Biomedical Approach: What’s Next, Other Options

Autism One Conference
Down Syndrome Track
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Naperville, Illinois

Disclaimer

• Information is for educational purposes only
• Not to be taken as specific medical advice
• All medical decisions regarding your child’s health issues should be discussed with your health care provider
• Medical Director of True Health Medical Center

More than Genetics: Trisomy 21

Goal is raising healthy children regardless of diagnosis.

We Are All Toxic!!

• Each year chemical companies in the US manufacture over 6.5 trillion pounds of 9,000 different chemicals and release 7.1 billion pounds of over 650 chemical pollutants into the atmosphere and water.
• In addition, heavy metals are released from manufacturing and coal combustion, including 45 tons of mercury/year.
• EWG studied 9 healthy individuals with no exposure. 167 chemicals, 76 carcinogens, 94 chemicals with known toxicity to brain and nervous system were found.
• EWG studied 10 newborns. The cord blood contained 200 chemical pollutants including PCBs, dioxins, flame retardants, BPA, pesticides, and mercury.
• NHANES studied 2,560 individuals. They found widespread phthalate metabolites from plastics in 75% of participants.
• CDC studied 480 adults, 55% had bisphenol A (BPA) – a chemical from plastics.

Toxins and Children

“It is vitally important to recognize that children are far more susceptible to damage from environmental carcinogens and endocrine-disrupting compounds than adults.”

“Ideally, both mothers and fathers should avoid exposure to endocrine-disrupting chemicals and known or suspected carcinogens prior to a child’s conception and throughout pregnancy and early life, when the risk of damage is greatest.”
Total Body Burden
Mother’s Burden
Toxic Metals
Environmental Pollutants
Electromagnetic Fields
Sensory Input
Stress/Internal Conflicts
Dietary Factors
Allergens
Microbial/Biofilm
Immune/Inflammatory Burden

Patient Burden
- Environmental Toxic Exposures
  - Chemicals (remodeling, new house, new furniture, pesticides in home, plastics, pollution, ...)
  - Heavy Metals (toys, food, coal burning plant, factories, amalgams, ...)
  - Dietary
  - Pharmaceutical (antibiotics, acetominophen, anesthesia (MRI))
- Immune Triggers
  - Injected Antigens, Adjuvants, Viruses
  - Allergic (new foods, mold, food sensitivities)
  - Infectious (viral, tick borne, bacteria, fungi)
- Stressors, Other
  - Physical
  - Emotional
  - Surgical

Down Syndrome / Autism
Symptoms
- Memory
- Cognition
- OCD
Comorbid
- Thyroid/Endocrine
- Childhood Leukemia
- Heart Defects
- Alzheimer’s
- Celiac
- Sleep Disorder
- Vision/Hearing
- Metabolic
- Immune
- Mitochondria
- Methylation
- Oxidative Stress
- Neurologic

Symptoms
- Sterotypical Behavior
- Language
- Social
Comorbid
- Sleep
- Seizures
- Gastrointestinal Issues
Metabolic
- Immune
- Mitochondria
- Methylation
- Oxidative Stress
- Endocrine

Neurologic Issues Affecting Memory and Cognition in DS
- Impairment of Neurogenesis, low cerebellar volume and brain volume. (Sonic Hedgehog (SHH) signaling of granule cell precursor (GCP).
- Disrupted Neurosignaling, associated with elevated extracellular GABA causing inhibition.
- APP (amyloid precursor protein) gene overexpression and protein interference leading to degeneration of specific neural cell circuits, particularly forebrain to hippocampus.
- Age related loss of forebrain cholinergic neurons. (also seen in Alzheimer's) 

Hippocampal Dysfunction
- Linked to an imbalance between inhibitory and excitatory pathways.
- Disruption of communication between the basal forebrain and hippocampus.
- Basal forebrain cholinergic neurons (BFCN) utilize acetylcholine as a neurotransmitter.
- BFCN transports NGF (nerve growth factor) produced in the hippocampus back to the basal forebrain to remain active.
- This retrograde transport of NGF is greatly impaired in Ts65Dn mice.

Metabolic Aftermath of Body Burdens
Oxidative Stress
- Depletion of Antioxidants, Glutathione, Metallothionein, Cysteine, Vitamins, Minerals, Amino Acids and Phytonutrients
- Impaired Detoxtification - Methylation, Sulfation, Mitochondrial Dysfunction
Immune Dysfunction
Endocrine Dysfunction
Gastrointestinal Dysfunction
Neurological Issues

Chronic Inflammatory Disorders: Allergies, Asthma, Arthritis, Frequent Infections, Fatigue, Mood, Behavior and Cognitive Issues

Neurologic Issues

MRDD Research Reviews 2007

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Neurotrophins (NGF and BDNF)

- Function and structure are similar.
- NGF found in peripheral and CNS, promotes expression and growth of Basal Forebrain cholinergic neurons (BCFN).
- BDNF found globally in the brain, implicated in learning and memory, and long term potentiation.
- Supplementation improves memory in animal models of aging and AD.
- NGF improved cholinergic neuron atrophy as well as size and number.

Physiology and immunology of the cholinergic anti-inflammatory pathway

Tracy KJ.

- The nervous system, via an inflammatory reflex of the vagus nerve, can inhibit cytokine release and thereby prevent tissue injury and death.
- The efferent neural signaling pathway is termed the cholinergic anti-inflammatory pathway.
- Cholinergic agonists inhibit cytokine synthesis and protect against cytokine-mediated diseases.
- Stimulation of the vagus nerve prevents the damaging effects of inflammatory cytokines.

Acetylcholine treatment increases nerve growth factor levels and choline acetyltransferase activity in the central nervous system of aged rats


The hypothesis that cholinergic signaling events associated with aging of the central nervous system (CNS) may be due to a loss of neurotrophic support is receiving a resurgence of interest given the remarkable pharmacological strategies available to reverse the activity of age-related neurodegenerative agents. Here we report that treatment with acetylcholine (ACh) increases nerve growth factor (NGF) and choline acetyltransferase (ChAT) activity in the CNS of aged rats. The administration of NGF to the CNS can be achieved using ACh to power a long-lasting intervention in conscious animals of various ages, thus indicating a direct effect of the cholinergic system on the CNS (BCFN system) to be independent of the actual degenerative stage of the neuron. Furthermore, long-term treatment with ACh completely prevents the loss of cholinergic function in memory, activity, and cognition of aged rats, suggesting that ACh may rescue cholinergic pathways from age-associated degenerative effects. Levels of intracellular transported high.

As BDNF increases in trisomic animals, there is a decrease in memory errors.

Cortisol Levels During Human Aging Predict Hippocampal Atrophy and Memory Deficits

Lupien, S.P.

Nature Neuroscience 1998

- Elevated glucocorticoid levels produce hippocampal atrophy and correlate with individual deficits in spatial learning in aged rats.
- The degree of hippocampal atrophy correlated strongly with both the degree of cortisol elevation over time and current basal cortisol levels.
- Therefore, basal cortisol elevation may cause hippocampal damage and impair hippocampus-dependent learning and memory in humans.

Stress Effects on BDNF

Stress-mediated decreases in brain-derived neurotrophic factor as potential confounding factor for scopolamine depression-induced neurochemical effects.


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Improving BDNF, reverses hippocampal atrophy, and improves neurogenesis

- Elevated cortisol and chronic stress decrease BDNF.
  - Phosphatidyl serine and adaptogenic herbs, such as Ashwagandha help modulate cortisol
- Fluoxetine (Prozac)
  - In Ts65Dn mice, fluoxetine treatment restored the expression of 5-HT1A receptors and BDNF, and enhances neurogenesis.
- Lithium
  - Lithium Restores Neurogenesis in the Subventricular Zone of the Ts65Dn Mouse, A Model for Down Syndrome.

Offspring of Mom’s with a high fat diet, had increased oxidative stress, less BDNF, less neurogenesis, and decreased cognitive function. (mouse model)

Mom’s with high fat diets have babies with oxidative stress in the hippocampus, leading to decreased neurogenesis. (mouse model)

An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus

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Abstract

With increasing interest in the potential of exercise as a treatment for age-related cognitive decline, the study of exercise-induced neurogenesis in adults has gained attention. However, the mechanisms by which exercise promotes neurogenesis in the adult brain remain unclear. To better understand the effects of exercise on neurogenesis, we measured the expression of BDNF, a key regulator of neuronal growth and survival, and its downstream target, the c-fos gene, in the dentate gyrus of adult mice before and after a 10-week exercise program. Results showed that exercise significantly increased the expression of BDNF and c-fos in the dentate gyrus compared to sedentary controls. These findings suggest that exercise-induced neurogenesis in the adult brain may be mediated by enhanced BDNF expression, which could have implications for the treatment of age-related cognitive decline.
Omega 3 supplementation improved BDNF levels in rats with oxidative stress after trauma.

Maternally separated rats have increased cortisol and increased BDNF. Bifidobacterium replacement improves hippocampal BDNF, but not in maternally separated rats.

GABA₂ Antagonists and Hippocampal Function
- At high doses, can trigger seizures.
- At doses far below those used to induce seizure showed long term improvement in MWM (morris water maze), “object recognition” and “alternating T maze”.
- These experimental tests are used to assess hippocampal function.
- Decreased hippocampal function is associated with an imbalance of excitatory (norepinephrine) and inhibitory (GABA) circuits in the DS mouse model.
Oxidative stress:
A bridge between Down’s syndrome and Alzheimer’s disease (review)
Neurology of Aging (volume 56, issue 5, May 2007)
• The genetic, biochemical and neuropathological analogies between Down’s syndrome (DS) and Alzheimer’s disease (AD), there is ample evidence of the involvement of oxidative stress (OS) in the pathogenesis of both disorders.
• Oxidative Stress occurs decades prior to the signature pathology and manifests as lipid, protein and DNA oxidation, and mitochondrial abnormalities
• For Down’s Syndrome, no scientifically proven diet or drug is yet available.
• In the future, a balanced up-regulation of endogenous antioxidants, together with multiple exogenous antioxidant supplementation, may be expected to be one of the most promising treatment methods.

Oxidative Stress and Alzheimer disease
• Aging is the most obvious risk factor for AD. Free radicals are involved. Neurons are extremely sensitive to attacks by destructive free radicals.
• Lesions are present in the brains of AD patients that are typically associated with attacks by free radicals (eg, damage to DNA, protein oxidation, lipid peroxidation, and advanced glycosylation end products), and metals (eg, iron, copper, zinc, and aluminum) are present.
• β-Amyloid is aggregated and produces more free radicals in the presence of free radicals. β-amyloid toxicity is eliminated by free radical scavengers.
• AD has been linked to mitochondrial anomalies affecting cytochrome c oxidase.
• Finally, many free radical scavengers (eg, vitamin E, selegeline, and Ginkgo biloba extract EGb 761) have produced promising results in relation to AD.

ORAC: Oxygen Radical Absorbance Capacity
Measures the ability of foods to act as antioxidants, the higher the ORAC the greater reducing capacity

Fats/Lipids are good for your brain!
• Fats, are an integral part of all cell membranes, and are vulnerable to destruction through oxidation by free radicals.
• Fat Soluble Vitamins and Antioxidants are uniquely suited to pass thru the blood brain barrier and alleviate oxidative stress in the lipid (fat) portion of the brain:
  – 70% of the Brain is made up of fat.
  – 25% of our Cholesterol resides in the brain.
  – The myelin sheath is predominantly fat.
• Most neurotoxins, like mercury, are fat soluble and damage lipid membranes thru lipid peroxidation or oxidative stress.

Cell Membranes are Mostly Fat
• Phospholipids
  • Choline
  • Serine
  • Inositol
  • Ethanolamine
• Cholesterol
• Glycolipids
Cholesterol

- Cholesterol is abundant in the tissue of the brain and nervous system.
- Myelin, which covers nerve axons to help conduct the electrical impulses that make movement, sensation, thinking, learning, and remembering possible, is over one fifth cholesterol by weight.
- Even though the brain only makes up 2% of the body’s weight, it contains 25% of its cholesterol.
- Cholesterol was found to be the most important factor in the formation of synapses, the basis of our learning and memory.
- Cholesterol is a precursor to vitamin D.
- The human body uses cholesterol to synthesize bile acids, which are important for the digestion of fats.
- Cholesterol is the precursor to all steroid hormones.

Impact of Oxidative Stress on Methionine Metabolism

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methionine</td>
<td>Metabolized to produce homocysteine and进而合成同型半胱氨酸</td>
</tr>
<tr>
<td>Homocysteine</td>
<td>Produced from methionine and进一步合成同型半胱氨酸</td>
</tr>
<tr>
<td>B6</td>
<td>Vitamin B6, which is essential for the metabolism of methionine and同型半胱氨酸的代谢</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofolate, a coenzyme involved in the metabolism of methionine and同型半胱氨酸的代谢</td>
</tr>
</tbody>
</table>

Phosphatidyl Serine

- Supports the function of many vital enzymes.
- Acts as an antioxidant, and quells inflammation in the brain.
- In Europe and Japan, phosphatidylserine is sold as a prescription drug to treat memory and learning dysfunction.
- Aged rats with cognitive deficits have demonstrated decreased phosphatidylserine in the hippocampus.
- Helps with stress induced damage in the brain.

Phospholipid Methylation

- D4 receptor on cell membranes associated with attention.
- Methylation of Phospholipids (Phosphoethanolamine to Phosphatidylcholine) causes an increase in membrane fluidity.
- Membrane fluidity is important for proper signaling and flow of information and nutrients in and out of cells.
- Dopamine stimulated PLM (phospholipid methylation) requires 4 steps in which a new methyl group is provided by methylfolate or SAMe when methylfolate is low.

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Oxidative Stress and Mitochondrial Dysfunction

- The inner membrane of the mitochondria contains a large amount of antioxidants including:
  - Glutathione
  - Vitamin C
  - Vitamin E
  - Anti-oxidant enzymes such as superoxide dismutase
- Oxidative stress impairs mitochondrial function
- The brain is very sensitive to oxidative stress because of its high energy demands, its limited capacity to use substrates other than glucose for ATP synthesis, abundant lipid content, and relatively low antioxidant levels compared to other organs.

Mitochondria, Methylation, Fatty Acids and Carnitine connection

- Carnitine biosynthesis is initiated by methylation of lysine.
- The only firmly established function of carnitine is its function as a carrier of activated fatty acids and activated acetate across the inner mitochondrial membrane.
- Choline and carnitine supplementation lowers lipid peroxidation, and promotes conservation of retinol and alpha-tocopherol.

Gut Brain Axis

- A bidirectional communication system between the brain and gastrointestinal systems.
- Communication occurs along immunologic, neural, and biochemical pathways.
- Gut microbiota can affect both brain development and behavior.
- Stress also can alter the composition of Gut microbiota.

Microbial Flora

- pH balance
- Modulation of the immune system
- Digestion, Energy Production, Metabolism, Vitamin Production
- Destruction of toxins and mutagens
- Repression of pathogenic microbial growth
- Preventing allergy
- Preventing inflammatory bowel disease and inflammation
- Alleviate anxiety, improve mood

100 trillion bacteria in the gut
70% of immune system lies in the gut
Early disruption of gut flora, affects later immune function, potential allergies and autoimmunity
Aids with digestion of carbohydrates and fiber to form SCFA which in turn fuels enterocytes.

References:
- Oxidative stress and mitochondrial dysfunction in Down syndrome.
- Gut microbiota: An immunological link between gut and brain.
- The role of gut microbiota in cognitive and neurodevelopmental disorders.
**Tryptophan and IDO**

- Serotonin
- Kynurenine
- Kynurenic acid
- Quinolinate
- Quinolinic acid

**Leaky Gut Theory (Fasano)**

- Gluten causes leaky gut by releasing zonulin.
- The Paracellular Pathway – space between cells in the gut is impermeable to large molecules.
- Zonulin release causes cytokine and chemokine activation (CXCR-3, ligands CXCL 9, 10, 11) and migration of pathological Th1 cells.
- Gluten causes wbc (neutrophil) recruitment
- Impaired intestinal barrier is involved in Chronic INFLAMMATION!!!
- MS, strokes, asthma, cardiomyopathy, IDDM, thyroiditis, celiac disease, rheumatoid arthritis, inflammatory bowel disease and Autism.

**Clean up the Child’s Environment**

- Use natural, biodegradable and perfume free detergents and cleaning agents, do not dry clean clothes.
- Avoid chlorine: use water filters, limit pool and hot tubs.
- Wear 100% cotton clothes, avoid flame retardants.
- Use fluoride-free toothpaste (tin, titanium).
- Use an air purifier, especially in the bedroom.
- Avoid prolonged exposure to batteries (light up shoes, lap tops, cell phones, head phones).
- Check for recalled TOYS with lead.
- Use aluminium-free salt, baking powder, deodorant. Do not cook in aluminum foil or drink from aluminum cans.
- Avoid use of herbicides or pesticides or mosquito repellants, on lawns, garden, or self, (awned show when home).
- Use natural shampoo, soaps, and make-up (lative-PGMA).
- Avoid sources of electromagnetic (EMF), especially in the bedroom. (cordless phones, wi-fi, cell phones, baby monitors).

**Clean up the Diet**

- Casein-free/Gluten-free/Soy-free Diet Trial for 3-6 months.
- Avoid sugar and refined starch, replace with whole grains
- Maximize antioxidants and phytonutrients (colorful foods)
- Limit processed and preserved foods; organic is best.
- Avoid mesothelioma (ex. Caffeine, MSG, NutraSweet, red-yellow food dyes, nitrates, sodium, glutamates, propionates, benzoates)
- Limit intake of phenolics (apples, grapes, strawberries...).
- Drink plenty of filtered water.
- Never microwave in plastic or Styrofoam, do not store food in plastic or foil, or cook on Teflon coated pans.
- Eliminate seafood.
- Avoid processed meats (avocado, olive, coconut, flax).
- Buy hormone-free, antibiotic-free, grass fed organic meat and eggs.
- Add fermented foods (kefir, kombucha, cabbage...).
Opioid Peptide Theory
- Casein/gluten peptides are broken down by the enzyme DPPIV (dipeptidyl dipeptidase 4). This enzyme can be inhibited by toxic metals and yeast.
- If DPPIV is not optimal dairy and gluten protein are not digested and partially broken down peptides or peptides accumulate. These peptides act as false neurotransmitters and have an opiate effect, creating problems with behavior, focus, attention, mood regulation, and processing information. Other symptoms include high pain tolerance, dilated pupils, addiction to dairy and gluten products.
- High levels of opioid peptides (gliadorphin and caseomorphine) found in urine of autistic children. (Reichelt, 1997)
- Casein-free, Gluten-free diet may be an effective intervention (Whiteley, 1999)

Clean Up the Gut
- **Address Malabsorption**
  - Add Probiotics and Prebiotics, Essential Fats, Biotin
  - Address Fat Soluble Vitamin Deficiencies (A, D, E, K)
- **Start Foundational Nutrients**
- **Address Dysbiosis**
- **Diagnose and Treat Immune Dysregulation**
  - Address Food Allergies and Hypersensitivities
  - Treat Immunodeficiencies
  - Treat Chronic Inflammation
- **Address Motility/Constipation**

Foundational Nutrients
- **Minerals**
  - Zinc
  - Magnesium
  - Selenium
- **Antioxidants**
  - Vitamin C
  - Vitamin E
  - Vitamin D
- **Good Fats**
  - Omega 3 EFA
  - Coconut oil
  - Phosphatidyl Choline/Serine
- **Vitamins**
  - Vitamin D3
  - Epsom Salts Baths

Behavioral and Brain Functions
- **Mercury exposure, nutritional deficiencies and metabolic disruptions may affect learning in children** (Renee Dufault)
  - Nutritional deficiencies, including deficiencies in the long chain polyunsaturated fatty acids (LCPUFA), have been shown to influence neural function and production of key brain neurotransmitters. These inadequacies can also lead to neurochemical dysregulation, which can be reversed with nutritional supplementation and avoidance of mercury toxicants.
- High fructose corn syrup has been shown to decrease the levels of long chain polyunsaturated fatty acids (LCPUFA) in the brain, which can lead to deficiencies in neural function.
- Dietary zinc is essential for maintaining the metabolic processes required for mercury elimination.

The Oxford-Durham Study: A Randomized, Controlled Trial of Dietary Supplementation With Fatty Acids in Children With Developmental Coordination Disorder
- **Mounting evidence suggests that a relative lack of certain polyunsaturated fatty acids (PUFA) may contribute to related neuropsychiatric and cognitive disorders such as dyslexia and attention-deficit/hyperactivity disorder**.
- No effect of treatment on motor skills was apparent, but significant improvements for active treatment versus placebo were found in reading, spelling, and behavior over 3 months of treatment in parallel groups.
- After the crossover, similar changes were seen in the placebo-active group, whereas children continuing with active treatment maintained or improved their progress.
Laboratory testing options are varied and based on the individual.

Basic Biomedical Blood Testing
- CBC
- Comprehensive Metabolic Panel
- Serum Copper
- Plasma Zinc
- Thyroid profile
- Blood Lead
- Iron, blood
- Geliac panel
- Ammonia, blood
- Vitamin D 25 OH
- Carotine Panel
- Lactic Acid
- Reduced Glutathione
- Total Cholesterol/Triglycerides

Biomarkers: Oxidative Stress
- 8 OH deoxyguanosine
- 8 OH guanosine
- Isoprostane F2 alpha
- Malondialdehyde (urine)
- Lipid Peroxides
- Reduced Glutathione

Antioxidants
- Vitamin E
- Vitamin A, vitamin K
- Vitamin C
- Selenium, Zinc
- Reduced Glutathione (r-GSH)
- Bioflavinoids (catechins) and Carotenoids
- Superfruits (noni, goji, acai, mangosteen…)
- Kangen water

Support Neurogenesis and GABA Balance
- Diet, Low oxidized fats/trans fats
- Exercise
- Omega 3
- Cholinergics
  - Phosphatidyl choline/serine
  - Acetylcholinesterase inhibitors
- Bifidobacterium breve
- Curcumin
- Gingko biloba

Address Adrenal Balance
- Keep stressors to a minimum
- Plenty of sleep
- Limit sugar and refined carbs
- Adaptogenic herbs
  - Ashwaganda
  - Ginseng
  - Holy Basil
- Vitamin C
Support Methylation
- Methylation
  - DMG
  - TMG
  - Hydroxy B12
  - Folinic Acid
  - Methyl Folate

Support Mitochondrial Function
- Vitamin B1, B2, B3, B5, and Biotin
  - Antioxidants
    - Glutathione
    - Alpha Lipoic Acid - careful
    - Coenzyme Q10
  - L-Carnitine
  - Magnesium

Hyperbaric treatment for children with autism: a multicenter randomized, double blind, controlled trial

Children with autism who received hyperbaric treatment at 1.3 atm and 24% oxygen for 40 hourly sessions had significant improvements in overall functioning, receptive language, social interaction, eye contact, and sensory/cognitive awareness compared to children who received slightly pressurized room air.
PMID: 19284641

Thank You for opening your minds and hearts to learning to help heal our kids.

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