Memory Loss and MTHFR
Help from the Human Genome Project
Katie Karlson, MD
Neil Rawlins, MD
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MTHFR Deficiency and Memory

- I am not selling anything
- This is to help you decide what might be useful for your situation
- This research is new enough that most physicians have not become aware of this information in the vast sea of research data that is available
“Nearly Everything we know to be true in Medicine was once considered Heresy”

RUSSELL HIRST JR  1983
Disruptive Ideas in Medicine

- Dr James Lind 1747
  - Lemons for scurvy
- Dr James Lister 1865
  - Sterilize surgical instruments
- Dr Ignaz Samuelwiess 1847
  - Wash your hands before patient care
- Robin Warren, Barry Marshall 1985
  - H Pylori causes gastric ulcers
My Goal

- Convince you MTHFR is another one of the Disruptive and very beneficial ideas
The ultimate goal of the Human Genome Project was:

- determination of the molecular sequence of the entire human chromosomal complement.
- Development of powerful new tools for diagnosis, prevention, and treatment in all medical fields,...

- Started 1990  Finished 2003

- The Human Genome Project: implications for the treatment of musculoskeletal disease.
Human Genome Project
Finished 2003
Public investment $3.6 Billion

How have we done?
Human Genome Project
Health Risks (nice start)

- Celiac Disease: HLA-DQA1
- Thromboembolism: Lieden V/P20210
- Melanoma: MC1R
- Alzheimer’s: APOE
- Breast Cancer: BRAC1/2

- Increased Risks but no treatment yet
Human Genome Project
Predicting Medication Response (better)

- **Panitumumab** 40% of colorectal cancers have mutations (defects) in the \textit{KRAS} gene which make these expensive drugs ineffective.
  
  A.R. Sepulveda and J.P. Lynch (eds.), \textit{Molecular Pathology of Neoplastic Gastrointestinal Diseases}, Molecular Pathology Library 7, 33
  

- **Warfarin** Defects in CYP2C9 and VKORC1 increase bleeding. In the US if testing were done we could prevent 85,000 serious bleeding events, 17,000 strokes $1Bil savings

Current Solutions not Great
Percentage of patient for whom Drugs are ineffective

- Paving the Way for Personalized Medicine. FDA Oct 2013 p13
# Human Genome Treatments
(Best we have)

<table>
<thead>
<tr>
<th>GENE</th>
<th>FDA review</th>
<th>Pop affected</th>
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<tbody>
<tr>
<td>MTHFR</td>
<td>2006</td>
<td>70% +</td>
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<tr>
<td></td>
<td></td>
<td>Deplin, Cerefolin, MetaNX and NEEVO</td>
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<tr>
<td>PKU (HPABH4)</td>
<td>2007</td>
<td>0.007%</td>
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<tr>
<td></td>
<td></td>
<td>Kuvan ($85,000/month)</td>
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<tr>
<td>BRAF V660E</td>
<td>2011/13</td>
<td>1%</td>
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<tr>
<td></td>
<td></td>
<td>Benefits 50% of melanoma patients</td>
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<tr>
<td>ALK</td>
<td>2011</td>
<td>0.04%</td>
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<tr>
<td></td>
<td></td>
<td>5% of non-small cell lung cancers</td>
</tr>
<tr>
<td>CFTR(G551D)</td>
<td>2011</td>
<td>0.0004%</td>
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<tr>
<td></td>
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<td>4% of Cystic Fibrosis patients</td>
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5-MTHF = 5-methyltetrahydrofolate; DHF = dihydrofolate; MTHFD1 = methylenetetrahydrofolate dehydrogenase 1; THF = tetrahydrofolate.

Onset Cerebral Folate Deficiency (CFD) Is Devastating (But Potentially Entirely Reversible)

**Infantile CFD**
- Infantile Autism ± neurological deficits
  - Autism spectrum disorders

**Secondary CFD syndromes**
- Rett syndrome±MECP-2 gene Defect
- Variant of Aicardi-Goutieres syndrome
- FOLR-1 and FOLR-2 mutants ?

**Prenatal conditions**
- Neural tube defect
- Malformations ?

**Parental FR antibodies and risk of infantile autism**

**Developmental Stages**
- Birth
- 1 year
- 2 years
- 11-14 years
- > 50 years

**Secondary Effects**
- Dystonia
- Catatonic schizophrenia
- Spastic-ataxic syndrome
- Dementia and myoclonus

Folate Deficiency May Lead to Progressive DNA and Brain/Body Changes

- Reduced DNA methylation
- Increased homocysteine
- Increased uracil in DNA
- Increased DNA breaks & abasic sites
- Increased sensitivity to genotoxicity from Aβ42 & ROS
- Centromere dysfunction
- Epigenetic drift
- Telomere dysfunction or reduced telomere length
- Increased gene mutation
- Increased mtDNA deletion
- Increased cell death
- Reduced regenerative potential
- Increased CH 17, 21 aneuploidy
- Abnormal gene expression
- Reduced telomere length
- Increased CH 17, 21 aneuploidy
- Effects on brain development
- Increased DNA breaks & abasic sites
- Increased sensitivity to genotoxicity from Aβ42 & ROS
- Increased cell death
- Reduced regenerative potential
- Increased CH 17, 21 aneuploidy
- Effects on brain development

Bottom Line

Genetics
Dietary
Environmental
Medications

Fenech M. *Mechanisms of Ageing and Development* 2010;131:236–241
Methyl Folate Deficiency
Impact Both Brain and Body

Methyl Folate Deficiency
Dietary • Genetic • Drug Induced

Low CNS 5-MTHF

Incorporation of DEOXYURIDINE MONOPHOSPHATE into DNA causes permanent Damage

Oxidative stress with Decreased SAM/SAH Ratio

Decreased BH4

Increased dUMP

Increased Homocysteine

Impaired Methylation DNA Proteins Phospholipids

Impaired Neurotransmitter Metabolism

Permanent DNA Damage

Endothelial Dysfunction Excitotoxicity Oxidative Stress

CNS Disorders
ie, Depression, Dementia, Seizures, Developmental Delay, Neoropathy, Myelopathy


L-methyfolate—Is Critical in Monoamine Synthesis

Inflammation Oxidative Stress

Seipiapterin Reductase

5-Methylfolate
MTHFR is secondary

BH4

Inactive BH4 and takes it out of the cycle

XPH2

PAH
phe → tyr

TH

tyr → L-DOPA

TPH

tryp → 5-HTP

NOS

arg → NO

BH2

Epinephrine
Norepinephrine
Dopamine
Serotonin
Melatonin
NMDA Fx

Adult Onset Cerebral Folate Deficiency Has Now Been Reported

Reported from University of Texas Medical School in Houston

A 58-year-old woman with progressive memory loss and myoclonus presented for medical attention

| Initial Labs: Cerebrospinal fluid (CSF) analysis showed low levels of |
|------------------|---------------------------------------------------------------|
| • BH4 (8 nmol/L; ref 10-30 nmol/L) |
| • L-methyfolate (29 nmol/L; ref. 40-120 nmol/L). |
| • The patient’s serum folate level was normal (20.4 ng/mL; nl ref, 5.4 ng/mL or above) |

| Serum contained |
|-----------------|---------------------------------------------------------------|
| • Folate receptor 1–blocking antibody titer of 0.41 pmol/mL (ref <0.2 ML/mL) |
| • Folate receptor 1–binding antibody titer of 0.81 ML IgG/mL (ref <0.5 ML IgG/mL) |

6 month treatment with non-folic acid form of folate for 6 months. Full reversal of symptoms and normalized CSF L-methyfolate

How common is Memory Loss?

By age 80 between 50-80 % will have some memory loss. Genetic problems like MTHFR make it worse.
• 2/3 of patients with vascular dementia have a compromised ability to get L-methylfolate into the brain\(^1\)
• Patients with the MTHFR C677T polymorphism and elevated homocysteine are \(6\times\) more likely to develop progressive memory loss\(^2\)

Why does my memory get worse????

1. Elevated Homocysteine levels
2. Low levels of Vitamin B12 levels
3. Low Glutathione
4. Low Methylfolate
5. Low Acetylcholine
   (these are all related to the MTHFR gene defect)
Memory Loss
Current Treatment Option

- Cerefolin NAC is a combination of
  - 5-L-Methylfolate 6 mg
  - Methylcobalamin 2 mg
  - N-Acetyl- Cysteine 600 mg
Folate and B12 Status in Relation to Cognitive Impairment

- High folate and normal B-12 are associated with a 50% decrease in risk of cognitive impairment compared to those with normal folate levels.

- Normal folate and normal B-12 are not enough to decrease the risk of cognitive impairment.

The 2007 Morris Study showed normal B-12 along with high levels of folate was associated with a 50% decrease in risk of cognitive impairment.

CEREFOLIN®NAC is an orally administered prescription medical food for the dietary management of certain metabolic processes identified with early memory loss.
Elderly patients can reduce risk of cognitive impairment and improve cognitive function by maintaining adequate **B-12** levels and optimizing **L-methylfolate** levels.

33% of elderly NHANES 2001-2002 participants had detectable circulating unmetabolized folic acid.

- Patients consuming folic acid, as low as 84 mcg/d, with low B-12 showed a significant decline in cognitive scores (p=0.026)

- Patients with high serum L-methylfolate with normal B-12 showed a significant increase in cognitive scores (p<0.001)

**NAHNES** National Health and Nutrition Examination survey
VITACOG Study

PET volume with Digital subtraction after 2Y

• 70 y/o with pre and Post PET volume
  Active group treated with Cerefolin NAC
• Randomized, Placebo controlled, n156
• As high as 53% neuro protection in the active treatment group compared to placebo
• Elevated Hcy strong prognostic marker for cognitive decline
  • brain atrophy

CEREFOLIN® NAC is an orally administered prescription medical food for the dietary management of certain metabolic processes identified with early memory loss.

- Evidence has shown that lowering homocysteine levels, resulted in a SLOW DOWN in the rate of BRAIN ATROPHY found in patients with MILD COGNITIVE IMPAIRMENT.

- As HIGH AS 53% difference in NEURO PROTECTION in the active treatment group compared to placebo group.
N-acetylcysteine (NAC) Prevents Oxidative Stress Associated with Homocysteine and Beta Amyloid

Homocysteine (Hcy) increases beta amyloid induced oxidative stress

- Oxidative stress can lead to neuronal cell death

- N-acetylcysteine provides potent antioxidant protection and prevents neuronal death

CEREFOLIN®NAC is an orally administered prescription medical food for the dietary management of certain metabolic processes identified with early memory loss.

How do I know if I Have memory loss?

1. Memory loss that disrupts daily life
2. Challenges in problem solving
3. Difficulty completing tasks
4. Confusion with time or place
5. Trouble with visual images
How do I know if I Have memory loss?

6. New problems with words
7. Misplacing things
8. Decreased or poor judgment
9. Social withdrawal
10. Mood changes

Alz.org
What do I do to help?

1. Good diet
2. Exercise
3. Keep brain active
4. Nutritional support especially with MTHFR Deficiency
Nutritionally
What can we do about our Memory?

Low Methylfolate

- Give Methylfolate rather than Folate
Clinical Progression of Mild Cognitive Impairment

Progression of Alzheimer’s Disease

Cerefolin NAC

Disease Progression

Cognitive Function

Presymptomatic Preclinical

Prevention

Prodromal

Early Intervention and Prevention

Clinical Dementia

Treatment
CerefolinNAC® Drug Interactions, Safety

1. Water soluble, rapidly excreted via the kidneys.

2. Only reported Drug interaction is with first generation anticonvulsants reducing their effectiveness (fosphenytoin, phenytoin, phenobarbital, primidone, valproic acid).

3. Side effects and/or discontinuation rates similar to placebo. May incur rare and transient headache or stomach disturbance.
Nutritional component
Methyfolate

- Methyfolate - containing medication
  - Deplin, for depression, Active forms of B9
  - Metanx, active forms of B6, B9, B12
  - Cerefolin, Memory, Methyfolate and NAC
  - NEEVO, Prenatal Vitamins
  - L-Methyfolate (over the counter doses)
Nutritional components
Methyl B12

- Methyl B12
  - Not absorbed well with regular oral tablets
  - Oral Dissolving tablets work well for most
    - 5000 mcg. Jarrow brand works well
  - Pharmacy compounded subcutaneous injections work very well but are more expensive
  - Light and Temperature control very important with injections - refrigerate
  - Oral drops now available for children with symptoms or to help prevent problems in susceptible children.
Nutritional component
NAC

N Acetyl Cysteine
- 600 mg to 2400mg per day
- This helps make glutathione, which clears heavy metals, helps with memory, additions, behavior, depression, bi-polar depression

Dean, O. et al, N-Acetylccysteine in psychiatry
Memory Protection
Conclusion

- Methylfolate, MethylB12 and NAC prevent memory loss
- Decrease brain atrophy
- Improve metabolic markers associated with memory loss
- Minimal side effects
“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)
LOST
CONFUSED
UNSURE
UNCLEAR
PERPLEXED
DISORIENTED
BEWILDERED
QUESTIONS?