MTHFR

Methyhtetrahydrofolate Reductase

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Introduction

- Some of this presentation involves complex information, and some studies are not as clear as we’d like.
- However, there is evidence of real and well-researched information that may be beneficial to many and with little if any harm.
MethylTetraHydroFolate (MTHFR) Deficiency

- This is new enough in the research that most physicians are not aware of this information in the vast sea of information that is available
Thank You Human Genome Project!
The Human Genome Project

• The Human Genome project has developed a new approach to medical problems

• There are several of the B vitamins that require activation before they are useful to the body

• It has been found that by taking the active forms of these vitamins you are able to bypass metabolic glitches and compensate for genetic and environmental problems
5-MTHF = 5-methyltetrahydrofolate; DHF = dihydrofolate; MTHFD1 = methylenetetrahydrofolate dehydrogenase 1; THF = tetrahydrofolate.

Crossing the Blood Brain Barrier

FOLIC ACID BLOCKS L-METHYLFOLATE TRANSPORT ACROSS THE BLOOD BRAIN BARRIER

UNHINDERED TRANSPORT OF L-METHYLFOLATE ACROSS THE BLOOD BRAIN BARRIER

Vascular system  Blood barrier  Cerebral spinal fluid

L-methylfolate  L-methylfolate

Vascular system  Blood barrier  Cerebral spinal fluid

L-methylfolate  L-methylfolate  L-methylfolate  L-methylfolate

Folic Acid  Folic Acid  Folic Acid
MTHFR Gene

- Not everyone is born equal, as far as methylation is concerned
- As much as 70% (in the US) inherit a defective or partially defective gene; so that this key methylating gene, MTHFR does not work well
- Thus, if with this defect, there is an increased need for B12 and folic acid
MTHFR polymorphisms From the Human Genome project

- In 2009, >70 identified mutations of MTHFR gene (so far, approximately 40 linked with disease)
- You can have one gene defective, two genes defective, one gene defective from each type, partial defects, or other combinations

MTHFR Polymorphisms and Disease, ED. Ueland, Rozen, Landes Bioscience 2005
Who is at risk for MTHFR Gene Problems?

- Depressed patients are thought to be at risk for MTHFR polymorphisms because they would have lower serum L-methylfolate and thus lower CNS folate—thus lower monamine levels (serotonin, dopamine, NE)
- Hispanic and Italian population
- All of us......
Laboratory Evaluation

- Of note: Folate and B12 levels may be normal in MTHFR but since it is measuring inactive and active form it may not be reflective of what is actually happening in the body.
MTHFR deficiency With FDA reviewed treatments

- Depression (Deplin)
- Anxiety (Deplin)
- Memory Loss (CerefolinNAC)
- Diabetic neuropathy (MetaNX)
- High Risk Pregnancies (Neevo, NeevoDHA, Thorne Prenatal)
Other conditions that treating methylation has helped

- Fibromyalgia
- Chronic Fatigue
- Irritable Bowel
- Migraines
- Bipolar, Schizophrenia, Parkinson’s
- Autism, Autism spectrum disorders
- Prevention of Birth Defects

Ueland, Rozen, Landes; MTHFR Polymorphisms and Disease, ED., Landes Bioscience 2005
Other conditions that treating methylation has helped

- Without treatment, People with MTHFR deficiency may be more prone to viral infections because the methylation process is critical in shutting off viral replication.
- Without treatment, also more prone to retaining heavy metals and other environmental toxins.

Ueland, Rozen, Landes; MTHFR Polymorphisms and Disease, Ed., Landes Bioscience 2005
MTHFR
Who would benefit from Rx

- 30% have both genes defective
  - ~10-15% of normal function
- 40% have one gene defective
  - ~55-70% of normal function but also can’t increase in times of increased need (infection, healing, puberty, toxin load)
- 100% have exposure to toxins that affect this pathway
Low Methyfolate effects

- Low Serotonin, Dopamine, Norepinepherine
- Low Glutathione, Needed for memory and toxin removal
- Low BH4 Tetrahydrobiopterin, Needed for nerve protection, Serotonin function
## Risk Factors for Low L-methylfolate

<table>
<thead>
<tr>
<th>Category</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drugs</strong></td>
<td>Anticonvulsants such as lamotrigine and valproate, methotrexate, sulphasalazine, oral contraceptives, metformin, niacin, fenofibrates, fluoxetine, and warfarin</td>
</tr>
<tr>
<td><strong>Disease</strong></td>
<td>Diabetes, atrophic gastritis, Crohn’s, colitis, renal failure and hypothyroidism</td>
</tr>
<tr>
<td><strong>Lifestyle</strong></td>
<td>Excessive alcohol, smoking, and poor nutrition, Toxin exposure (BPA, Heavy metals, Pesticides)</td>
</tr>
<tr>
<td><strong>Aging</strong></td>
<td>L-methylfolate in the brain decreases with age</td>
</tr>
<tr>
<td><strong>Genes</strong></td>
<td>MTHFR, MTRR, MTR and other genetic polymorphisms</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td>Body Mass Index (BMI) ≥30</td>
</tr>
</tbody>
</table>

Heavy Metal Symptoms

- Social Deficits, Withdrawal
- OCD, Depression, Bipolar, Suicide
- Schizophrenia, Aggression, Tantrums
- Chronic Fatigue, Fibromyalgia
- Poor Concentration, Memory
- Hearing Loss, Seizure, Stroke
- Peripheral Neuropathy, Paresthesia
Heavy Metal Symptoms (cont)

- Nausea, Diarrhea, Abdominal Pain
- Colon Cancer, Pancreatic Cancer
- Liver Dysfunction, Kidney Dysfunction
- Hypertension, Tachycardia
- Pulmonary Fibrosis, Asthma
- Immune Problems, Low WBC
- Hair loss, Premature Graying, Rashes
- Others....
Environmental concerns that can effect metabolic pathways

- Heavy Metal Toxicity is very prevalent
  - Low level arsenic associated with diabetes
- Bisphenol A is common in plastics
  - Inhibits methylation in rats and rat fetuses
  - Is associated with Diabetes, Heart Disease, Stroke, Liver Disease
- Estrogen disrupter, associated with PCOS, endometriosis
Diabetes in Asia

- 2-10 fold increase in diabetes
- Little change in Body Mass index
- Associated with organic pollutions (BPA)
- Associated with low level Arsenic

JAMA May 27, 2009 pp 2129-40
Glutathione

- Antioxidant
- Clears heavy metal toxins
- Is decreased in MTHFR
- Low levels correlate with memory problems, infections, and other problems
CONFUSED YET???
Link with Autism, ASD

- MTHFR 677 and 1298 in 98% of children with autism
- Primary damage leading to ASD in later life is likely to take place in utero and/or in the immediate postnatal period
- Two hit model, Genetic Predisposition and environmental challenge (heavy metal exposure)
  - American Journal of Biochemistry and Biotechnology, 2008
Mercury Autism Link

- CDC admits Feb 28, 08 that Thimerisol (a mercury containing organic compound which was widely used as a preservative in vaccines) “aggravates” autism in children with a genetic predisposition
- Dietary protocol to improve methylation helps improve Autism symptoms
MTHFR and Autism Link

- Women not taking prenatal vitamins immediately before and during a pregnancy were twice as likely to have a child with autism.
- If the women also had MTHFR, they were seven times as likely to have a child with Autism.

Epidemiology: July 2011 - Volume 22 - Issue 4 - pp 476-485
MTHFR polymorphisms

What can I do If I think I have the problem?

- Testing? Test only looks at limited number of defects
- Have good nutrition
- Nutritional protocol
- If you have this defect, also be aware of toxins that may affect the pathway (may want to have mercury fillings removed)
Sample of My Defects
Green arrow shows what you get with commercial test

<table>
<thead>
<tr>
<th>Gene</th>
<th>SNP</th>
<th>DNA</th>
<th>RNA</th>
<th>Difference</th>
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<td>A</td>
<td>GG</td>
<td>+/-</td>
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<tr>
<td>MTHFR A1572G</td>
<td>rs17367504</td>
<td>G</td>
<td>AG</td>
<td>+/-</td>
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<td>MTHFR A1298C</td>
<td>rs1801131</td>
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<td>GG</td>
<td>+/-</td>
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<tr>
<td>MTHFR G1793A (R594Q)</td>
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<td>CT</td>
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<td>MTR C2756G</td>
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<td>+/-</td>
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<tr>
<td>MTRR H595Y</td>
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<td>CC</td>
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<td>AA</td>
<td>+/-</td>
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Recommendations

1. Decrease exposure to toxins
   - Water filters, locally grown foods
2. Improve the body’s Metabolism
   - Improve diet
   - Supplement around defects
3. Clear heavy metals if symptomatic
President’s Cancer Panel
Recommendations 2009

- Remove shoes when entering home
- Filter water, BPA free water bottles
- Don’t drink from bottled water
- Microwave in glass or ceramic
- Use non-toxic cleaners
- Wash fruits and vegetables
- Avoid pesticides

President’s Cancer Panel annual report 2009.
“Reducing environmental cancer risk, What we can do now”
www.ourstolenfuture.org/basics/chemlist.htm
Measures that improve symptoms

- Dietary, vegetables, berries, fruits
  - Better if grown locally
- Mathematics, Accounting
  - Engineers, creative people
- Piano, Classical music
- Exercise
- Band (not rock band) participation (structured music)
Excellent Resource
Helps with the emotional aspects of this gene

Change Your Brain, Change Your Life

Magnificent Mind at Any Age: Natural Ways to Unleash Your Brain's Maximum Potential

by Daniel G. Amen, MD
Improve metabolism

General guidelines

- Only add one supplement at a time
- Drink/Cook with filtered water
- If mod/severe symptoms consider Heavy Metal testing---rarely necessary
“If you're not confused, you're not paying attention.”

— Tom Peters, *Thriving on Chaos: Handbook for a Management Revolution*
Methylfolate Options

- Metafolin from Merck (Best Studied)
  - Deplin, 7.5 or 15 mg
  - Breckenridge Generic
  - Solgar Metafolin 400mcg, 800 mcg
- Extrafolate, Extrafolate-S, Quatrefololate
  - Made by Gnosis
  - Thorne, Methyl-life, etc.
## Cost Comparison
### 5-Methylfolate

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<thead>
<tr>
<th>Product</th>
<th>Mg</th>
<th>Cents per MG</th>
<th>% abs</th>
<th>cents/mg absorbed</th>
<th>Form</th>
<th>Note</th>
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<tbody>
<tr>
<td>Deplin (Brand direct Pharm)</td>
<td>15</td>
<td>13</td>
<td>76</td>
<td>17</td>
<td>Metafolin</td>
<td>Crystal</td>
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<td>Solgar Folate</td>
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<td>SeekingHealth</td>
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<td>Methyl-Life</td>
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<td>56</td>
<td>33</td>
<td>Quatrefolic</td>
<td>Glucosamine</td>
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<tr>
<td>Thorne MTHF</td>
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<td>27</td>
<td>76</td>
<td>36</td>
<td>Extrafolate-S</td>
<td>Amorphous</td>
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<tr>
<td>Thorne MTHF</td>
<td>1</td>
<td>41</td>
<td>76</td>
<td>54</td>
<td>Extrafolate-S</td>
<td>Amorphous</td>
</tr>
</tbody>
</table>
Recommendations:
Deplin for Depression
Supplement Options B12

- Methyl B12
  - Not absorbed well even in Meta NX, Cerefolin
  - Oral Dissolving tablets work well for most
    - Jarrow brand works well
  - Compounded subcutaneous injections work very well but more expensive
  - Light and Temperature control very important with injections
  - Oral drops now available for children with symptoms. (Malley’s Pharmacy)
Supplement Options
N-Acetyl-Cysteine

- **N Acetyl Cysteine**  500-2400 mg daily
  - This helps make glutathione, which clears heavy metals, seems to help with memory
  - Shown to improve Addictions, Skin Picking, Nail Biting, Hair Pulling, Bipolar, Schizophrenia

J. Psychiatry Neurosci 2011:36(2):78-86
Supplement Options (cont)

- **Vitamin D3** The “sunshine” vitamin, critical to health.
  - 2,000 IU or more daily: 25-hydroxyvitaminD3 test recommended

- **Full Spectrum Minerals** This is a mineral supplement with Amino Acid Chelate (AAC). Raw sea salt also an excellent mineral source.
  - Daily dose. NOW brand has the AAC
Supplement Options

- **Epsom Salt bath** Soak feet or body with 1-2 cup of salts 2/3 times/week
  - The magnesium absorbs directly. It helps with improving the mineral balance. It also adds the sulfate that is critical in clearing toxins. It is not well absorbed orally.
Tetrahydrobiopterin (BH4)

0.025 or 0.5mg 1-2 tablets daily. Available at Malley’s

Inactive BH4 and takes it out of the cycle

Inflammation Oxidative Stress

Seipiapterin Reductase

5-Methylfolate
MTHFR is secondary

BH4

PAH
phe → tyr

TH
tyr → L-DOPA

TPH
tryp → 5-HTP

NOS
arg → NO

BH2

XPH2

Epinephrine
Norepinephrine
Dopamine
Serotonin
Melatonin
NMDA Fx

Supplement Options (cont’d.)

- **Vitamin B6 P5P, 25 mg** daily for the first 3 mo.
- **Vitamin C** 1,000 mg, 1-3 times a day (helps with constipation, regenerates glutathione)
- **DMG-Dimethylglycine or TMG-trimethylglycine**
  200-250mg/day  This adds methyl groups to the amino acids that your body uses in the methylation process
- **Zinc** 20-40 mg/ day
  - Especially important in eye sensitivity which is common in MTHFR defects. Also for brain, prostate, blood sugar, digestion function, etc. Helps detoxify, builds and repairs cells, regulates essential body chemical pathways.
Supplement Options (cont’d)

- **Omega 3** (Flax seed or Fish oil - calamarine best - that has mercury removed) 1-2 capsules per day. Helpful with Brain/Nerve Healing and circulation
  - Some of the fish oil tablets don’t have the mercury removed.

- **Vitamin E** 400 IU Daily – mixed tocopherols best to balance E vitamins

- **Silymarin** 150mg twice a day - improves glutathione usage and protects the liver.

- **Glutathione SR** (thorne) 2 capsules/day helps with detoxification.
Summary

- B12 and Folate may have important roles and uses, especially with new insight gained by the human genome project to incorporate the use of active forms
- Supplements are a trial and error, but easy to try and may have very beneficial effects with low if any toxicity
- Consider trying to reduce toxins if symptoms may suggest toxins are affecting the methylation pathways
- Future: More to discover..........................
“Before I came here I was confused about this subject. Having listened to your lecture I am still confused. But on a higher level. ”

Enrico Fermi (Developed first nuclear reactor)
QUESTIONS?