MTHFR
and Autism

Help from the
Human Genome project.

Neil Rawlins, MD
What is Autism, Autism Spectrum disorder, Asperger's, etc?
Autism

- Not a single disease
- No definitive test available
- Many treatments
- Some treatments work for one person but not for others
- Nutritional supplementation have worked well for many with Autism
AUTISM and current models for disease

- Two hit model, Genetic Predisposition and environmental toxins
  - American Journal of Biochemistry and Biotechnology, 2008
- Many Gene defects have been associated with Autism including MTHFR
- Many of these gene defects function in the Detox pathway
The Redox/Methylation Hypothesis of Autism
Some Genes associated with Autism

- MTHFR
- Transcobalamin II
- COMT
- GST-M1
- PON1
- GLOX
- GSH

- SLC40A1
- MTF1
- ALAD
- CPOX
- SNN
- GSSG
- GST
Autism Associated Toxins

- Bis-Phenol A
- Mercury
- Lead
- Highway exhaust
- Pesticides PCB’s
- Arsenic/Cadmium
- Fluoride
- Dry Cleaning PERC
- Flame Retardants
- Paint thinner
- Radiation
- Soy Formula
- Mold
- Etc....
Nutritional Things to Avoid

- Food dyes
- Artificial colors
- High Fructose Corn Syrup
- Artificial Flavorings
- Artificial Preservatives
- Artificial Sweeteners
Treatments for Autism Spectrum Disorders

Not covered in talk
- Healthy Diet
- Food sensitivities
- GFCF Diet
- Gut Treatments
- Thyroid
- Immune regulation
- Hyperbaric Oxygen

Covered in talk
- Vitamin/Mineral
- High dose B6/Mg
- Essential Fatty acid
- Amino Acids
- Chelation
- Methylation
- Sulfation
- Microbiome
Onset Cerebral MethylFolate Deficiency (CFD) Is Devastating (But Potentially Entirely Reversible)

Prenatal conditions
- Neural tube defect
- Malformations?

Parental FR antibodies and risk of infantile autism

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?

Dystonia

Spastic-ataxic syndrome

> 50 yea

Dementia and myoclonus

Chronic illness

1 year

2 years

11-25 years

> 50 years

Birth

L-methyfolate—Is Critical in Monoamine Synthesis

- BH4
- BH2
- Sepiapterin Reductase
- 5-Methylfolate
  - MTHFR is secondary pathway
- Inflammation
- Oxidative Stress
- XPH2
  - Inactive BH4 and takes it out of the cycle

- phe → tyr → TH → L-DOPA → TPH → tryp → 5-HTP → NOS → arg → NO
- PAH

Chemicals:
- Epinephrine
- Norepinephrine
- Dopamine
- Serotonin
- Melatonin
- NMDA Fx

MTHFR and Autism Link

Folate Study

- Women not taking prenatal vitamins immediately before and during a pregnancy were **2X** as likely to have a child with autism,

- If the women didn’t take folate and also had MTHFR deficiency, they were **7X** as likely to have a child with Autism

- Epidemiology: July 2011 - Volume 22 - Issue 4 - pp 476-485
Autism and MTHFR subtypes

Example of how multiple defects makes things worse

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Autism Rate</th>
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<tbody>
<tr>
<td>677CT</td>
<td>50% increase</td>
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<tr>
<td>677TT</td>
<td>300% increase</td>
</tr>
<tr>
<td>1298CC</td>
<td>Increased</td>
</tr>
<tr>
<td>677CT/1298AC</td>
<td>811%</td>
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Studies on Psychiatric Disorders, Oxidative Stress in Applied Basic Research and Clinical Practice
(Genetic Polymorphism Related to Oxidative Stress in Autism, Hee Jeong You)
Autism and environment

- Living within 1000’ of freeway had a 4 times higher incidence of Autism compared to those living further away

  - Environ Health Perspect. Mar 2013;121(3) 380-386
  - JAMA Psychiatry 2013;70(1):71-77
Methylfolate and Environment

- Heavy metals build up without MTHF
- Medications such as Glucophage, Birth control pills decrease MTHF utilization
- Other gene defects compound the problem
- BPA, Heavy Metals and other organic toxins build up because of lack of Glutathione
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
- Autism, ASD, Etc.....
Conditions that treating methylation has helped

- Fibromyalgia
- Chronic Fatigue
- Irritable Bowel
- Migraines
- Bipolar, Schizophrenia
- Autism, Autism spectrum disorders
- Prevention of Birth Defects
Where do we go from Here?
General Recommendations

1. Decrease exposure to toxins
   - Water filters, locally grown foods

2. Improve the body’s Metabolism
   - Improve diet, supplements

3. Clear heavy metals if symptomatic
   - Urine challenge test
   - Check Multiple Heavy Metals
President’s Cancer Panel Recommendations 2009

- Remove shoes when entering home
- Filter water, Stainless steel, Glass, BPA free
- Avoid Drinking 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 environmenta cancerl risk, What we can do now
- www.ourstolenfuture.org/basics/chemlist.htm
Non supplement Measures that improve symptoms

- Dietary: More vegetables, berries, fruits
  - Better if grown locally, organic
- Mathematics, Accounting
  - Engineers, creative people
- Piano, Classical music
- Exercise
- Band (not rock band) participation (structured music)
General guidelines

- Only add one supplement at a time
- Drink/Cook with filtered Water
- If mod/severe symptoms consider Heavy Metal testing (Urine is more accurate)
- Supplements will be discussed in order of importance.
- For doses use autism.com
Autism Treatment Reference

- Review of treatments
- Summary of Dietary, Nutritional and Medical treatments
- Survey of treatment effectiveness by parents/caregivers
- Best reference for pediatric doses
Methylfolate Options
(Older form was Folinic acid)

- Metafolin from Merck (Best Studied)
  - Deplin, 7.5 or 15 mg
  - Solgar Metafolin 400mcg, 800 mcg
- Extrafolate, Extrafolate-S, Quatrefololate
  - Thorne, Methyl-life, etc

Data is for Folic Acid

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<th>Better</th>
<th>Better/worse</th>
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<tr>
<td>5%</td>
<td>50%</td>
<td>44%</td>
<td>10:1</td>
<td>2505</td>
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Methyl B 12 (Methylcobalamin)

- Oral Dissolving tablets
  - Jarrow Brand has best results
- Oral drops available (Malley’s Pharmacy)
- Compounded Shots are the best studied but harder to do
  - Local Pharmacies are Malley’s and Moses Lake. National Pharmacy Hopewell.

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<tr>
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<td>22%</td>
<td>72%</td>
<td>12:1</td>
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Pyridoxyl 5 Phosphate
Vit B6 (P5P)

- Best studied of any nutritional supplement.
- Used in conjunction with Magnesium
- Only B vitamin that has been associated with toxicity in a small percentage.
- Stop for numbness/significant headache

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<tr>
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<td>37%/46%</td>
<td>51%/49%</td>
<td>4:1/11:1</td>
<td>213/7256</td>
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First numbers are for P5P alone. Second are for P5P and Magnesium.
N-Acetyl Cysteine

- Shows improvement in behavior in randomize trial
- Critical component in Glutathione production
- Use to treat obsessions, skin picking, bipolar, schizophrenia and addictions


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Newer supplement, Added to help glutathione
**Tetrahydrobiopterin**

Intermediary for neurotransmitters

- **BH4 (Tetrahydrobiopterin)**
  - Used for ADD/ADHD
  - Difficult to treat Depression
  - Improves behavior problems
  - Compounded version at Malley’s Pharmacy
    - Two compounded doses 0.5mg, 0.025mg
  - Homeopathic version was available at Nutrimedical

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L-methyfolate/ BH4—Is Critical in Neuroutransmitter Synthesis

Sulfation

- **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.
- Molybdenum 50mcg improved results

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<td>6%</td>
<td>65%</td>
<td>29%</td>
<td>4.6:1</td>
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Vitamin C

- **Vitamin C** 1,000 mg, 1-3 times a day
  - Regenerates Glutathione
  - Helps regulate bowel movements
  - Powerful antioxidant

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<td>52%</td>
<td>46%</td>
<td>20:1</td>
<td>3077</td>
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TMG or DMG

- Critical in Protein building
- TMG can sometimes interfere with B12 absorption
- Important in step to clear homocysteine

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<td>43%</td>
<td>43%</td>
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<tr>
<td>DMG</td>
<td>8%</td>
<td>50%</td>
<td>42%</td>
<td>5.3:1</td>
<td>6363</td>
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Essential Fatty Acids

- **Omega 3 (Flax seed or Fish oil that has mercury removed)** 1-2 tablets per day. Helpful with Brain/Nerve Healing (Chia or Flax seeds)
  - Some of the fish oil tablets don’t have the mercury removed.
  - Important in brain development

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<td>39%</td>
<td>59%</td>
<td>31:1</td>
<td>1680</td>
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Glutathione Sustained release will absorb

- Glutathione SR by Thorne. Twice a day
  - Can be given orally in sustained release
  - May precipitate increased symptoms if removes toxins
  - Usually start with pulse therapy. (3 days on and 4-11 days off)
  - Most glutathione is destroyed by the stomach. Glutathione SR by Thorne has good absorption

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Zinc 20-40 mg/day
- Especially important in eye sensitivity
- Critical to replace when chelating
- Seems to help with COMT genetic deficiency

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<td>44%</td>
<td>54%</td>
<td>24:1</td>
<td>2738</td>
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Vitamin D

- Essential for development
- Very Low levels are common in Autism
- Usually supplement at 1000-2000 IU D3

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## Mineral supplement

- Helps replace trace minerals
  - Molybdenum, Manganese, Selenium etc
- Essential to take after chelating.

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Microbiome treatment for Autism

- Gut Bacteria in children with autism is different than normal controls
- Treating with Probiotics has shown improvement in autistic symptoms
- Microbiota transplant is now being studied but is showing promise
Summary

- Supplements are a trial and error
- Most are water soluble (Low Risk)
- For Children's doses check Autism.com
- Need for removal of toxins depends on symptoms
- Future: tests for genetic and environmental factors are coming but limited benefit today
Questions?
Impaired Detox Metabolism

Genetic Risk Factors

Environmental Exposures

PON1, GSTM1

Impaired Detox Metabolism

Oxidative Stress

MTHFR, ASL

RFC, TCN2

↓ Methionine Synthase Activity

COMT, ATP10C, ADA

↓ D4 Receptor Phospholipid Methylation

MeCP2, ADA

↓ DNA Methylation

MET, NLGN3/4

FMR-1, RELN

↓ Neuronal Synchronization

MET, NLGN3/4

FMR-1, RELN

↓ Attention and cognition

Δ Gene Expression

Developmental Delay

AUTISM

Lead, Mercury, Arsenic