTHFR is associated with depression in the British Women's Heart and Health Study and a meta-analysis. *Molecular Psychiatry* 11: 352-360.
25. Peerbooms OL, van Os J, Drukker M, Kenis G, Hoogveld L, et al (2011) Meta-analysis of MTHFR gene variants in schizophrenia, bipolar disorder and unipolar depressive disorder: evidence for a common genetic vulnerability? *Brain, Behavior, and Immunity* 25: 1530-1543.
26. Bymaster FP, Dreshfield-Ahmad LJ, Threlkeld PG, Shaw JL, Thompson L, et al. (2001) Comparative affinity of duloxetine and venlafaxine for serotonin and norepinephrine transporters in vitro and in vivo, human serotonin receptor subtypes, and other neuronal receptors. *Neuropsychopharmacology* 25: 871-80.