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The Prevalence and Role of MTHFR Polymorphisms in Opiate Dependency

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Abstract

Studies of genetic polymorphisms associated with the diseases of opiate dependency and abuse have focused primarily on genes related to dopamine and opioid receptors, neurotrophic factors, or the catechol-o-methyltransferase (COMT) gene [1,2]. Despite the high prevalence of methylene tetrahydrofolate reductase (MTHFR) polymorphisms in numerous neuropsychiatric and neurodegenerative diseases, only one prior study examined the prevalence of MTHFR C677T variants in opiate dependency [3].

We screened consecutively admitted patients who were dependent on heroin and/or other opiates, for C677T and A1298C polymorphisms. Over a six-month period, 86 of 96, or 90% of subjects, were positive for at least one of these MTHFR variants.

The mean age of all qualifying patients was 31.6 years, and majority of subjects, 68%, were female. The MTHFR distribution was fairly even; of the 89 patients who were MTHFR positive, 28% were heterozygous for only C677T (CT:AA), 11% were homozygous for only C677T (TT:AA), 22% were heterozygous for only A1298C (CC:AC), 13% were homozygous for only A1298C (CC:CC), while 26% were heterozygous for both mutations (CT:AC).

We theorize that impaired methylation, and the inadequate monoamine synthesis that result from MTHFR variants, likely contribute to the illness of opiate use disorder. These vulnerable individuals are incapable of adequate monoamine balance, and may seek opiates as compensation. These findings may further imply a new treatment option, in the form of fully metabolized folate. This therapy would circumvent the less functional MTHFR enzymes expressed by the C677T and A1298C mutations, and therefore allow for more optimal monoamine synthesis.

Introduction

Opiate-overdose deaths in the US continue at a record-breaking pace. For the 12 months preceding January, 2017, total drug overdose deaths reached 64,070. The majority of these were attributed to; heroin, natural, synthetic and semi-synthetic opiates, or methadone. Specific to heroin, from 2002 to 2015, there was a 6.2-fold increase in the total number of deaths related to heroin use [4]. Reporting thus far indicates that by January 2018, deaths will top 2016 levels [5]. Our study was based in one of this epidemic's most significantly affected areas: Guilford County is currently fourth in total number of opiate-overdose deaths in the State of North Carolina [6].

Genetic markers associated with opiate dependency and abuse could provide insights as to which patients may be at higher risk for addictive disease, and may further lead to treatment options based on addressing specific polymorphisms. Past studies of genetic variants in opiate use disorders have largely focused on polymorphisms of the COMT gene, or genes for dopamine receptors, opioid receptors, or the synthesis of neurotrophic factors [1,2]. However, one recent study of heroin-dependent Egyptian patients found the CC, or normal genotype of the C677T gene (coding for a fully functional MTHFR enzyme), represented 75% of the control group, yet only 38% of heroin dependent subjects. While controls demonstrated a low prevalence of CT and TT polymorphisms, (21% and 3%, respectively), 42% of heroin-dependent subjects were found to have the CT type, while the heterozygous TT patients represented 19%. The study only

explored C677T prevalence, not the possibility of A1298C, or other MTHFR mutations. Given that MTHFR prevalence is highly correlated with ethnicity, results cannot be extrapolated to non-Egyptian populations.

The MTHFR enzyme has been found to be expressed in at least 34 rare, yet deleterious mutations, as well as a total of 9 more common polymorphisms, each possessing decreased enzymatic activity [7]. Clinical and research testing of MTHFR mutations generally focus on (what are currently believed to be) the two most common variants, C677T, and A1298C, both single nucleotide substitutions (SNPs). The MTHFR enzyme conveys the last step in transforming dietary folate (dihydrofolate) or supplemental folate (folic acid) into the co-enzyme, 5-methyltetrahydrofolate (sometimes referred to as l-methyl-folate).

In the CNS, the coenzyme 5-methyltetrahydrofolate is necessary for homocysteine metabolism, monoamine synthesis, the synthesis of methyl donors, and, it also plays a critical role in antioxidant production. Suboptimal conversion of ingested folates to 5-methyltetrahydrofolate is theorized to result in suboptimal monoamine production and cause (or contribute to) depressive disorders [8]. An MTHFR polymorphism has been reported to exist in as many as 76% of patients with treatment resistant MDD, compared to a rate of 48-66% in the general population [9,10].

The opiate epidemic in the United States has claimed tens of thousands of lives, yet it is estimated that up to 80% of addicted individuals receive no treatment [11]. It is critical to determine if MTHFR polymorphisms are associated with the disease of opiate dependency, as this family of genetic variants can be addressed clinically with the use 5-methyltetrahydrofolate, which circumvents defective MTHFR activity. Other metabolized B vitamins and micronutrients associated with homocysteine metabolism and monoamine synthesis may also be necessary for therapeutic benefit, as MTHFR is rarely present as a patient's sole polymorphism [8].

Methods

Patients admitted for opiate detoxification to the general adult psychiatry ward at the High Point Division of the University of North Carolina Healthcare System, from January 1, 2017 to July 1, 2017 were screened for inclusion. Participants were screened to meet the DSM-V criteria for "opiate use disorder" as their primary, and admitting diagnosis. Subjects could also be dependent on, or abusing, other compounds, however only if such use qualified as a secondary diagnosis. Patients with comorbid major depression, or who reported a history of being diagnosed with major depressive disorder (MDD), were excluded, due to the known correlation of MDD and positive MTHFR status. The study was approved by the University of North Carolina Institutional Review Board, and assigned study number 16-3092.

Approximately 80% of screened and qualifying patients consented to participate. One patient withdrew consent. Five patients left against medical advice within 24 hours of admission, yet none of these withdrew study consent. Genetic testing kits were provided by AltheaDx, of 10578 Science Center Drive, San Diego, CA 92121, and processed at their laboratories. A buccal swab of subjects was performed under standard conditions, in accordance with manufacturer's recommendations. Two subjects were tested twice for quality control, and their results were identical on repeat testing.

All patients were informed that participation or nonparticipation would have no impact their treatment plans of inpatient detoxification and rehabilitation arrangements. The majority of subjects were female, and the average age of female patients being 29.8. This prevalence did not reflect a bias towards consent, as the male to female ratios of admitted and consenting patients was identical.

Only 12 subjects were dependent upon opiates while abusing or dependent on no other compounds. The other compounds of abuse and dependency in the remaining 84 included cannabis, synthetic cannabis, cocaine, alcohol, amphetamines, and benzodiazepines. Opiate forms included; prescription pills forms, methadone, heroin, and buprenorphine. Our standard opiate detoxification protocol includes an intramuscular loading dose of phenobarbital, and a subsequent oral tapper of phenobarbital over three days, the use of methocarbamol for muscle cramps, ondansetron, or promethazine for nausea and vomiting, and various other PRN medications excluding all schedule II compounds. At the end of detoxification, and at discharge form inpatient care, approximately 20% transitioned to inpatient rehabilitation, 35% were referred to specific outpatient rehabilitation programs, while 45% chose no rehabilitation when offered and were discharged with referrals to outpatient therapy, psychiatric appointments, and Narcotics Anonymous meeting schedules in their communities.

Results

Of the 96 subjects, only 10% were normal for both C677T and A1298C polymorphisms. Thus, 90% were positive for at least one MTHFR variant tested for. Of these MTHFR positive patients, 35% tested normal for the A1298C polymorphism, while 25% of the total sample were heterozygous for C677T, and 10% were homozygous for C677T. Of the subjects who tested normal for C677T, yet positive for A1298C, 20% were heterozygous, while 11.55 were homozygous. The remaining 11% were compound heterozygous, for both AT and AC polymorphisms. These findings are summarized in Table 1.

MTHFR 677 and 1298 status	n (of 96)	%
CC/AA Normal 677/1298	10	10.4
CT/AA Heterozygous C677T	24	25
TT/AA Homozygous T677T	10	10.4
CC/AC Heterozygous A1298C	19	20
CC/CC Homozygous C1298C	11	11.5
CT/AC Compound heterozygous	22	23

Table 1: MTHFR variant test.

Discussion

Considering the numerous potentially addicting compounds, perhaps the progression from opiate exposure to dependency is more dependent upon genetic vulnerability than any other. A large twin study (which included 3372 male twin pairs, 1874 monozygotic, and 1498 dizygotic), investigated the co-occurrence of the abuse of drugs of different categories (cannabis, stimulants, sedatives, heroin, and psychedelics) within an individual, and also, as compared with their co-twin, in order to determine genetic and environmental factors may contribute to concurrent drug abuse patterns. When using the common vulnerability model to analyze the data, it was determined that 31% of the variance in drug abuse behavior was attributed to additive genetic effects, while 25% and 44% were attributed to family and non-family environmental factors respectively. Thus, single independent models of drug abuse patterns showed that heroin abuse had the largest contribution from specific genetic factors that were unshared with other drugs [12].

Polymorphism that have had been demonstrated to correlate in various ways with opiate use disorders include; dopamine receptors D1, D2, and possibly D3 and D4, COMT, the ankyrin repeat and kinase domain containing 1 gene (ANKK1) gene, and one prior study noted a higher MTHFR C677T polymorphism in Egyptian patients dependent upon heroin [1,2,3,13].

MTHFR polymorphisms exist in numerous varieties, of varying severities. They rarely exist as the sole polymorphism associated with the HCY cycle and the production of monoamine production [8]. The two most commonly studied and clinically tested for (C677T and A1298C) have been correlated with numerous neuropsychiatric, neurodevelopmental and neurodegenerative diseases [14]. However, the literature regarding MTHFR as a risk factor for, or contributor to, the illnesses of chemical dependency, is just now unfolding.

The MTHFR gene codes for the enzyme methylenetetrahydrofolate reductase, and enzyme that facilitates the last step in the transformation of dietary folate, (dihydrofolate) or folate supplements (folic acid) into methyltetrahydrofolate. This end product (methyltetrahydrofolate) is a coenzyme necessary in the CNS for numerous pathways.

Methyltetrahydrofolate is necessary with methylcobalamin for the conversion of HCY to methionine, the first step in the HCY (or the carbon-1) cycle. Adequate and ongoing HCY metabolism in the CNS is necessary for methyl donor production, antioxidant production, the methylation of DNA and monoamines, and the synthesis of numerous other entities. Further, the toxic burden of HCY must be constantly reduced in order to protect neuronal, DNA, and vascular integrity. In addition, all forms of folate are necessary for DNA and RNA transcription [14].

The coenzyme methyltetrahydrofolate is also necessary for the transformation of dihydrobiopterin to tetrahydrobiopterin, (BH2 to BH4). BH4 being a cofactor for both tyrosine hydroxylase and tryptophan hydroxylase. If BH4 is in suboptimal supply despite l-methyl folate supplementation, methyltetrahydrofolate can "stand-in" for BH4 and act as the cofactor it has helped to synthesize [8]. Thus, an optimal supply of metabolized folate is not only necessary for ongoing HCY metabolism, but also for adequate monoamine production.

The HCY theory of depression argues that MTHFR and/or any cluster of enzymes and coenzymes associated with monoamine production and HCY metabolism may exist in less function forms. The theory further states that suboptimal monoamines are not the cause of depression, but rather, a symptom of depression. The root cause being one in a set of thousands of possible combinations of defective enzymes and coenzymes present in each patient. Still, the primary and most prevalent of these polymorphisms is likely MTHFR.

Much in the way depressed patients suffer from inadequate monoamine production, it is possible that the high prevalence of MTHFR polymorphisms in other patients leads to a similar disposition of mental discomfort. And as a way of compensating, opiate use, with its artificial and temporary euphoria, offers these individuals a form of relief they are compelled to repeat. The initial relief from suboptimal monoamine production will rapidly become more elusive, due to tolerance, addiction, and drug withdrawal. It is noteworthy that three of the five subjects who left the detox ward against medical advice within 24 hours of admission, were positive for the C677T - TT polymorphism, coding for one of the least functional MTHFR variants.

In a disease as complex and chronic as opiate use disorder, no single SNP or polymorphism can be a full explanation. Yet a recent study demonstrated that depression in MTHFR positive patients (C677T and/or A1298C) can be effectively treated with metabolized B vitamins, and a strategy designed to address MTHFR and other polymorphisms associated with suboptimal monoamine production [15]. An identical strategy may benefit patients with opiate use disorders, as the high prevalence of various MTHFR SNP's is common to both illnesses.

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