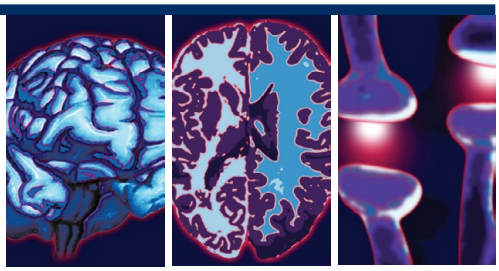

MTHFR Gene Polymorphism Positive Treatment-Resistant Depression: Prevalence and Treatment Recommendations

Robert P Duprey

Abstract

Background: Major depressive disorder affects 7% of the US population with up to 50% of cases treatment resistant. These cases are associated with a genetic polymorphism of the methylenetetrahydrofolate reductase gene (*MTHFR)*. Little is published specifically on the prevalence of the mutation specific to treatment resistant depression or the frequency of the gene state.

Objective: To assess the prevalence of the *MTHFR* polymorphism specific to treatment resistant depression and to assess the prevalence of the heterozygous and homozygous allele presentations and generate treatment recommendations.

Method: A cross sectional retrospective study

Results: With 29 treatment resistant cases genetically tested, 22 (76%) were positive for the *MTHFR* mutation. Of these 22 cases, 17 (77%) were heterozygous and the rest homozygous.

Conclusion: Depressed patients identified as treatment resistant have a 76% chance of having the *MTHFR* mutation with a 77% chance of being heterozygous. This warrants specific treatment strategies.

Keywords: Treatment resistant; Depression; MTHFR; Folic acid

Introduction

Major depressive disorder (MDD) is a treatable mood disorder with an estimated 15.7 million adults aged 18 or older in the United States having at least one major depressive episode in the past year [1]. This number represents a prevalence of 6.7% of all adults in the US population [1, 2]. Ten to 15% of MDD cases can be classified as treatment resistant (TR) [3, 4]. The prevailing theory of MDD is rooted in neurobiology and the monoamine neurotransmitters serotonin (5HT), norepinephrine (NE), and dopamine (DA), in a series of neural circuits in the brain that contribute to depressive symptoms [3, 5-7]. Within this medical biological model, methylenetetrahydrofolate reductase (*MTHFR)* genetic mutations cause low levels of *MTHFR* enzyme. Low enzyme levels cause low methylenetetrahydrofolate (MTHF) levels. Low levels of MTHF cause lower levels of monoamines. Lastly, lower levels of monoamine neurotransmitters causes MDD. Thus, MDD is in part associated with a folate metabolism deficiency.

TR patients have little-to-no response to psychopharmacotherapy, which may include trials of different anti-depressant medications, a combination of psychotropic agents, adjunctive

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therapy, or off-label use of alternative agents [3, 4]. TR MDD is known to be associated with the *MTHFR* gene polymorphism [3-5]. While this association is well-known in TR MDD, little has been published specifically regarding the prevalence of the mutation specific to TR MDD nor the frequency of the polymorphism in the homozygous (677TT) or heterozygous (677CT) state.

The goals of this study are to (a) determine the prevalence of the *MTHFR* mutation specific to TR MDD, (b) ascertain the prevalence of the 677CT and 677TT *MTHFR* gene polymorphisms, and (c) make treatment recommendations. Based on our reviewed literature and preliminary data, we suspect (a) the overall prevalence of the *MTHFR* mutation to be higher in TR MDD than in non-TR MDD and the general population and (b) the heterozygous presentation are more prevalent. To date, no study has directly addressed the prevalence of MTHFR mutation in TR MDD with the emphasis on treatment resistance, or the prevalence of the polymorphic 677CT or 677TT gene states.

Methods

A cross-sectional retrospective study was conducted between January 2015 and May 2016. Institutional Review Board and Ethics Committee approval was granted through Newport County Community Mental Health Center and Oceania University of Medicine. Because this was a retrospective study, no recruitment was required. A convenience sample of the author's clinical patients already enrolled in care from a community mental health center in coastal Rhode Island was used. Patients were already receiving the standard of care for TR MDD to include genetic testing for the MTHFR gene. Age, race, and ethnicity were not accounted for in the sample. A total of 29 TR cases were identified. Inclusion criteria required: (a) the diagnosis of MDD based on DSM V diagnostic criteria [2], (b) evidence of treatment resistance [3, 4] and (c) having already been genetically tested for the MTHFR polymorphism. Laboratories used for testing included patient-selected laboratories as part of their routine medical care. Genetic testing was conducted in accordance with these laboratory standards.

Results

Of the 29 treatment resistant cases genetically tested, 22 cases (76%) were positive for the *MTHFR* mutation. Of these 22 recorded TR MDD patients positive for the *MTHFR* polymorphism, 17 (77%) were heterozygous, and 5 (23%) were homozygous, giving a ratio of 3.4:1 for the heterozygous to homozygous state.

Discussion

Studies [8-12] have addressed the risk of developing mental illnesses, given a particular allele frequency of the MTHFR gene, and its association as a factor, or contributing cause, of TR depression. Although these studies did not directly address specific allele prevalence, data were extracted for the purpose of comparing the prevalence of the polymorphic gene frequencies to the current study. El-Hadidy [8] resulted 52 cases (80%) of 677CT and 13 cases (20%) of 677TT. Peer booms [9] resulted 1487 677CT cases (80%) and 363 677TT cases (20%). Gilbody [11] resulted 563 677CT cases (78%) and 161 677TT cases (22%). Flint [12] meta-analysis data found 20% of MDD cases (not identified as TR) positive for the MTHFR gene. The prevalence of these mutations in the general population who do not suffer from MDD is reported in Gilbody to be between 2-20% with variance depending on ethnicity and geographic location. Gilbody meta-analysis data compared depression rates for individuals with given allele presentations and found MDD occurred in 11% of individuals positive for either MTHFR T allele presentation (compared to 7% prevalence of MDD in the general population) [9]. Age, race, and ethnicity were not extracted from the above studies.

The mutation of the MTHFR gene is a single nucleotide polymorphism that causes an alanine-to-valine amino acid substitution [8, 13-15]. For the 677T polymorphism, homozygote variants have 30% enzyme activity in comparison with homozygotes for the wild-type 677C allele, while heterozygotes retain 65% wild-type MTHFR enzyme activity [8, 16]. The wild type *MTHFR* gene is 677CC [17].

The major assumption in this study is that the MTHFR polymorphism is important in TR MDD cases. Other symptoms and risks of MDD may respond to or be mitigated by psychopharmacology with psychotherapy. One limitation is the small sample size. The 29 TR MDD patients identified in this study represents about 8% of the author's total patient case load (#345). The 29 TR MDD cases from the current study furthermore represent 11%

the case load from patients with a depressive disorder diagnosis (#275) consistent with above reported 10 to 15% [3, 4] of all MDD patients are TR. The current study's 22 TR MDD cases positive for the *MTHFR* polymorphism represents 11% out of all MDD cases in the author's caseload. This is less than the reported 20% [12] of cases out of all MDD cases positive for MTHFR mutation. When compared to the general population without MDD, the percentage of people positive for the MTHFR polymorphism is 2 to 20% [11], similar to the 20% [12] reported for all MDD patients positive for the MTHFR polymorphism. One could say there is little difference between MDD and the general population in individuals positive for the MTHFR polymorphism. Of the author's total caseload, the 22 MTHFR positive cases represent 8% of the total caseload, consistent with that reported in general population (2-20%) and less than that out of all MDD cases reported above, (20%). While reported data showed that 20% [12] of all MDD cases are positive for the *MTHFR* polymorphism, the current study accounted for the dimension of treatment resistance and found 76% of TR MDD positive for the polymorphism.

From our data, MDD cases identified as TR have a 74% chance of being positive for the *MTHFR* genetic polymorphism. Clinically this is relevant in that current recommended therapies for MTHFR polymorphism are high doses of folic acid (2-7 mg) or L-methylfolate (7.5-15 mg) [18, 19]. This stands to yield better outcomes in the treatment of TR MDD than standard therapies alone which by the nature of being TR have already failed trials of psychotropic agents. Genetic testing for the *MTHFR* polymorphism is recommended where feasible, however the results of the current study would indicate that once identified as TR, MDD patients are likely to be *MTHFR* polymorphism positive and therefore genetic testing is not required for recommended treatment to begin. The results of the current study are also consistent with extracted data from the literature review that the heterozygous polymorphism occurs at a ratio of approximately 3.4:1 when compared to the homozygous polymorphism state. Thus, the heterozygous presentation is more prevalent in TR MDD cases positive for the MTHFR polymorphism. That is, a 77% chance of the MTHFR gene being 65% functional. Given that the results of the current study are consistent with extracted data from the existing literature, generalizability can be extended to all patients with TR MDD.

In conclusion, once identified as TR MDD with a 76% likelihood of being positive for the MTHFR polymorphism and a 77% chance of this being heterozygous (with 65% functionality) [8, 16], we recommend the use of treatments at the lower dose range (folic acid 4 mg and L-Methylfolate at 7.5 mg) [18, 19].

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Disclaimer

The views expressed herein are those of the authors and do not necessarily reflect the views of the Department of Defenses or NCCMHC.

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