Methylation’s Role in Neurological Health, Aging & Recovery: Beyond Methylene tetrahydrofolate Reductase (MTHFR) Deficiency
Kendal Stewart, M.D.

ABSTRACT
Methylation deficiency plays a key role in the pathology of neuro-immune syndromes and neurological aging. The aims of this paper are to offer an introduction to general methylation biochemistry and methylation deficiency. The methylene tetrahydrofolate reductase (MTHFR) polymorphisms and lesser known abnormalities with methylation, their causes and consequences, and how to address these problems, will all be discussed.

INTRODUCTION
Most doctors spend little time thinking about methylation, yet they unknowingly see patients with problems caused by methylation deficiencies on a daily basis. Common disorders in adults in which methylation deficiency plays a role include:

- Migraines, headache;
- Vertigo, dizziness;
- Chronic fatigue, fibromyalgia;
- Chronic pain / neuralgias / neuropathies;
- Adult attention deficit disorder (ADD), adult attention deficit hyperactivity disorder (ADHD);
- Seizure disorders;
- Post-concussion syndrome;
- Neurological cancer;
- Anxiety disorders / depression / bi-polar;
- Alzheimer’s disease and dementias;
- Infertility, hormonal regulation issues;
- Asthma;
- Psoriasis;
- Food Sensitivities;
- Hypothyroidism;
- Auto-Immune Disorders (lupus, rheumatoid, Hashimoto’s, etc.);
- Chronic immune dysfunction (yeast, viral, Lyme’s disease, etc.);
- Diabetes

Deficiencies in the methylated B vitamins, methyl vitamin B12 (methylcobalamin) and methylene tetrahydrofolate (MTHF) are a common cofactor in all of the problems above. So, although very few doctors know little about methylation, we can see that it is a huge problem for a large majority of our patients. You cannot get away from methylation, because it is vital for health.

METHYLATION’S ROLE IN NEUROLOGICAL HEALTH, AGING & RECOVERY

The Biochemistry of Methylation
Methylation involves the addition of a “methyl” chemical group to a substrate. Methylation has more than 200 functions in the body, and is vital for dopamine status, nitric oxide production, cell turnover and division, membrane properties, mitochondrial function, and limbic status. Methylation deficiency causes 3 major biomedical issues:

1. General methylation deficiency due to MTHF and/or Methyl B12 deficiency:
   a. Mitochondrial weakness;
   b. Nitric oxide deficiency;
   c. Cell division and recovery deficiency;
   d. Poor neurotransmitter activity;
   e. Poor growth factor functionality;
2. T cell deficiency/weakness causing Th1 to Th2 skew due to 5-MTHF deficiency, which creates inflammation;
3. Poor neurotransmitter synchronization – dopamine and serotonin inefficiency due to tetrahydrobiopterin (BH4) deficiency and catechol-O-methyltransferase (COMT) polymorphism.
Therefore, problems with methylation will affect the cellular delivery, epigenetics and intra-cellular functionality of almost all cells. Basically, anyone who is suffering from methylation deficiency is going to experience poor neurological healing, mitochondrial weakness, fatigue, poor neurotransmitter production, food and inhalational allergies, T-cell immune weakness (and therefore prone to viral, bacterial, and fungal infections, and cancer), poor inflammation control, poor toxin clearance, and limited dopamine production. Dopamine has important functions for memory, focus, concentration, sleep, emotional stability, and fine motor skills, thus people who do not have enough dopamine will have problems in all of these areas.

To begin to understand the problems that methylation deficiency can cause, we need to start by thinking about what the body does with the folic acid we ingest. Folic acid has to be processed by methyltetrahydrofolate reductase (MTHFR) to convert it to methyltetrahydrofolate (MTHF), the biologically active form of folic acid. MTHF then has to cross a fatty barrier, and this is where we start to hit problems. The B vitamins are water-soluble, however the nervous system and immune system are covered in fatty membranes, and as we all know, water and oil do not mix. To overcome this problem, the body sends MTHF through a different folate carrier called the reduced folate carrier. The reduced folate carrier then transports MTHF to folate receptors on cells. Once the reduced folate carrier binds to the folate receptors, the MTHF is transported into the cells.

**Methylation Deficiency**

**Methylenetetrahydrofolate Reductase Polymorphisms**

The most common genetic predisposing risk factor for the diseases linked to methylation deficiency is MTHFR deficiency. MTHFR is responsible for the production of MTHF. There are 3 common genetic polymorphisms that cause MTHFR deficiency:

- **C677T** – confers weakness in MTHF production;
  - Heterozygous – 30-40% reduction in MTHF production;
  - Homozygous – 70-75% reduction in MTHF production;
- **A1298** – confers mild weakness in MTHF production;
  - Heterozygous – 5-10% reduction in MTHF production;
  - Homozygous - 20% reduction in MTHF production;
- **Mixed 677/1298** (compound heterozygous);
  - Confers a 40-50 % reduction in MTHF production.

How common are these polymorphisms? In my patient population (n=161), just 4% have none of the above polymorphisms. This figure is likely as a result of the type of patients in my practice – these people come to see me because they have medical problems that are linked to methylation deficiency. In a normal patient population, it is likely that half of your patients will be free of these polymorphisms.

However, even in a homoyzygous state, neither of these variations is strong enough to cause all of the diseases mentioned above. What this means is that a patient who is genetically, or otherwise, predisposed to developing one or more of these illnesses will not do so until they experience a triggering event. Unfortunately, there are a large number of factors that can act as a triggering event, from vaccines (live viral), severe infections, environmental exposures, trauma, and surgery, to emotional states such as stress.

**The Homocysteine Quandary**

Low homocysteine levels are more common than high homocysteine levels. Many doctors might think that this is great news, however what these doctors don’t know is that having too little homocysteine levels is far worse than having too much. Why? Having too little homocysteine is of great importance because homocysteine is vital for the body to manufacture the potent antioxidant glutathione. That is not to say that having too much homocysteine is not an issue, it is, but doctors also need to be aware that having too little also warrants attention. Where does methylation fit in here? MTHFR is a co-factor for methionine-synthase, the enzyme needed to convert methionine into homocysteine. So, without methylation, the body cannot produce homocysteine, and without homocysteine the body cannot produce glutathione.

Thirteen years ago, I decided to do my own study on homocysteine levels. I decided that a homocysteine level of 9 was ideal and that 6.75 – 10.5 was within the normal range. Firstly, I investigated the homocysteine levels of children with autism. I was aware that virtually all of these children have MTHFR polymorphisms, therefore I was not too shocked to find that 93% of the 413 children I looked at had a homocysteine level <7, and that 76% had a level of <5. What about adults? Of the 276 patients with neuro-immune syndromes in my study just 11% had a high homocysteine level of >12, whereas 73% had a level <7.

It is very important to determine your patients’ homocysteine level as it is a simple, but very important indicator of mitochondrial problems.
**Folic Acid Autoantibodies**

Another major cause of methylation deficiency is folic acid autoantibodies. As many as 72% of our neuro-immune syndrome patients have membrane bound folic acid receptor auto-antibodies, which prevent the reduced folate carrier from binding to folate receptors. The consequence of this is that MTHF cannot be transported into the cells of the nervous and immune systems.

Membrane bound folic acid receptor auto-antibodies are an acquired risk factor for neuro-immune syndromes. Why do people have these auto-antibodies? Research suggests that the development of these auto-antibodies is triggered by β-2 (cow) casein exposure during infancy or with bowel irritation. There is a very simple way of determining if a patient has these auto-antibodies, and that is to measure folic acid in the plasma. Normal plasma folic acid levels are around 3-12. If the blocking auto-antibody is present, the patient's folic acid will be >15, and more often than not >24. Why do plasma folic acid levels get so high? This is simply because the folic acid is not being transported into the cells.

Membrane bound folic acid receptor auto-antibodies are 10-times more important than MTHFR deficiency in terms of functional recovery. If your body can't transport MTHF into the cells, it makes no difference whether you are MTHFR deficient or not.

**The Bucket Theory of Methylation**

I have found that the bucket theory is useful for explaining the importance of methylation. This theory works clinically. It is not perfect biochemically, but clinically it makes perfect sense. In Figure 1 you can see that there are 4 sequential buckets that we have to fill with methylated vitamins – the mitochondrial bucket (energy), the growth factor bucket (delivery of nutrition and anabolic growth), the immune system bucket, and the dopamine bucket (quality sleep, good cognition, emotional stability, etc.). When our methylation supply is adequate all the buckets are full, and we are healthy and happy.

![Bucket Theory](image)

*Figure 1: The bucket theory of methylation – when proper methylation takes place there is a plentiful supply of methylation for all body processes requiring methylation.*

Problems start to arise when people have a methylation deficiency. What happens to the buckets if we have a methylation deficiency and we get ill? As we can see in Figure 2, if we get ill it is akin to having a hole in the immune bucket. The body is plowing all of its energies into the immune system in order to fight infection, and the methylation supply drains out of the immune bucket. This means that there is now nothing going into the dopamine bucket, thus we end up with decreased dopamine levels. Think about how you feel when you are ill, you feel tired, you find it difficult to think and concentrate, and you feel miserable. This is all due to decreased dopamine levels.
Figure 2: Oxidative challenge leads to methylation deficiency and decreased dopamine levels.

After illness, the situation gets worse. As can be seen in Figure 3, in order to overcome infection and repair damaged cells and tissues, the body has to pour more of its methylation supply into the immune system bucket, the growth factors bucket, and the mitochondria bucket. If our supply of methylation products is adequate this is not a problem, but for people with a methylation deficiency this is where the real problems start to appear. We start to see impaired healing and recurring infections, because there is not enough methylation supply to keep the immune system working properly or to manufacture growth factors. This is when we start to see all the problems mentioned previously – increased inflammation, severe allergies, and food and chemical sensitivities.

Figure 3: Methylation deficiency results in an inadequate methylation supply for repair processes. This has numerous deleterious consequences.

It is important to remember that methylation needs differ according to age. The need for methylation follows growth hormone and peaks at about 11 in girls and about 14 in boys. Demand then stays high throughout the teenage years and then starts to drop back down to baseline in the 20s. By the time we reach our 30s the need for methylation starts creeping back up, and this is the reason why we start to see so many health problems in the elderly. Most people simply aren’t keeping up with the bodies need for methylation. For this reason, methylation support (which will be discussed below) in the elderly is vital.
Recovery

Clinical Evaluation of Patients with Suspected Methylation Deficiency

Clinical evaluation of people with suspected methylation deficiency disorders often reveals:

- Dopamine deficiency symptoms – mood instability, poor focus and concentration, sleep disorders, hormonal regulation, fatigue, bowel motility issues;
- High levels of severe allergies and/or food and chemical sensitivities;
- Fluctuant symptoms – ‘good’ times / ‘bad’ times;
- High levels of immune dysfunction (CD4/CD8);
- Familial patterns of neurological disorders, autoimmune syndromes, cancer, and/or mood disorders.

How do we go about assessing the nervous system? When assessing the nervous system we need to consider balance, sensation, cognition, and mood. The complexity involved in functionally assessing the nervous system is what deters many doctors from trying to treat the neuro-immune syndromes linked to methylation deficiency. However, help is at hand. Sensory View™ is a proprietary software system that combines multiple FDA-approved medical diagnostic testing devices into a seamless, functional platform and provides easy-to-interpret objective graphic summaries of the function and stability of the sensory systems. Sensory View™:

- Objectively evaluates the patient’s current neurological status and stability;
- Enables us to see inflammation in the sensory nervous system and measure dopamine in "real time”;
- Allows us to objectively verify the success of a particular biomedical intervention;
- Allows us to establish functional timelines to recovery.
Figure 4: Normal Sensory View test.
The information that Sensory View™ provides can be seen in Figure 4. In this instance, we have a normal result.

With the right treatment, the patient will achieve a normal result on the Sensory View™ test within just a few months.

Blood work and allergy testing should also be conducted on each patient:

- **Blood testing:**
  - MTHFR;
  - Plasma folic acid;
  - Homocysteine;
  - Vitamin D;
  - T cell subsets;
  - Thyroid Panel;
  - Pregnenalone, progesterone, testosterone, DHEA, estrogen;

- **Allergy:**
  - Food testing (IgG);
  - Inhalant testing (IgE).
Optimizing Neurological Health and Aging

There are 5 primary rules for successful optimization of neurological health and aging:

1. Overcome methylation deficiency if present;
2. Control (eliminate) inflammatory triggers;
3. Have proper cellular energy (mitochondria);
4. Deliver necessary nutritional elements;
5. Symptomatic support if needed.

Because we need methylation for the immune system, because we need methylation for the mitochondria, because we need methylation for symptomatic control, we have to start with methylation support – it is the foundation for recovery (Fig. 5) and will enable the patient to overcome any underlying genetics. Without it, nothing else we do will work.

Figure 6: Methylation support increases methylation supply and helps the body to recover from problems caused by methylation deficiency.

Methylation support should include:

- Methyltetrahydrofolate (MHTF) – cofactor activation of enzymes / hormones;
- Methyl B12 – cofactor activation of enzymes / hormones;
- Hydroxy B12 – cofactor activation of enzymes / hormones;
- Pyridoxal-5’-phosphate (P-5-P) – cofactor activation of enzymes / hormones;
- Vitamin D – immune regulation as epigenetic trigger

Methylation support will:

- Restore co-factors for T cell recovery and immune balance;
- Restore co-factors for mitochondria energy production;
- Restore co-factors for growth hormone production and growth factor delivery;
- Restore co-factors for dopamine production.

MTHF is not absorbed well if taken orally. Therefore, methylation support is more effective if it is delivered either transdermally or subcutaneously twice daily. Most people are not keen on injecting themselves twice a day, thus patients are more likely to opt for transdermal delivery. I use a lot of leucovorin calcium for methylation support. Why? Simply because it is cheap (with insurance it is usually $10 co-pay) and it is very powerful. Some people will say that leucovorin (which is formyltetrahydrofolate) does not work, but in my experience it works very well in approximately 90% of patients.

Note: It is important to start with a low-dose and get the patient to incrementally increase it every 3-4 weeks. It is vital to let the body adjust slowly to methyl support. If you start on a high-dose it is likely that your patients will complain of anxiety and/or new immunological issues.
Methylation support will help to reduce inflammation, however it may also be necessary to treat infectious agents / dysbiosis and remove or limit exposure to allergens. Immune modulation or steroid manipulation may also be needed. I would recommend carrying out the following laboratory tests:

- Pregnenolone, testosterone, progesterone, estrogen;
- Plasma titers for Epstein-Barr virus, cytomegalovirus, mycoplasma, chlamydia, candida;
- IgG / IgE food panel;
- Inhaled allergen testing;
- Gluten antibody assessment;
- T-cell quantification;
- Immunoglobulin quantification;
- Stool culture

Treatment is obviously dependent upon laboratory results, however things to consider include:

- Bioidentical hormone replacement therapy (BHRT);
- Antivirals/antibiotics (natural and allopathic)
- Proline-rich polypeptides (PRPs) / colostrum, beta glucans;
- Allergy desensitization;
- Dietary changes;
- Immunoglobulins, enzymes and probiotics.

What about mitochondria, how do we even know if a patient has mitochondrial weakness? The simplest test for mitochondrial weakness is a quick chat with the patient. How well do they recover from exercise? How is their muscle tone? The classic symptoms of mitochondrial weakness are poor muscle tone, fatigue, slow healing, and slow recovery from exercise. Laboratory findings that are suggestive of mitochondrial weakness are high ammonia levels and elevated coproporphyrin III. Several nutritional supplements can help restore the mitochondria, including:

- CoQ-10, acetyl carnitine, arginine, alpha-ketoglutarate (AKG), citrulene, ornithine – useful for mitochondrial replenishment;
- N-acetyl cysteine (NAC), alpha lipoic acid (ALA), resveratrol, quercetin, turmeric extract – to aid intracellular cleansing;
- Zinc, biotin – activators.

Finally, we need to overcome the symptoms of low dopamine and low serotonin. There are a number of supplements that can help to make the patient’s dopamine more effective, these include:

- Dimethylglycine (DMG), trimethylglycine (TMG), methionine, choline, taurine, inositol – methyl donors for increased dopamine turnover;
- Phosphatidylserine, huperzine A – increase acetylcholine activity;
- Tyrosine, L-theanine – precursors and modulators of dopamine.

**CONCLUSIONS**

Methylation deficiency is the missing component of neurological and immunological recovery. Genetic and acquired factors predispose many people to developing methylation deficiency. However, an adequate supply of methylation vitamins can override the deleterious effects of these predisposing factors, and therefore prevent or treat many of the problems that are associated with methylation deficiency. Methylation support, controlling (or if possible eliminating) inflammatory triggers, and mitochondrial support can all help to optimize neurological health.

For information about Dr. Stewart visit [www.DrKendalStewart.com](http://www.DrKendalStewart.com) or [www.CoffeeWithDrStewart.com](http://www.CoffeeWithDrStewart.com)

Media Contact: Kara Mullens / (866) 500-5388 or kds@neurobiologix.com