Severe Mood Lability and Depression in an Adolescent Girl with a Methylene-tetrahydrofolate Reductase Gene Mutation

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Abstract:
Methylene-tetrahydrofolate Reductase (MTHFR), an enzyme that controls the rate of production of N-methyltetrahydrofolate (a molecule which is necessary for the N-methyltetrahydrofolate-homocysteinemethyltransferase reaction), is vital for many of the human body’s biological processes, including DNA and RNA synthesis. Mutations in the MTHFR gene, which have far reaching effects on the negative feedback systems that regulate nucleic acid synthesis (via thymidylate synthesis) and homocysteine levels, are believed to be of clinical significance and have been widely studied. The neurological and neuropsychiatric consequences of these changes have been long suspected but have only recently begun to be characterized. In this case report we discuss M., a fourteen-year-old Caucasian girl with a past diagnosis of major depressive disorder, and a recent history of suicide attempt by overdose, who presents for inpatient hospitalization after attempting to suffocate herself by placing a plastic bag over her head and then submerging her head in the bathtub. She deprived herself of oxygen until her vision began to blur, she grew dizzy, and her mental status was altered, but then she abandoned the attempt out of frustration about the amount of time it was taking before she lost consciousness. The patient considered this a failed suicide attempt, not an aborted one, and she continued to endorse suicidal ideation upon her admission to the inpatient unit. She did not want psychiatric help but was checked into the unit by her mother, who noticed the commotion from the bathroom after the patient abandoned her suffocation attempt and began crying and yelling.

1. Chief Complaint and Presenting Problem:
M. is a fourteen-year-old Caucasian girl with a past diagnosis of major depressive disorder, and a recent history of suicide attempt by overdose, who presents for inpatient hospitalization after attempting to suffocate herself by placing a plastic bag over her head and then submerging her head in the bathtub. She deprived herself of oxygen until her vision began to blur, she grew dizzy, and her mental status was altered, but then she abandoned the attempt out of frustration about the amount of time it was taking before she lost consciousness. The patient considered this a failed suicide attempt, not an aborted one, and she continued to endorse suicidal ideation upon her admission to the inpatient unit. She did not want psychiatric help but was checked into the unit by her mother, who noticed the commotion from the bathroom after the patient abandoned her suffocation attempt and began crying and yelling.

2. History of Present Illness:
M. reports a history of severe mood swings beginning at age twelve. She describes episodes of severe depression triggered by off-hand comments and minor perceived slights, usually leading to suicidal ideation, along with feelings of hopelessness and insomnia. In a euthymic state she admits that the events that trigger these episodes are minor compared to her response to them, but she does not feel that she can control her mood changes regardless.
When she is not depressed she described often slipping into a hypomanic state, starting many new projects in a flurry of activity, such as learning to play a new instrument, having extreme self-confidence and an inflated sense of importance, and talking excessively without being able to stop. She enjoys these periods of elevated mood and they were one of the things that she felt made her life worth living, but she has decided recently that the highs of her life are not worth the lows.

Accordingly, M. has developed multiple suicide plans, all of which she describes with an inappropriately happy and casual affect. The elaborate plan to suffocate herself in a bag under water was only the first of these, and others included a plan to drink antifreeze (along with an internet-researched way to avoid vomiting and ensure lethality) and a more foolproof way to secure a plastic bag for suffocation. She has researched medication overdose suicides over the internet extensively, but based on her own previous overdose attempt she no longer believes this is an effective method.

Throughout the interview M. is bright, pleasant, and cooperative, with a happy mood and broad affect. She says that she has learned to hide her emotions and depression very well. To demonstrate this she explains that she saw her outpatient psychiatrist (who, she knows, is also the attending physician on the inpatient unit) a few days before her admission, and he interviewed her extensively about possible suicidal ideation given her recent history of overdose, and she successfully lied to him, claiming to have no suicidal ideation while actively planning and intending to carry out the suffocation plan that led to this admission.

When asked about her life situation M. reports that she has a good life and a supportive family, along with several friends and hobbies, but denies that any of them are a thing worth living for. She knows her parents will be sad if she kills herself, but says that this is not a sufficient deterrent. She resolutely denies any major psychosocial stressors, even when prompted about possible conflicts and issues by her mother. She described her decision to commit suicide as a coldly calculated and rational decision based on the great subjective personal suffering she experiences during her depressed periods, even though she has the insight to understand that these episodes are only matters of brain chemistry, given the lack of psychosocial stressors in her life.

She views psychiatrists and other mental health staff in an adversarial way despite her pleasant demeanor and happy affect. She says she feels safe on the inpatient unit because she has access to nothing that could kill her, despite her active suicidal ideation and intent. Asked about the possibility of stabbing herself with a pen, or otherwise harming herself in an improvised way, she laughs and explains that she knows that nothing on the inpatient unit will be lethal, and she knows too much about suicide methods and the realistic lethality of various objects to try something of that nature. “I don’t want to hurt myself or feel any pain,” she explains, “I just want to kill myself quickly.”

3. past Psychiatric History:
M. denies any significant mental health problems prior to turning 14, except for a brief episode of complicated grief following the death of her grandfather when she was 11. She saw a psychiatrist for this, who recommended talk therapy and counseling without pharmacotherapy. She next saw a psychiatrist when she was hospitalized in an inpatient psychiatric unit after her suicide attempt by Benadryl overdose two months before her current admission. Her primary care doctor had diagnosed her with major depressive disorder several weeks prior to this and prescribed escitalopram 10mg daily, but this was presumed to be ineffective due to the patient’s suicide attempt and so the patient was started on sertraline during her first inpatient stay.
This allowed the patient to be stabilized for discharge after a four day hospitalization. During this admission it came to the attention of her psychiatrist that genetic testing performed after her mother’s hemorrhage during her birth found the patient to have two methylenetetrahydrofolate reductase (MTHFR) mutations. She is heterozygous for the single gene polymorphisms C677T and A1298C, both of which are of interest as risk factors for mood disorders, though the relationship is still controversial. She was also found to have a platelet factor-2 mutation that increased her risk for venous thrombosis.

During outpatient follow-up the patient complained that sertraline was causing her to have short term memory problems and staring spells, and she reported feeling happier and less depressed due to her regular counseling sessions, and so sertraline was discontinued.

The day before she was hospitalized for the present admission the patient saw her outpatient psychiatrist and resolutely denied any suicidal thoughts, intent, or plan, despite her elaborate suffocation plan, in order to prevent any interference with this plan. During this admission the patient was treated with escitalopram again, which she reported as being helpful in retrospect.

4. Developmental History:

M.’s birth was complicated by her mother hemorrhaging after her birth due to a then-uncharacterized MTHFR gene mutation, leading to a von Willebrand’s-like picture and necessitating a blood transfusion to restore her mother’s blood pressure. Her mother later developed a venous thrombus as a complication. This was her mother’s third pregnancy brought to term and the second time the hematological problem presented itself: her mother’s first pregnancy also resulted in a hemorrhage but the cause was unknown at the time and the genetic issue was not worked up until the second hemorrhage. M’s development was otherwise normal; she began walking and talking and other milestones at the normal age and progressed within a normal time frame. The patient reports that her mother suffered several miscarriages prior to her birth. These were never medically investigated. Her mother was 43 years old at the time of her birth. The patient’s ancestry, so far as can be determined, is exclusively Caucasian.

5. Educational History:

M. is in the ninth grade taking regular classes with good grades and is involved in several extracurricular activities. She has never had any learning problems or attention difficulties. She has never had any behavioral issues or disciplinary actions taken against her. Her school performance has mostly been above average. She has many academic interests and has ambitions to attend college and become a professional someday.

6. Social History:

M. lives at home with her biological parents and two older siblings. They are a close and supportive family. Her two older siblings are 22 and 19 years old, and both work at the nursing home where their mother is a social worker. The patient is especially close to her older brother, and enjoys several hobbies with him. At school the patient has a small social circle by choice, as she likes to avoid crowds and she feels that her classmates at school are unlike her. She reports that most kids at her school use street drugs and pressure her to send nude photos or engage in other sexual acts, and she has made the deliberate decision to avoid these activities at this stage of her life. She denies feeling socially isolated, however, as she has two close friends who share her athletic hobbies and academic interests.

7. Family History:

M.’s mother describes an extensive family history of mental illness, starting with alcoholism in M.’s father (though he is now sober and has been for much of M.’s life), and depression in M.’s mother. Anxiety disorders, depression, and mood swings...
run in the mother’s side and there is a history of a completed suicide on the father’s side.

8. Medical History:
The patient has no known chronic medical conditions or history of medical problems. She has never had a thrombus or embolus or any known hematological event. Her only medical complaints are joint and muscle pains secondary to her athletic training.

9. Medication History:
When the patient first began having depression after her fourteenth birthday her primary care doctor prescribed escitalopram, which was not able to prevent the patient’s first suicide attempt. During her first inpatient stay M. was treated with sertraline, which was stopped by her outpatient psychiatrist after she reported the resolution of depressive symptoms but persistent short-term memory loss and staring spells. During this admission the patient was re-started on escitalopram due to her report of its efficacy in retrospect.

10. Mental Status Examination:
Upon admission M. is a 14-year-old Caucasian female, who appears her stated age. She is alert and oriented to person, place, time, and situation. She is in no acute distress. She is appropriately dressed and groomed. Her speech is normal in rate, rhythm, and volume. Her mood is happy and her affect is broad, but inappropriate to content. Her thought process is linear and goal-directed. Her thought content is non-bizarre and normal except for suicidal ideation. She endorses suicidal ideation with intent and a plan to drink antifreeze or suffocate herself. She denies any auditory or visual hallucinations. Her attention and concentration are within normal limits. Her intelligence is above average and her insight and judgment are good.

11. Brief Formulation
M. is a 14-year-old girl who developed severe depression and mood lability after her fourteenth birthday, which rapidly progressed to suicidal thoughts and two suicide attempts, and it was discovered upon taking a medical history and ordering genetic testing that she carried two MTHFR mutations, an enzyme whose polymorphisms are suspected to correlate to mental illness generally and to mood disorders specifically.

12. Multi-axial Diagnoses:
Axis I: Bipolar II disorder
Axis II: None
Axis III: History of MTHFR-2 mutations and PF-2 mutation
Axis IV: Mild, due to minor stressors at school
Axis V: Global Assessment of Functioning is 20, at admission

13. Pertinent Issues / Questions for Discussion:
Methylenetetrahydrofolatereductase (MTHFR) is an enzyme that controls the rate of production of N-methyltetrahydrofolate, a molecule which is vital for the N-methyltetrahydrofolate-homocysteinemethyltransferase reaction, which is the reaction that reduces homocysteine to methionine with the aid of cobalamin (vitamin B-12), which carries the methyl group between the two reactants. Many of the human body’s biological processes, including DNA and RNA synthesis, are dependent on this one-carbon transfer reaction. A missense mutation in the MTHFR gene at location 677, where cytosine is replaced with thymine, is of clinical significance and has been widely studied (Green 2015). This mutation is referred to as C677T, and results in a thermolabile form of MTHFR that has different enzyme kinetics and produces a different distribution of N-methyltetrahydrofolate and its
precursor molecule compared to the wild type enzyme (Green 2015).

The change in the concentration of these two molecules has far reaching effects on the negative feedback systems that regulate nucleic acid synthesis (via thymidylate synthesis) and homocysteine levels (which tend to rise due to lack of a methyltransferase reaction to break homocysteine down into methionine). The hematological, cardiovascular, oncological, neurological, and neuro-psychiatric consequences of these changes have been long suspected but have only recently begun to be characterized.

Controversy surrounds the proposition that MTHFR mutations may have clinical significance in regard to mood disorders. Studies have found variable results depending on the population studied, the precise mutation analyzed (C677T or A1298C), and the psychiatric pathology in question (with mood disorders and psychotic disorders being the most widely studied). One prominent theory involves the role of MTHFR and vitamin B-12 in the one carbon transfer pathways (Mitchell 2014). A deficiency in either MTHFR activity or vitamin B-12 availability can lead to elevated homocysteine levels, which has been implicated in amyloid buildup, and damage to neurons via mitochondrial dysfunction, direct DNA damage and initiation of apoptosis (Mitchell 2014). Dysregulation of the complex methyl donor system can also lead to the buildup of methylmalonic acid, a toxic intermediate metabolite, and low levels of S-adenosylmethionine (SAM), a necessary component of neurotransmitter metabolism (Frankenburg 2007).

Another proposed theory focuses on MTHFR’s effect on the dopaminergic system via the catechol-O-methyltransferase (COMT) enzyme. Because mood dysregulation is believed to be tied to the dopaminergic system, and COMT is essential in dopamine metabolism, it is plausible that MTHFR could affect mood through its purported effect on COMT methylation (Wang 2015).

A recent study of Han Chinese patients with bipolar II disorder provided preliminary empirical support for this theory (Wang 2015). A third theory about the biochemical mechanism by which MTHFR may affect mood disorders claims that certain variants of the MTHFR gene (A1298C and C677T) lead to low folate and vitamin B-12 levels, but high total homocysteine levels, a state that may put patients at risk for bipolar disorder. This theory has also found empirical support (Ozbek 2008).

Unfortunately for all of the mechanistic theories, the relationship between MTHFR and mood dysregulation has found only mixed support in the literature. For example, an Egyptian study of the C677T polymorphism found evidence of an association between that polymorphism and the risk of developing bipolar disorder and schizophrenia (El-Hadidy 2014), while a recent meta-analysis found that C677T polymorphism was associated with the risk of developing schizophrenia and bipolar disorder only in Asian and African populations, and not in the white population (Hu 2015). This meta-analysis also found that the A1298C polymorphism was not associated with bipolar disorder at all, but was associated with schizophrenia in Asian populations (Hu 2015).

Such results appear to overturn earlier research that established a connection between A1298C and bipolar disorder (Kempisty 2007), as well as research tying A1298C to affective psychoses in general, including unipolar depression (Reif 2005). The C677T polymorphism has likewise had a complex and conflicting evidence base: a 2004 Chinese study narrowly missed finding a statistically significant association between C677T and mood pathology (Tan 2004), and ten years later a western study of several genetic variants believed to be associated with bipolar disorder failed to find any association between
C677T and bipolar disorder, with the researchers noting that this finding seemed to conflict with other published literature (Permoda-Osip 2014).

Complicating this picture are other meta-analyses, each one attempting to reconcile the contradictory results of the previously literature into one cohesive conclusion, that find either a small but statistically robust association between C677T and bipolar disorder (Rai 2011), or a broader association between both MTHFR polymorphisms and mood dysregulation and psychosis more generally (Peerbooms 2011). One meta-analysis concludes that C677T is associated with schizophrenia, bipolar disorder, and unipolar depression, while A1298C was associated with bipolar disorder only (Peerbooms 2011).

In addition to the exact polymorphism and psychiatric pathology being studied, it may well be of significance which demographic group is being examined. An older but possibly unique study of unipolar depression and schizophrenia in C677T-carrying Japanese patients found highly significant associations with large odds ratios compared to other studies (Arinami 1997). A 2006 meta-analysis looked at both polymorphisms and several psychopathologies, and separated the Caucasian and east Asian population data (Zintzaras 2006). It found that the C677T polymorphism was associated with bipolar disorder only in the Asian subpopulation, with no significant association in the Caucasian population or the general population overall (Zintzaras 2006). This might seem to provide a way to resolve the contradictory findings of different studies, but a combination study / meta-analysis that focused on Chinese patients failed to find any evidence of an association between C677T and bipolar disorder (Chen 2009).

Focusing on specific sub-populations could provide data that explains the inconclusive nature of whole population studies: perhaps some groups and affected and others are not, and the effect is washed out in the population at large. An Iranian study of C677T and both schizophrenia and bipolar disorder failed to find any association between either condition and the mutation (Arzaghi 2011). A Norwegian study of both C677T and A1298C and bipolar disorder did not substantiate any association between the mutations and the psychiatric pathology, though the authors note that previous positive meta-analyses still yield evidence of an association (Jonsson 2008).

More evidence is always needed to solve such questions, and it seems to be imperative that future data be collected with sub-population analysis in mind. Perhaps the best way to do this is found in the approach of a recent review of meta-analyses, which examined 329 candidate genes for five major disorders (unipolar depression, bipolar disorder, schizophrenia, anxiety disorders, and attention deficit hyperactivity disorder (ADHD), and found 13 genetic variants that were associated with at least two different disorders (Gatt 2015). Among these 13 genes were both MTHFR polymorphisms, A1298C and C677T, which indicates that the relationship between these polymorphisms is likely real, with a pleiotropic mechanism that leads to the inconsistent results seen in the literature today (Gatt 2015). As progress is made in understanding the big picture of genetic interactions and their impact on mental illness, the apparent contradictions produced by crude analysis of only two variables will likely be resolved.

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