How to Assess and Manage Neuroinflammation to Optimize Cognitive Function

Andrea Gruszecki, ND
St Charles, IL
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Disclosure Statement

Dr. Gruszecki is a client consultant in the Scientific Support Department of Doctor’s Data, Inc.
Education Objectives

• Review the evaluation of biogenic amine & neurotransmitter metabolism and the effects of dysfunction in synthesis or metabolism

• Review how toxic exposure, inheritance, and nutrition may affect enzyme functions and neurotransmission

• Review strategies for nutritional support of neurotransmitter synthesis and metabolism, as outlined in scientific literature

• Review strategies to diminish oxidative stress and neuroinflammation
Neurotransmitter Function

**Excitatory**
- Restlessness, insomnia
- Increases the likelihood the neuron will fire
- Neurotransmitters:
  - Glutamate
  - Epinephrine
  - Norepinephrine
  - Dopamine
  - Acetylcholine

**Inhibitory**
- Calming, sleep
- Decreases the likelihood the neuron will fire
- Neurotransmitters:
  - GABA
  - Serotonin
  - Glycine
  - Dopamine
  - Acetylcholine

The effect of a neurotransmitter depends on the type of receptor it binds with.


#SHEICON2016
Neurotransmitter Inactivation

- Diffusion
- Re-uptake
  - Glial cells maintain low extracellular NT levels
- Enzymatic degradation
  - May metabolize both NTs and toxicants

The monoamine neurotransmitter disorders consist of a rapidly expanding heterogeneous group of neurological syndromes characterised by primary and secondary defects in the biosynthesis degradation, or transport of dopamine, norepinephrine, epinephrine, and serotonin. Disease onset can occur any time from infancy onwards. Clinical presentation depends on the pattern and severity of neurotransmitter abnormalities. Many neurotransmitter disorders mimic other neurological disorders; may be misdiagnosed. Early clinical suspicion and appropriate investigations, including analysis of neurotransmitters in CSF, are essential for accurate clinical diagnosis.

CSF, platelet and urine levels of neurotransmitters, such as serotonin, have been correlated in humans.

Audhya et al. Biochimica et Biophysica Acta 2012 Oct; 1820(10): 1496-1501
Clinical Utility of Urinary Biogenic Amines and Neurotransmitters

### Neuro-Biogenic Amines, Comprehensive; urine first morning void

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>RESULT/UNIT per g creatinine</th>
<th>REFERENCE INTERVAL</th>
<th>PERCENTILE</th>
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<tr>
<td>Dopamine, free</td>
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<td>Epinephrine, free</td>
<td>1.6 µg</td>
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<td>Tryptamine</td>
<td>0.17 µmol</td>
<td>0.2- 1.3</td>
<td></td>
</tr>
<tr>
<td>Glutamate</td>
<td>120 µmol</td>
<td>6- 52</td>
<td></td>
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<tr>
<td>Gamma-aminobutyrate (GABA)</td>
<td>2.9 µmol</td>
<td>1- 8</td>
<td></td>
</tr>
<tr>
<td>Tyrosine</td>
<td>148 µmol</td>
<td>28- 120</td>
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<td>2.6 µmol</td>
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<td>Phenethylamine (PEA)</td>
<td>61 nmol</td>
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<td>1573 nmol</td>
<td>220- 1300</td>
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<td>Glycine</td>
<td>5491 µmol</td>
<td>350- 3500</td>
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<td>34 µg</td>
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Where to start?

Toxicants, lifestyle, environment (epigenetics) + inheritance

Synthesis → synapse → Intraneuronal Metabolism → Extraneuronal/liver

Detoxification
Global antioxidant status
Exercise
Stress Management
Nutrition

Diet
Light
Sleep

Treat the cause

• All enzymes of neurotransmitter degradation have multiple metabolic functions
  • Evaluate and remove potential obstacles
    • Toxic elements and chemical exposures
    • Lipopolysaccharides
    • Poor diet or digestive disorders
    • Neuroinflammation (TBI)
    • Lifestyle
    • Stress
  • Obstacles may contribute to neuroinflammation
    • Associated with depression, autism symptoms, ADHD, neurodegenerative disease, psychiatric disorders
    • Often present with comorbid peripheral inflammation

Sarris et al. (2015) *The Lancet Psychiatry* vol. 2 (3) p. 271
Neurologic Toxicants

- Chemicals – ingested, inhaled or adsorbed
  - Pesticides, solvents, PCBs, PAHs
  - POPs may persist in environment for years
  - Alcohol, nicotine, bacterial lipopolysaccharides
  - Formaldehyde
    - Environment
    - Metabolic – disturbances in folate metabolism
- Metals
  - Toxic & excess of some nutrient elements
    - Al, As, Ba, Br, Cd, Cs, Cr, Cu, F, Ge, Hg, Li, Mn, Tl, Se, Sn, U, Zn

Mechanisms of Neurotoxicity

- Induce epigenetic changes
- Alter enzyme functions
  - Neurotransmitter metabolism; GSH synthesis; methylation; mitochondrial functions
- Exhaust anti-oxidant reserves
  - ↓GSH, ↑ 8-OHdG indicate ↑ oxidative stress
- Overwhelm detoxification pathways
  - GSH, methylation (↓ SAMe availability)
  - Phase I/Phase II mismatch
- Mom chemical sensitivity ↑ risk of ASD/ADHD

Evaluation

• History and evolution of symptoms, exposures

• Physical exam
  • Electrolytes, glucose, cortisol, liver & renal function evaluated to distinguish metabolic encephalopathy
  • EEG, neuro-imaging studies to rule out other disease

• Neurologic exam
  • sensation, gait, strength, coordination

• Behavioral exam for cognitive function
  • Learning and attention; short-term memory; problem-solving

• Urinary neurotransmitters (neuro-biogenic amines)

Functional Medicine in Psychiatry

- Current pharmacology has achieved only modest benefits addressing the burden of mental health worldwide.

- Conflicting evidence from studies of many different individual nutritional supports and therapies:
  - NAC, B vitamins; vitamins C,D,E and ß-carotene; green tea; Fe chelation; anti-inflammatory diets, etc.

- But few studies of complete protocols…..


Slide elements courtesy of Dr David Quig
“Reversal of cognitive decline: A novel therapeutic program”

• “MEND” – metabolic enhancement for neurodegeneration and neuro-inflammation
  • Small pilot study of 10 early cog. decline patients
  • Slowed or stopped decline in 8/10 by addressing underlying causes
  • Balances neurological plasticity signaling
  • Remediate neuroinflammation and oxidative stress

• Provides a useful template for treatment, after lab assessments have been completed…

Metabolomics

Risk Factors for Metabolic Syndrome
- Increased waist size
- High triglycerides or need for cholesterol medication
- Low HDL cholesterol or need for cholesterol medication
- Hypertension or need for hypertension medication
- Fasting Glucose > 100 mg/dL

- resveratrol and zinc (RBC elements)
- Fast 12 hours each night, start 3 hours hs
  - ↓ insulin levels and amyloid-β formation
- Exercise 30-60 minutes 4-6 days weekly

Chung et al. Neurology 10.1212/WNL.0000000000001820 American Association for Clinical Chemistry.
Exercise

• Positive association between aerobic fitness and brain volume density

• ↑ physical activity associated with
  • ↓ risk of cognitive decline and dementia
  • ↓ risk of late-life depression

• Exercise ↑ neurotrophic factors, ↓ inflammatory cytokines, activated microglia in neurodegenerative animal models

• Exercise ↑ plasma serotonin and epinephrine in ADHD boys

• Early life exercise may ↑ beneficial bacteria in gut and promote long-term brain and metabolic health (animal study)

• 40% improvement in depression with both exercise/meditation


Alderman et al. *Translational Psychiatry* (2016) 6, e726; doi:10.1038/tp.2015.225
Lee et al. *J. Phys. Ther. Sci.* 2015 Sep; 27(9): 2915-9; doi: 10.1589/jpts.27.2915

Mika. *Immunol. Cell Bio.* 9 Dec 2015; doi: 10.1038/icb.2015.113
Promote gastrointestinal health

• Stool Analysis

<table>
<thead>
<tr>
<th>Expected/Beneficial flora</th>
<th>Commensal (Imbalanced) flora</th>
<th>Dysbiotic flora</th>
</tr>
</thead>
<tbody>
<tr>
<td>4+ Bacteroides fragilis group</td>
<td>4+ Alpha hemolytic strep</td>
<td></td>
</tr>
<tr>
<td>4+ Bifidobacterium spp.</td>
<td>1+ Enterobacter cloaceae</td>
<td></td>
</tr>
<tr>
<td>4+ Escherichia coli</td>
<td>4+ Mucoid Escherichia coli</td>
<td></td>
</tr>
<tr>
<td>NG Lactobacillus spp.</td>
<td>1+ Proteus mirabilis</td>
<td></td>
</tr>
<tr>
<td>NG Enterococcus spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1+ Clostridium spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NG = No Growth</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Intestinal Permeability testing

• Improved gut barrier functions minimize levels of LPS in circulation and CNS

Kellow et al. The American Journal of Gastroenterology 105, 739 (April 2010)
doi:10.1038/ajg.2010.61
**Neuroactive molecules**

- **Microbiome may synthesize and release**
  - Tryptophan, Tyrosine, Glycine
  - *Escherichia* and *Streptococcus* (probiotic spp.)
  - Norepinephrine and serotonin
  - *Bifidobacteria* and *Lactobacilli* spp.
  - GABA and acetylcholine

- **“Cross-talk”**
  - Modulates balance of pro- and anti-inflammatory molecules
  - Histamine, TLR & TGR5 agonists, cytokines
  - Sensory and extrinsic nerve activation
  - Signals to and from CNS via vagus nerve (90% of neurons from gut to brain)
  - Oral GABA mechanism of action?

*Animal and in vitro studies


GI and Neurology

- Bacterial lipopolysaccharide (LPS)
  - Gram neg. bacteria; activates immune system
  - TLR4 – activates NF-κB and pro-inflammatory cytokines

- Sickness Behavior
  - CNS recognizes cytokines and LPS as sickness signals
  - Lipopolysaccharides/peptidoglycans

Symptoms: confusion, fatigue, muscle/joint aches, psychomotor retardation, impaired memory, decreased motivation, anxiety and depression
Restoration of microbiome

• Plant- based Diet
  • Microbiota from high-fat diet induce behavioral changes and neuroinflammation (animals); “fast food” diets associated with ↑ gut permeability and depressive symptoms and ↑ LPS translocation
  • “Rural” high fiber and ↑ plant polyphenols may improve Firmicutes:Bacteroidetes ratio and microbe diversity

• Correct Digestion
  • Repair barrier and support digestion
  • “Rest and digest” promote parasympathetic/vagal tone

• Probiotics
  • ≥10^{10} CFU per day Transient colonizers – cannot “repopulate gut”
  • May normalize cross-talk with immune cells and CNS


Diet

- Diet – brain’s structure and function (intra- and intercellular communication) requires amino acids, fats, vitamins and minerals and trace elements

- high intake of vegetables, fruits, potatoes, soy products, mushrooms, seaweed and fish have recently been associated with a decreased risk of suicide

- ↑ fruit/vegetables, fish may decrease risk of depression

- Mediterranean diet may result in better cognitive outcomes; ↓ risk of dementia

- Brassica vegetables ↑ GST expression and phase II detox

- Ketogenic diet reversed effects of NMDA receptor hypofunction (schizophrenia model) in animals; used for drug-resistant epilepsy

Remove toxicants

### Evaluate Net Retention (bioaccumulation)

#### Unprovoke (Exposure)

<table>
<thead>
<tr>
<th></th>
<th>Unprovoke</th>
<th>Post DMSA</th>
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<tbody>
<tr>
<td>Lead</td>
<td>0.4</td>
<td>79</td>
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<tr>
<td>Mercury</td>
<td>2.3</td>
<td>29</td>
</tr>
</tbody>
</table>

**Compare Pre and Post RESULTS to estimate net retention**


Slide elements courtesy of Dr David Quig
### Hepatic Detoxification

**Evaluate Exposure and Phase II Status**

#### Phase I Exposure Marker

<table>
<thead>
<tr>
<th>ANALYTE</th>
<th>RESULT nmole/mg crea</th>
<th>REFERENCE RANGE</th>
<th>2.5th</th>
<th>16th</th>
<th>50th</th>
<th>84th</th>
<th>97.5th</th>
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<tbody>
<tr>
<td>D-Glucaric Acid</td>
<td>287</td>
<td>32 - 322</td>
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</table>

#### Phase II Detoxification Marker

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<th>ANALYTE</th>
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<tr>
<td>Mercapturic Acids</td>
<td>43</td>
<td>36 - 90</td>
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Slide Elements courtesy of Dr David Quig
Detoxification

• Phase I: cytochrome P450, oxidase, reductase and dehydrogenase enzymes
  • Heme-dependent enzymes
  • Bacterial LPS in CNS downregulates phase I
  • Support with Se, Zn; vitamins A, D, E, K, C, sulforaphane

• Phase II: glucuronidation, sulfation, methylation, N-acetylation, GSH, amino acid conjugation
  • Support with reduced GSH, NAC, B vitamins and calcium-D-glucarate; normalize SAMe synthesis

• Phase III efflux pumps
  • Excretes from cells into bile or circulation for excretion from the body
  • Needs B vitamins, Mg, Mn, Fe, CoQ10

Methylation Capacity

- Maintain serum B12 > 500
- Normalize homocysteine levels

Function of enzymes may be affected by:

- Nutrition
- Antioxidant status
- Toxic exposures

SNPs (inheritance) not the only factor

SNPs are not “on/off” switches; patients require functional assessments of genetic potential


Smulders et al. J Inherit Metab Dis. 2011 Feb; 34(1): 75
Functional assessment of the transmethylation pathway

<table>
<thead>
<tr>
<th>Methylation Profile: plasma</th>
<th>( \text{Oxidative Stress} )</th>
<th>( \text{âCNS myelin, GSH} )</th>
<th>( \text{â DNA methylation?} )</th>
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<tbody>
<tr>
<td>Methionine</td>
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<tr>
<td>Cysteine</td>
<td>[ ]</td>
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<tr>
<td>S-adenosylmethionine (SAM)</td>
<td>[ ]</td>
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<tr>
<td>S-adenosylhomocysteine (SAH)</td>
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Decrease Inflammation and ROS

- Normalize inflammatory and oxidative stress biomarkers
- 8-OHdG indicates DNA damage from ROS
- GSH – cellular antioxidant
  - Evaluate glutathione status within erythrocytes
- Optimize antioxidant status with nutrients such as mixed tocopherols and tocotrienols, curcumin, selenium, α-lipoic acid, vitamin C, Ω3 fatty acids
- Erythrocyte fatty acids
- Evaluate intra-cellular minerals (Mg, Se, Zn) within erythrocytes

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Hon et al. Inflammation. 2011 Dec; 34(6):681-687
Support Mitochondria

- Optimize mitochondrial function with nutrients such as CoQ10, α-lipoic acid, acetyl-L-carnitine, selenium, zinc, resveratrol, vitamin C, thiamine (B1)
  

- “Low Brain Intracellular Free Magnesium in Mitochondrial Cytopathies”

- Cystosol free Mg (i.e. energy) was found abnormally low in all patients with defective mitochondrial respiration

- Evaluate intra-cellular minerals (Mg, Se, Zn) within erythrocytes

Hormone Regulation

- Optimize sleep and rule out sleep apnea to reduce cortisol releasing factor and cortisol
- Sleep apnea may also disrupt neurotransmitter levels
- Normalize and optimize thyroid and other hormone levels
- Normalize vitamin D levels
  - Low D associated with Parkinson’s disease
  - Vitamin D serum or bloodspot

Cognitive Function

**Neuro-Biogenic Amines, Comprehensive; urine first morning void**

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<td>Norepinephrine, free</td>
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<td>350-3500</td>
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Stress and neurotransmission

MEDITATION

Because some questions can't be answered by Google!
Night and Day

- Circadian rhythms regulate the homeostasis of ROS species
- Sleep disruption is an early symptom of neurodegenerative disease
- Circadian disruption with high sugar, high fat diet disrupts gut microbiome (animal model)
- Sleep-disordered breathing
- Children with OSA ↑ urinary GABA, norepi and epi, ↓ taurine
- Altered GABA and taurine predicted cognitive dysfunction
- Evening screen media consumption (light at night/LAN)
  - **Suppress melatonin levels** and compromise sleep
- Associated with a prioritization of unhealthy foods choices
- LAN increases inflammatory response to high-fat foods (animal model)
10 yo male

- Diagnosis of ADHD
- Tried stimulant, worsened symptoms
- Parents seek alternative
- Standard diet
- No supplements
10 yo male ADHD

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<td></td>
</tr>
<tr>
<td>Normetanephrine</td>
<td>107 µg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epinephrine, free</td>
<td>1.6 µg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metanephrine</td>
<td>117 µg</td>
<td>50 - 270</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serotonin</td>
<td>141 µg</td>
<td>70 - 350</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-Hydroxyindolacetic acid (5-HIAA)</td>
<td>2999 µg</td>
<td>1250 - 11000</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tryptamine</td>
<td>2.1 mmol</td>
<td>0.6 - 1.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glutamate</td>
<td>47 µmol</td>
<td>10 - 80</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gamma-aminobutyrate (GABA)</td>
<td>3.6 µmol</td>
<td>1 - 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tyrosine</td>
<td>TAT/liver ?</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tyramine</td>
<td>222 µmol</td>
<td>60 - 225</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenethylamine (PEA)</td>
<td>34</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taurine</td>
<td>303 µmol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycine</td>
<td>1180 µmol</td>
<td>560 - 3400</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histamine</td>
<td>55 µg</td>
<td>8 - 80</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>133 mg/dL</td>
<td>25 - 180</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Notes:**
- MAO-B/A
- Cu & C SAMe
- AADC vs. diet, dysbiosis
- TAT/liver ?
- Diet vs digestion
10 yo male

Phenylalanine → Tyrosine → L-DOPA → Dopamine → MAO-A → Normetanephrine
Phenylethylamine → Tyramine → MAO-B → MAO-A
Phenylethylamine → MAO-B
Tryptamine
Tryptophan → TPH2 (brain) → 5-HTP → AADC → Serotonin → MAO-A → 5-HIAA
Glutamine → Glutamate → Succinate semi-aldehyde

Precursors | Neurotransmitters | Intermediary Metabolites | Final Excretion Products
---|---|---|---

#SHEICON2016
10 yo male ADHD

**Comprehensive Stool Analysis / Parasitology x1**

<table>
<thead>
<tr>
<th>BACTERIOLOGY CULTURE</th>
<th>Expected/Beneficial flora</th>
<th>Commensal (Imbalanced) flora</th>
<th>Dysbiotic flora</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>4+ Bacteroides fragilis group</em></td>
<td><em>2+ Gamma hemolytic strep</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>2+ Bifidobacterium spp.</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>4+ Escherichia coli</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>2+ Lactobacillus spp.</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>3+ Enterococcus spp.</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>1+ Clostridium spp.</em></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NG = No Growth</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**BACTERIA INFORMATION**

Expected /Beneficial bacteria make up a significant portion of the total microflora in a healthy & balanced GI tract. These beneficial bacteria have many health-protecting effects in the GI tract including manufacturing vitamins, fermenting fibers, digesting proteins and carbohydrates, and propagating anti-tumor and anti-inflammatory factors. Clostridia are prevalent flora in a healthy intestine. Clostridium spp. should be considered in the context of balance with other expected/beneficial flora. Absence of clostridia or over abundance relative to other expected/beneficial flora indicates bacterial imbalance. If *C. difficile* associated disease is suspected, a Comprehensive Clostridium culture or toxigenic *C. difficile* DNA test is recommended. Commensal (Imbalanced) bacteria are usually neither pathogenic nor beneficial to the host GI tract. Imbalances can occur when there are insufficient levels of beneficial bacteria and increased levels of commensal bacteria. Certain commensal bacteria are reported as dysbiotic at higher levels. Dysbiotic bacteria consist of known pathogenic bacteria and those that have the potential to cause disease in the GI tract. They can be present due to a number of factors including: consumption of contaminated water or food, exposure to chemicals that are toxic to beneficial bacteria; the use of antibiotics, oral contraceptives or other medications; poor fiber intake and high stress levels.

**YEAST CULTURE**

<table>
<thead>
<tr>
<th>Normal flora</th>
<th>Dysbiotic flora</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>2+ Candida albicans</em></td>
</tr>
</tbody>
</table>

May promote antigen sensitization*  

---

*Animal studies

---

Gut 2007 Nov; 56(11): 1522-1528

#SHEICON2016
10 yo male - GI

- Correct digestion and restore microbiome
- Treat 2+ Candida per sensitivities; probiotics
- Change behavior
  - Quiet distraction-free meals
  - Thorough chewing to promote parasympathetic tone

- Diet
  - Evaluate status of precursor amino acids
  - plasma amino acids
  - Subgroups of ADHD may respond to oligoantigenic or elimination of artificial food colors and salicylates
  - Increase fruits and vegetables in diet
  - Eliminate dietary sources of trace amines

10 yo male - diet

• Avoid histamine and trace amines in diet
  • Cured meats (sausage, bacon), game
  • Fresh pork
  • Canned fish and processed fish products
  • Hard cheeses, mold cheeses, Brie
  • Oranges, bananas, tangerines, pineapple, grapes, strawberries
  • Nightshades, pickled cabbage, spinach, broad beans, peanuts, tree nuts
  • Ferments - soy sauce, miso
  • Green tea, champagne, coffee, chocolate, wine beer, fresh fruit juices or smoothies (above fruits)

• Support sulfite processing
  • Evaluate molybdenum status (RBC elements)

10 yo male unprovoked urine

### Toxic Metals; Urine

<table>
<thead>
<tr>
<th>TOXIC METALS</th>
<th>RESULT µg/g creat</th>
<th>REFERENCE INTERVAL</th>
<th>WITHIN REFERENCE</th>
<th>OUTSIDE REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum (Al)</td>
<td>8.6</td>
<td>&lt; 60</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Antimony (Sb)</td>
<td>0.08</td>
<td>&lt; 0.3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Arsenic (As)</td>
<td>420</td>
<td>&lt; 120</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Barium (Ba)</td>
<td>&lt; 7</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bismuth (Bi)</td>
<td>&lt; 1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cadmium (Cd)</td>
<td>&lt; 2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Copper (Cu)</td>
<td>&lt; 0.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Cobalt (Co)</td>
<td>&lt; 12</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Chromium (Cr)</td>
<td>&lt; 0.4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Lead (Pb)</td>
<td>0.4</td>
<td>&lt; 3</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Mercury (Hg)</td>
<td>0.7</td>
<td>&lt; 4.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nickel (Ni)</td>
<td>4.8</td>
<td>&lt; 14</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Palladium (Pd)</td>
<td>&lt; dl</td>
<td>&lt; 0.15</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Platinum (Pt)</td>
<td>&lt; dl</td>
<td>&lt; 0.1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tellurium (Te)</td>
<td>&lt; dl</td>
<td>&lt; 0.5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thallium (Tl)</td>
<td>0.2</td>
<td>&lt; 0.8</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thorium (Th)</td>
<td>&lt; dl</td>
<td>&lt; 0.05</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tin (Sn)</td>
<td>0.6</td>
<td>&lt; 9</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tungsten (W)</td>
<td>0.08</td>
<td>&lt; 0.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Uranium (U)</td>
<td>&lt; dl</td>
<td>&lt; 0.04</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Urine Creatinine

<table>
<thead>
<tr>
<th>RESULT mg/dL</th>
<th>REFERENCE INTERVAL</th>
<th>-2SD -1SD MEAN +1SD +2SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>135</td>
<td>25 - 180</td>
</tr>
</tbody>
</table>

Sources: Water, rice, chicken, high fructose corn syrup, apples, grapes, etc.

Loss of cognitive function, learning, memory, ↑ ADHD. Se antagonist.
Arsenic Detoxification

- Arsenic exposure may alter cognition, learning, memory; modest assoc. with ADHD
  - Poor nutritional status may ↑ effects
- iAs\textsuperscript{III} must be methylated 2x to detoxify and excrete
  - Requires SAMe as methyl donor
  - Increases nutritional demand for folates; shown to decrease blood As by 13.6%
    - Unmetabolized folic acid blocks folate receptors
    - ↑ Dietary or supplemental folinic acid to compensate
  - Ensure that SAMe can be metabolized and methionine recycled
  - Evaluate plasma methylation biomarkers
    - Genetic studies evaluate potential, not physiologic function
    - PNMT (epinephrine), HNMT and COMT SAMe dependent

Obeid et al. 2011 May;60(5):673-80. doi: 10.1016/j.metabol.2010.06.020
Functional Assessment of the transmethylation pathway

**Methylation Profile; plasma**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>PERCENTILE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methionine</td>
<td>2.5&lt;sup&gt;th&lt;/sup&gt; 16&lt;sup&gt;th&lt;/sup&gt; 50&lt;sup&gt;th&lt;/sup&gt; 84&lt;sup&gt;th&lt;/sup&gt; 97.5&lt;sup&gt;th&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cysteine</td>
<td></td>
</tr>
<tr>
<td>S-adenosylmethionine (SAM)</td>
<td></td>
</tr>
<tr>
<td>S-adenosylhomocysteine (SAH)</td>
<td></td>
</tr>
<tr>
<td>Homocysteine</td>
<td></td>
</tr>
<tr>
<td>Cystathionine</td>
<td>68&lt;sup&gt;th&lt;/sup&gt; 95&lt;sup&gt;th&lt;/sup&gt;</td>
</tr>
<tr>
<td>SAM : SAH</td>
<td></td>
</tr>
</tbody>
</table>

CNS myelin, GSH â€“ DNA methylation?

MAT SNPs? CTH SNPs?

---

10 yo male Support and detoxify

- Mineral status (red blood cell elements)
  - Cu, Mg, Se, Zn
- Vitamin C (Dish, histamine)
- Evaluate hepatic functions
  - Support Phase I, II, III functions as indicated
  - Remove environmental amine exposures
    - Dietary amines, environmental amines (dyes, pigments, plastics, insecticides)
    - Monitor for sensitivity to smog, cigarette smoke, motor vehicle exhaust, formaldehyde; production of resins, polyurethane, polyester plastics; food additives (↓ ALDH; ↑ Zn, B3, Vit. A)

Apte et al. Molecular Pathology of Liver Diseases
Fowler et al. (1996) PNAS vol. 93 (24) p. 14065-14069
Molecular Pathology Library Volume 5, 2011, pp 147-163
10 yo male

• Solar intensity affects geographical variance of ADHD by 34-57% (protective)

• ↑ Vit. D directly affects T cell antigen receptor signaling, mucosal immunity, inflammation

• Essential cofactor for serotonin synthesis in brain

• Adult ADHD assoc. with altered circadian rhythm

• Exercise

• ↑ plasma serotonin and epinephrine in ADHD boys

• Improves behavior, neurocognition, scholastic performance in ADHD

Eur Child Adolesc Psychiatry. 2014 Jul;23(7):
Lee et al. J. Phys. Ther. Sci. 2015 Sep; 27(9):
2915-2919.
Education Objectives

• Review the evaluation of biogenic amine & neurotransmitter metabolism and the effects of dysfunction in synthesis or metabolism

• Review how toxic exposure, inheritance, and nutrition may affect enzyme functions and neurotransmission

• Review strategies for nutritional support of neurotransmitter synthesis and metabolism, as outlined in scientific literature

• Review strategies to diminish oxidative stress and neuroinflammation
Questions?