ABSTRACT

The aim of this paper is to offer the reader an introduction to the neuro-immune syndromes, a large and growing group of disorders that involve the nervous system and the immune system. Methylation deficiency plays a key role in the pathology of neuro-immune syndromes. The causes and consequences of methylation deficiency, and how to treat it will be discussed.

INTRODUCTION

The neuro-immune syndromes are a large and growing group of disorders that involve the nervous system and the immune system. These disorders tend to be defined by their symptoms, simply because we do not know what is causing them. Neuro-immune disorders affect people of all ages, and are extremely common – affecting as many as 30% of the population. Common neuro-immune disorders in adults include:

- Migraines, headache;
- Vertigo;
- Dizziness;
- Chronic fatigue;
- Fibromyalgia;
- Chronic pain / neuralgias / neuropathies;
- Adult attention deficit disorder (ADD);
- Anxiety disorders / depression / bi-polar;
- Auto-immune disorders (e.g. lupus, rheumatoid arthritis, Hashimoto’s thyroiditis);
- Alzheimer’s disease and dementias;
- Chronic immune dysfunction (e.g. yeast infection, viral infection, Lyme disease);
- Infertility;
- Hormonal regulation issues.

Most doctors don’t enjoy treating neuro-immune disorders. The main reason for this is simply because of a lack of access to functional testing of the nervous system. Another reason is that successful therapeutic intervention for neuro-immune disorders requires a practitioner with a great depth of knowledge in many different areas. Basically, the complexity of neuro-immune syndromes can be overwhelming.

NEURO-IMMUNE SYNDROMES AND METHYLATION DEFICIENCY

Clinical evaluation of people with neuro-immune 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 functionally assess 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. 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 patients 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.
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Figure 1. Normal Sensory View™ test.

The information that Sensory View™ provides can be seen in Figure 1. In this instance, we have a normal result. I treat an average of 2000 to 2500 new patients with neuro-immune syndromes each year. With the right treatment, the patient will achieve a normal result on the Sensory View™ test within just a few months.

Functional testing of patients with neuro-immune syndromes has revealed that these patients often have:

- Sub-clinical inflammation in the nervous system;
- Fluctuant precision in neurological transmissions;
- Dopamine insufficiency (almost all patients);
- Poor sensory integration in the nervous system;
- Symptom severity was related to inflammation status and/or inconsistency of sensory information.
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People with neuro-immune syndromes have a lot in common, they often suffer from severe food allergies and chemical sensitivity, they have low muscle tone, and they don’t heal well. Testing will frequently reveal heavy metal toxicity, neurochemical deficiency, hormone deficiency, immune dysfunction, aggressive inflammation, infectious overgrowth, poor toxic clearance, and mitochondrial weakness. Why do people with neuro-immune syndromes tend to have all of these problems? This suggests that there must be a common cofactor. So, we set out to see if we could find one. We did. The common cofactor in all of the aforementioned problems is methylated B vitamins. Methyl vitamin B12 (methylcobalamin) and methyltetrahydrofolate (MTHF) are common cofactors in every one of the abnormalities shown in Figure 2.

**What is abnormal in Neuro-Immune Disorders?**

- Severe Food Allergies
- Immune Dysfunction
- Aggressive Inflammation
- Low Muscle Tone
- Infectious Overgrowth
- Poor Healing
- Chemical Sensitivity
- Mitochondrial Weakness
- Poor Toxic Clearance
- Neurochemical Deficiency
- Heavy Metal Toxicity
- Hormonal Deficiency

![Figure 2. Methylated B vitamins are a common cofactor in many of the abnormalities seen in neuro-immune syndromes.](image)

**Methylation Deficiency**

How do neuro-immune syndromes occur? It is important that we answer this question because the incidence of the neuro-immune syndromes has risen rapidly in recent decades. This hasn’t happened over generations, so the cause of this increase is not purely genetic. To help us answer this question it is necessary to consider the four foundation principles of neuro-immune syndromes:

1. Can anyone develop a neuro-immune syndrome? Genetic or acquired predisposition is necessary, but not causative;
2. What role do genetics play? Genetic inefficiencies seem to only affect the recovery and severity of the syndrome;
3. What initiates and propagates a neuro-immune syndrome? Oxidative Stress is an epigenetic trigger and propagator;
4. What links the nervous system and immune system together in these disorders? The common “co-factor” concept (methylated vitamins).

The first foundation principle states that genetic or acquired predisposition is necessary, but not causative. What this means is that a patient who is genetically or otherwise predisposed to developing a neuro-immune syndrome 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 most common genetic predisposing risk factor for neuro-immune syndromes is methyltetrahydrofolate reductase (MTHFR) deficiency. MTHFR is responsible for the production of 5-MTHF. There are 2 common genetic variations that cause MTHFR deficiency:

- C677T – confers weakness in 5-MTHF production, affects approximately 10% of the population;
- A1298 – confers very mild weakness in 5-MTHF production.

However, even in a homozygous state, neither of these variations is strong enough to cause all of the problems seen in neuro-immune syndromes. This confused me for a long time. MTHFR deficiency does not help us, and it certainly may worsen the situation, but is not the primary cause of our problem. So, what is?

We need to start by thinking about what the body does with the folic acid we ingest. Folic acid has to be processed by MTHFR to convert it to 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. The problem we have is that 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 B-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 5-12. If the blocking auto-antibody is present, the patient’s folic acid will be >16, and more often than not >24. The patient’s plasma folic acid levels are elevated 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. Methylation has more than 200 functions in the body, and is vital for dopamine status, nitric oxide production, cell turn over 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.

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 are going to have problems in all of these areas.

I have found that the bucket theory is useful for explaining the importance of methylation. In Figure 3 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,
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emotional stability, etc.). When our methylation supply is adequate all the buckets are full, and we are healthy and happy.

Figure 3. 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 4, 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 4. Oxidative challenge leads to methylation deficiency and decreased dopamine levels.
After illness, the situation gets worse. As can be seen in Figure 5, 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 associated with neuro-immune syndromes – increased inflammation, severe allergies, and food and chemical sensitivities.

**Figure 5.** Methylation deficiency results in an inadequate methylation supply for repair processes. This has numerous deleterious consequences.

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**Figure 6.** Methylation support increases methylation supply and helps the body to recover from problems caused by methylation deficiency.
**Recovering from Neuro-Immune Syndromes**

There are 4 primary rules for successful recovery from neuro-immune syndromes:

1. Control, or ideally eliminate, inflammation;
2. Have proper cellular energy (mitochondria);
3. Delivery necessary nutritional elements;
4. Symptomatic support until healing occurs.

Methylation support is the foundation for recovery as it will enable the patient to overcome any underlying genetics. Methylation support should include:

- Methyl folate – 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 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.

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;
- Plasma titers for virus, mycoplasma, chlamydia, yeast;
- 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:

- Pregnenolone, DHEA, testosterone, progesterone;
- Proline-rich polypeptides (PRPs);
- 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, quercitin, tumor extract – to aid intracellular cleansing;
- Zinc, biotin – activators.

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

- 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. An adequate supply of methylation vitamins is vital for health and the prevention of neuro-immune syndromes. However, genetic and acquired factors predispose many people to developing methylation deficiency. Treatment of methylation deficiency can prevent and treat the neuro-immune syndromes.