The emergence of a new autism model

Older model
- Genetically determined
- Brain based
- Hard-wired
- Treatable but not curable

Newer model
- Environmentally triggered
- Genetically influenced
- Both brain and body
- Metabolic abnormalities play big role
- Treatable and recovery possible

OR is it A DISORDER THAT AFFECTS THE BRAIN?

Genetics Don’t Cause Epidemics

- Increases Over the Past 20 Years
  - Autism: 6000% Increase
    - 1/10,000 to 1/150 (Fombonne et al, JAACAP, 2001)
    - 1/75 (1/94 boys; National Children’s Health Survey, 2007)
  - ADHD: 400% Increase
    - 7x increase in prescriptions (Swanson et al, Neuropsych Rev 2007)
  - Asthma: 300% Increase
  - Allergies: 400% Increase
  - Diabetes: 103% Increase
    - 5 x increase in <5 year old (Bingley, 2007)

What Is The Disease Process of Autism?

- Behavioral/Neurologic
  - Brain inflammation
  - Dysregulated neurotransmitters
  - Autonomic dysfunction
- Gastrointestinal
  - Food sensitivities
  - Intestinal dysbiosis
  - Nutritional deficits
  - Gut inflammation
- Immune
  - Frequent infections
  - Chronic inflammation
  - Autoimmune reactions
  - Environmental allergens
- Biochemical/Metabolic
  - Oxidative stress
  - Mitochondrial dysfunction
  - Glutathione depletion

Vicious Cycles
History, General

- **Family**
  - Autoimmune (Valicenti-McDermott)
  - GI, allergies, IDDM
- **Prenatal**
  - Maternal amalgams/vaccines/meds/diet
- **Neonatal**
  - Birth trauma/meds/vaccines
  - Hyperbilirubinemia (Croen et al, 2005, Pediatrics)
  - Breastfeeding/colic/reflux/sleep
- **Environmental**
  - EMF, water, mold, ticks

History, Specific

- Onset and Triggers
- Diet – cravings, reactions
- Stool – constipation, diarrhea, encopresis, overflow around impacted stool
- Illness/Injuries/Medications
- Vaccines/Reactions
- Signs/Symptoms
- Questionnaire

The Gut-Brain Link

- Many studies have shown abnormalities:

Concept of brain effects secondary to pathology elsewhere in body

Gut brain axis

Historical clues: gut dysfunction

- Difficulty breastfeeding
- Persistent colic
- Gastro-esophageal reflux
- Food sensitivities
- Failure to thrive
- Frequent antibiotics (abnormal flora)
- Abnormal posturing
- Hands in pants/probing
- Self injurious behavior
- Poor sleep

Physical/Lab clues: Gut Dysfunction

- Abnormal Stools
  - Grainy (insoluble bile salts)
  - Diarrhea/constipation/encopresis
- Wasted buttocks
- Distended abdomen/bloating/doughy
- Esophagitis
- Gastritis
- Lymphoid nodular hyperplasia
- Colitis (duodenitis/ileitis/proctitis)
- Insatiable appetite
Historical Clues & Physical Exam Pearls - Other

• Zinc Deficiency
  - Acne/sparse hair/psoriasis
  - White spots/lines on nails
  - Canker sores

• Essential Fatty Acid Deficiency
  - Keratosis pilaris
  - Dry, coarse hair

• Magnesium deficiency
  - Muscle twitches/tingling
  - Sighing
  - Salt craving

Gut Dysfunction

Historical and Physical Exam Clues for Dysbiosis

• Parasites
  - Anal itching and probing
  - Picking, biting, licking, grinding

• Yeast
  - Rash/peeling feet/ridged, discolored nails
  - Inflamed cheeks/red anus
  - Ring worm/tinea corporis or capitis

Alteration of Intestinal Function in Autism

Endoscopic examination of 36 autistics presenting intestinal symptoms showed:

- Reflux eosophagitis 69.4%
- Chronic gastritis 41.6%
- H. pylori infection 0.0%
- Chronic duodenal inflammation 66.6%

- Horvath, et al

Pathological Mucosal Alteration Observed with Autistic Subjects

• Increased size and number of lymphoid follicles particularly in ileum
• Merging of lymphoid follicles
• Luminal infiltration of neutrophils, and eosinophils
• Crypt cell proliferation
• Ulceration of epithelium*
• Thickening of basement membrane
• Decreased production of brush border associated digestive enzymes
• Up-regulated Th2 and Th1 response.

All above responses are consistent with the establishment of a chronic inflammatory condition

Lab Options for Gut Issues

• Urine Organic Acids Test (OATS, MAP)
• Stool Microbiology
• Stool Mycology
• Stool Parasitology
• IgG/IgE Food Panel
• Celiac Panel
• Fecal Fat
• Breath Test for Fructose Malabsorption
• Inflammatory Markers (ESR, CRP, calprotectin, ...)
• Ammonia - blood
• IBD Serology (prometheus testing)
• Endoscopy, Colonoscopy if necessary
What To Do

• Mucosal health = Promoting Immunity
  • Remove stressors (e.g., allergenic foods, gluten, yeast, bacteria, parasites, clostridia)
  • Supply nutrients (e.g., diet (GF/CF/SF/YF/SCD/BED/GAPS), vitamins, zinc)
  • Anti-inflammatories – Ibuprofen, EFAs (1000 mg), Mesalamine, Sulfasalazine, Steroids, Minocycline, Herbs
  • Supply probiotics (up to 50 bil CFU; discourage pathogens, control inflammation, encourage peristalsis)
  • Encourage digestion (e.g., disaccharidases, peptidases)

VICIOUS CYCLES OF INFLAMMATION

• Immune deficiency and dysfunction (ineffective or defective responses) – low IgA and IgG subclasses
• Hypersensitivity (overreaction to innocuous foreign material) – allergies, atopy
• Autoimmunity (inappropriate reaction to self) - PANDAS
• Inflammation (too robust attack on germs)
  – increased TNF-alpha
  – Esophagitis, Colitis (GI inflammation)
  – Atopic Dermatitis, Asthma
  – Neuroinflammation

The Immune-Brain Link

• Many Studies have shown abnormalities:

Allergy Testing

Historical Clues & Physical Exam Pearls - Immune Dysregulation

• Eczema/dermatographism
• Allergic shiners
• Allergic rhinitis/asthma
• Warts
• Molluscum contagiosum
• Herpes
• Thrush/fungal skin infections
Lab Clues: Immune Dysregulation

- T cell dysregulation: TH1 to TH2 shift
- Decreased NK cell function
- Increased TNF
- Decreased IL-10, secretory IgA
- Increased IgE, eosinophilia
- Increased autoimmunity
- Chronic viral, fungal infections
- Chronic gut inflammation, intestinal permeability, malabsorption and food sensitivities
- Allergies

Immune Balance

- Cellular (T and B)
- Humoral Response (Antibodies)
- Cytokines (regulate initiation and maintenance of immune response)
  - Th1 (IL-2, IFN) (Gupta, 1996)
  - Th2 (IL-4, 5, 13, TGF-beta)
  - Innate (TNF-alpha, IL-1, IL-6, IL-12) (Jyonouchi, 2005)
  - Pro-inflammatory (TNF-alpha, IL-1, IL-6)
  - Anti-inflammatory (TGF-beta, IL-10)
  - Regulatory (IL-10, IL-12, TGF-beta)

Autoantibodies in ASD

- Maternal Antibrain Antibodies in Autism
- Antibodies to brain proteins found in 30-37% of ASD vs 8-13% of controls
- Behaviors Associated with Fever in Children with ASD
  - “Rapid behavioral improvements reported during fever in ASDs suggest dysfunctional neural networks and insight into neurobiological basis of potential treatments”
  - Pediatrics Dec 2007; (120) e1386-e1392

Elevated Cytokine Levels in Children with ASD

- “Children with ASD had increased activation of both Th1 and Th2 arms of the adaptive immune response, with a Th2 predominance, and without the compensatory increase in the regulatory cytokine IL-10”
- DYSREGULATION!
  - Molloy et al
  - J Neuroimmunology
  - 2006 March; 172: 198-205

BASIC INTERVENTIONS FOR IMMUNE DYSREGULATION

- Heal the gut
- Avoid what harms-casein, gluten, soy, phenols, additives, sugar
- Give what heals-antioxidants, nutrients, EFAs, immunotherapy, HBOT
- Treat underlying problems-dysbiosis, inflammation, detoxification
Vicious Cycles: Metabolic

- Vital role of methylation and sulfation
- Downstream effects when cycle does not function
  - Cannot make creatinine
  - Cannot make normal neurotransmitters
  - Cannot control gene expression
  - Cannot make cell membranes

The Metabolic-Brain Link

- Many studies have shown abnormalities:
  - Oxidative stress (Chauhan et al, Pathophys, 2006; MacFabe et al, Behav Brain Res, 2007; Deth et al, Neurol, 2008)

Factors Contributing to Oxidative Stress in Autistic Children

- Inflammation
- Infection
- Genes
- Environment
- Timing
- Gut Inflammation
- Brain Inflammation
- Immune dysfunction

CONTRIBUTING FACTORS TO OXIDATIVE STRESS

- Radiation
- Stress
- Injury
- Trauma
- Aging
- Pollution
- Poor diet
- Infection
- Loss of GSH

GIVE P5P
ADD DPPIV
AVOID CASEIN
GIVE TMG
MB12 shots
Folinic acid

GIVE MPS
AUG DPPH
AVOID CASER
Vicious Cycles: Detoxification

- Reduced levels of mercury in first baby haircuts (Holmes et al, Int J Toxicol, 2003; DeSoto et al, J Child Neurol, 2006)
- Biliary mercury secretion tied to GSH (Clarkson et al, Scand J Work Environ Health, 1985)
- Environmental mercury release (Palmer et al, Health Place, 2006)

Texas autism rates, by school districts

Potential association between autism rates, environmental mercury other toxins in Texas

United Nations Environment Program
Global Mercury Assessment, 2002

Diagnostic Lab Findings

- General Screen
  - Urinalysis
  - CBC, ESR or CRP
  - Chem Screen – liver and kidney function
  - Thyroid – including antibodies
  - Iron, ferritin
  - Zinc (plasma or PRBC)
  - Mitochondrial markers (ammonia, lactate, carnitine, acylcarnitine, CK, amino acids)
  - Immune markers (Ig, C3D, strep pneumococcal serotypes)

Diagnostic Lab Findings - Other

- Methylmalonic acid (MMA)
- Vitamin A (retinal)
- Vitamin D (25 OH)
- ASO, antiDNAse
- Viral titers and vaccine titers (immunocompetency and not viral persistence)
- Autoantibodies (thyroid, endovascular, brain)
- Lyme testing
- Lead (ongoing exposure)
- Testosterone
- Fasting lipid profile
Diagnostic Lab Testing
Primary /Initial

- Urine metabolic analysis/organic acids (G, GP, MM)
- Comprehensive digestive stool analysis (G, DD)
- IgG food antibodies including antigliadin Ab (Allettess, Immuno, MM, G)
- Porphyrin (MM)
- Neopterin (urine immune marker)
- 8-OHG (marker of RNA oxidation)
- Cysteine (plasma)

Diagnostic Lab Testing - Secondary

- Natural Killer Cell Activity; T cell counts
- Urine/Hair/Fecal metals (DD, G, MM)
- Urine/RBC minerals (DD, G, MM)
- Plasma amino acids (MM)
- Plasma fatty acids (MM, G)
- Genetic Testing (Genomics – G, IT)

How does it all fit?
Fostering A Healthy Environment

- Breast is BEST!
  - ↑ Production of beneficial Bifidobacter
  - DHA rich
- Delay introduction of solid foods
  - Minimizing or avoiding wheat, milk, and foods first degree relatives are sensitive to
  - Best first foods – avocado, fruits and vegetables
- Support flora with probiotics
  - Infants with a family history of atopic allergy who received a Lactobacillus probiotic had a 50% ↓ in atopy @ 2yo

Where to Begin

- Build a Foundation
- Treat constipation
- Diet
  - GF/CF/SF/YF/SCD/BED/GAPS/LOD
  - The China Study (T. Colin Campbell)
- Basic Nutritional Changes
  - Fresh, unprocessed, unrefined, organic, whole foods
  - Varied and rotational
  - Non allergic (crave that which most sensitive to)
  - Protein (every 4-5 hours)
  - Avoid excitotoxins (caffeine, MSG, dyes); phenolics (grapes, strawberries)
  - Juicing; raw foods; fermented foods (kefir); good fats
  - Organic (especially pears, apples, celery, strawberries, cherries, grapes, spinach, lettuce, potatoes, rice and chicken)

Remove and Avoid Toxicities

- Eliminate toxins in food, water, environment
- Filter water, use air purifier/ionizer
- Avoid
  - Plastics/phthalates (#3, 6, 7)
  - Pesticides, chemicals
  - Flame retardants
  - Lead painted toys, jewelry
  - Mercury containing fish, amalgams, vaccines, factories, crematoriums
  - Acetaminophen (Ichibay et al, Asian; 2008)

Replenish Nutrients

- Good Flora (probiotics)
- Enzymes (Kirkman, Houston)
- Nutrients (MVI; Adams et al, 2004)
  - Mg/B6 (Mousain-Bosc et al, 2006)
  - B12 (Nakano et al, 2005)
  - Folate (Ramakers et al, 2007)
  - Ascorbic acid (Dolske et al, 1993)
- Essential fatty acids (Amminger et al, 2007)
- Anti-Glutamates (pycnogenol (Trebaticka et al. 2006), chamomile, taurine, GABA)
<table>
<thead>
<tr>
<th>Basic biomedical interventions</th>
<th>How to develop treatment plans?</th>
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<tbody>
<tr>
<td>• HEAL THE GUT</td>
<td>• Begin with considering the individual history of your patient</td>
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<tr>
<td>– Treat dysbiosis</td>
<td>• Test hypotheses about underlying problems by looking for physical exam clues and laboratory data</td>
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<td>– Treat constipation</td>
<td>• Figure out if they are getting something they should not or if they are not getting what they need</td>
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<td>– Decrease inflammation</td>
<td>• See treatments as clinical trials with an N of one</td>
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<td>• Avoid what harms</td>
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<td>– Gluten? Casein?</td>
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<td>– Omega 3 EFAs</td>
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<td>• FIX METABOLIC PROBLEMS</td>
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<td>– Methylcobalamin</td>
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