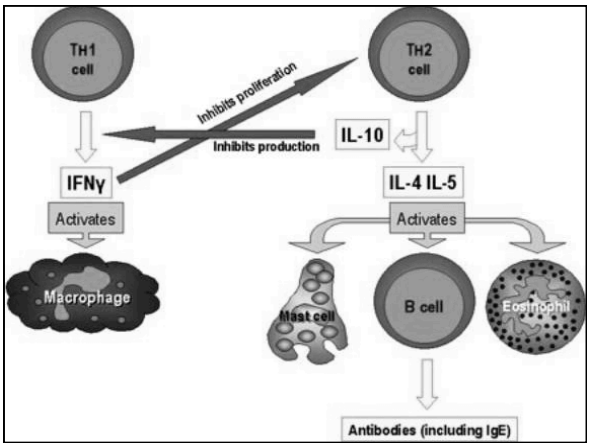
Immunological Disease & Autism (PANDAS)

Immune Dysregulation in Autism

August, 2011
Sydney, Australia
MINDD

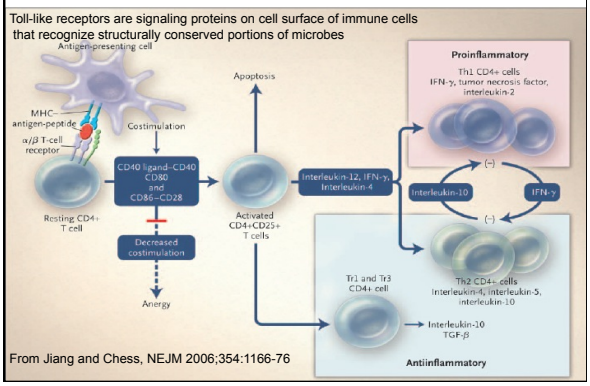
Nancy O' Hara, MD
www.ihealthnow.org

Innate Immunity	Adaptive Immunity
Skin, tears, mucus membranes	APCs present Antigen to T cells MHC genes involved
Phagocytes macrophages and neutrophils	Activated T cells provide help to B cells and kill infected/abnormal cells
Mast Cells and Natural Killer Cells	B cells produce antibody specific for Antigen
Complement	Humoral(Th2) Immunity Antibodies (IgG, IgE, IgM, IgA) IL-4, IL-5, IL-13, IL-10, TGF beta
Other Proteins, **Cytokines** TNF alpha, IL-1, IL-6, IL-12	**Cellular (Th1) Immunity** Lymphocytes Dendritic Cells IL-2, IFN gamma



THE CELLULAR IMMUNE SYSTEM

Toll-like receptors are signaling proteins on cell surface of immune cells that recognize structurally conserved portions of microbes



From Jiang and Chess, NEJM 2006;354:1166-76

IMMUNE CELL TYPES - SUBSETS OF T-CELLS

Helper T cells - Once activated, they divide rapidly and secrete small proteins called cytokines that regulate or "help" the immune response.

Cytotoxic T cells - Destroy virally infected cells and tumor cells, and are also implicated in transplant rejection. These cells are also known as CD8+ T cells, since they express the CD8 glycoprotein at their surface. Through interaction with helper T cells, these cells can be transformed into regulatory T cells.

Memory T cells - A subset of antigen-specific T cells that persist after an infection. They quickly expand to large numbers of effector T cells upon re-exposure to their cognate antigen, thus providing the immune system with "memory" against past infections. Memory T cells comprise two subtypes: central memory T cells (TCM cells) and effector memory T cells (TEM cells). Memory cells may be either CD4+ or CD8+.

Regulatory T cells - (a.k.a. suppressor T cells). These are crucial for the maintenance of immunological tolerance. Their major role is to shut down T cell-mediated immunity toward the end of an immune reaction and to suppress auto-reactive T cells that escaped the process of negative selection in the thymus. Naturally occurring Treg cells can be distinguished from other T cells by the presence of an intracellular molecule called FoxP3. Mutations of the FOXP3 gene can prevent regulatory T cell development, causing fatal autoimmune disease.

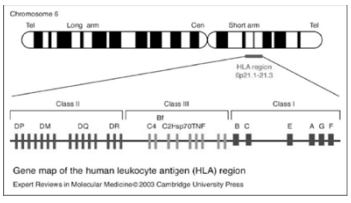
Natural Killer T cells - bridges the adaptive immune system with the innate immune system. NKT cells recognize glycolipid antigen presented by a molecule called CD1d, rather than MHC. Once activated, these cells initiate both cytokine production and release of cell killing molecules.

Pro-inflammatory Cytokines – TNF alpha, IL-1, IL-6
Anti-inflammatory Cytokines – TGF-Beta, IL-10

Slide from Immunology 101 by Dr. Jim Johnson, Ph.D. Assistant Professor, Dept. of Cellular and Physiological Sciences and Dept. of Surgery, University of British Columbia

GENETIC SUSCEPTIBILITY - HLA GENES

•In humans, the 3.6-Mb (3 600 000 base pairs) MHC region on chromosome 6 contains 140 genes. About half have known immunological functions.



•Human Leukocyle Antigen (HLA) important role in learning and memory (Sh??, Stanford, University.

Slide from Immunology 101 by Dr. Jim Johnson, Ph.D. Assistant Professor, Dept. of Cellular and Physiological Sciences and Dept. of Surgery, University of British Columbia

Developmental Immunotoxicology (DIT)

Adverse effects from the environment, nutrition, maternal health, infections and nutrition, and genetics on the development of the immune system

Programming= insults in utero during critical periods of development that has long term effects, pregnancy based experiences determine the health of the baby

Fetal Origins= alterations in fetal nutrition and endocrine status that results in developmental adaptations that permanently change structure, development, physiology, and metabolism which predispose to adult disease

Hertz-Picciotto, Prenatal exposures to persistent and non-persistent organic compounds and effects on immune system development. Basic Clin Pharmacol Toxicol, 2008.

Dietert, R.R. and J.M. Dietert, Potential for early-life immune insult including developmental immunotoxicity in autism and autism spectrum disorders: focus on critical windows of immune vulnerability. J Toxicol Environ Health B Crit Rev, 2008.

DEVELOPMENTAL IMMUNOTOXICOLOGY EFFECTS

- Th1/Th2 skewed immune system
- Deficiency of T regulatory cells
- Dysregulation of inflammatory cells
- Hyperinflammation
- Damage to a variety of systems and tissue
- Impaired maturation of dendritic cells
- Immunosuppression
- Autoimmunity
- Asthma, allergy, abnormal vaccine response, increased susceptibility to infections, neurobehavioral conditions, cerebral palsy, atherosclerosis, and more

PRENATAL EXPOSURE TO ANTIBODIES FROM MOTHERS OF CHILDREN WITH AUTISM PRODUCES NEUROBEHAVIORAL ALTERATIONS: A PREGNANT DAM MOUSE MODEL

J Neuroimmunol. 2009 Apr 9

Singer HS, **Morris C**, **Gause C**, **Pollard M**, **Zimmerman AW**, **Pletnikov M**.

- A pregnant mouse model was used to compare the effect of IgG, administered E13-E18, from mothers of children with autistic disorder (MCAD), to controls (simple- and IgG-) on behavioral testing in offspring.
- Mice, exposed in-utero to MCAD-IgG, as adolescents, were more active during the first ten minutes of central field novelty testing and, as adults, displayed anxiety-like behavior on a component of the elevated plus maze and had a greater magnitude of startle following acoustic stimulation. On a social interaction paradigm, adult mice had alterations of sociability.
- Pilot studies of immune markers in MCAD IgG-exposed embryonic brains suggest evidence of cytokine, glial activation.
- These studies demonstrate that the transplacental passage of IgG from MCAD is capable of inducing long-term behavioral consequences.

IMMUNOPATHOLOGY

- **Deficiency** – low Th1 and low Th2
- **Hypersensitivity/Allergy**- high Th2
- **Autoimmunity** – high Th1 and high Th2
- **Inflammation** – high Innate and/or Th1,Th2

IMMUNE DEFICIENCY

- Inadequate titer response to rubella vaccination (Stubbs 1976)
- Depressed lymphocytic transformation in response to antigenic stimulation (Stubbs 1977)
- Reduced numbers of T-cell lymphocytes and altered ratio of helper to suppressor T-cells (Warren 1986)
- Reduced natural killer cell activity (Warren 1987)
- Deficiency of T-suppressor cells (Warren 1990)
- Deficiency of CD4+ helper T cells (Yonk 1990)
- Deficiency of naïve CD4+ T cells (Ferrante 2003)
- Low normal immunoglobulins (MIND Institute)
- Low sIgA (Gupta, 1996)

All frequently sick kids deserve an evaluation for immunodeficiency

HYPERSENSITIVITY/ALLERGY

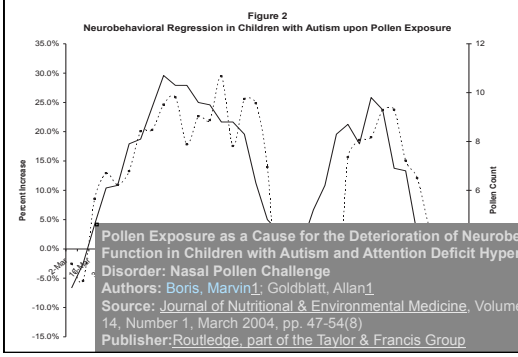
- High IgE (atopy)
  - Measured by RAST or skin testing
  - In neurotypical kids untreated allergies can cause poor memory, concentration, and sleep.
- High IgG
  - Measured by ELISA blood testing
  - High IgG to foods may relate to leaky gut
  - Elevated IgG4 thought to be a mediator of delayed hypersensitivity reactions (Sletten 2006)
  - Increases in IgG2 and IgG4 subclasses (Croonenberghs 2002, Enstrom 2009)
- Hyperimmune response to measles vaccine antigen (Singh 2003)
- A history of allergies in mom during pregnancy increases the risk of autism over 2-fold (Croen, 2005)
- Children with autism have more food allergies than controls (Lucarelli, 1996)

FOOD REACTIVITY: JYONOUCHI

- In response to challenge with bacterial toxins or dietary cow's milk protein, immune cells from autistic children with GI symptoms showed strong pro-inflammatory response and a reduced ability to switch off the immune response compared to typical children.
- Immune reactivity to milk and wheat common with or without GI symptoms.
- Yeast (Candida albicans) overgrowth also found in the stools of some children.

Jyonouchi et al., 2005 J Pediatr 146(5):605-10
Jyonouchi et al., 2005 Neuropsychobiology 51(2):77-85

Allergy Testing



Pollen Exposure as a Cause for the Deterioration of Neurobehavioral Function in Children with Autism and Attention Deficit Hyperactive Disorder: Nasal Pollen Challenge
Authors: Boris, Marvin1; Goldblatt, Allan1
Source: Journal of Nutritional & Environmental Medicine, Volume 14, Number 1, March 2004, pp. 47-54(8)
Publisher: Routledge, part of the Taylor & Francis Group

AUTOIMMUNITY

- Autoantibodies to Self and Brain
  - Myelin basic protein
  - Serotonin receptors
  - Caudate nucleus
  - Neuron axonal filament protein
  - Cerebellar neurofilaments
  - Nerve growth factor
  - Alpha 2-adrenergic binding sites
  - Anti-brain endothelial proteins
  - Gut epithelium basement membrane
  - Anti DNAse B antibody
  - Serum Autoantibodies to Brain (Connolly et al.)
- Result in tissue damage, local or systemic
- Positive family history of autoimmune disorders (thyroid)

Strep (PANDAS)

Pediatric Autoimmune Neuropsychiatric Disorder Associated with Strep

- Diagnostic Criteria (Swedo et al, Am J Psychiatry, 1997)
  - Presence of OCD, tic disorder or aggression
  - Pediatric onset of symptoms
  - Episodic course of symptom severity
  - Association with Group A Beta-hemolytic strep
  - Association with other neurologic abnormalities (motoric hyperactivity, choreiform movements)
  - Diagnosis based on symptoms; high ASO, AntiDNase
  - Autoimmune cross-reaction to basal ganglia
    - Chmelik et al, Clin Pediatr, 2004

PANDAS – Diagnosis Dx code: 300.3

- Sudden worsening of behaviors
- Not always history of recent strep
- ASO and AntiDNase Ab may not be elevated or helpful
- Symptoms may include chorea, tics, OCD, aggression, agitation, hyperactivity, emotional lability, anxiety, cognitive deficits, oppositional behaviors
- Milder form of Sydenham Chorea
  - Swedo, *Pediatrics*, 2004

Antibiotic Prophylaxis with Azithromycin or Penicillin for Childhood-Onset Neuropsychiatric Disorders

Lisa A. Snider, Lorraine Lougee, Marcia Slattery, Paul Grant, and Susan E. Swedo

Background: *The acronym PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) describes a subgroup of children with obsessive-compulsive disorder and/or tic disorder that experience symptom exacerbations following streptococcal infections. We hypothesized that the prevention of streptococcal infections among children in the PANDAS subgroup would decrease neuropsychiatric symptom exacerbations.*
Methods: *Twenty-three subjects with PANDAS were enrolled in a double blind, randomized controlled trial. Antibiotic prophylaxis with penicillin or azithromycin was administered for 12 months. Rates of streptococcal infections and neuropsychiatric symptom exacerbations were compared between the study year and the baseline year prior to entry.*
Results: *Significant decreases in streptococcal infections during the study year were found with a mean of .1 (.3 SD) per subject, compared to the baseline year with 1.9 (1.2 SD) in the penicillin group and 2.4 (1.1 SD) in the azithromycin group [p<.01]. Significant decreases in neuropsychiatric exacerbations during the study year were also found with a mean of .5 (.5 SD) per subject in the penicillin group and .8 (.6 SD) in the azithromycin group, compared to the baseline year with 2.0 (.9 SD) in the penicillin group and 1.8 (.6 SD) in the azithromycin group [p<.01].*
Conclusions: *Penicillin and azithromycin prophylaxis were found to be effective in decreasing streptococcal infections and neuropsychiatric symptom exacerbations among children in the PANDAS subgroup.*

Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood

Susan J Perlmutter, Susan F Leitman, Marjorie A Garvey, Susan Hamburger, Elad Feldman, Henrietta L Leonard, Susan E Swedo

Overall 50% improvement with treatments for PANDAS
Snider et al., 2005 Biol Psychiatry 57(7):788-92

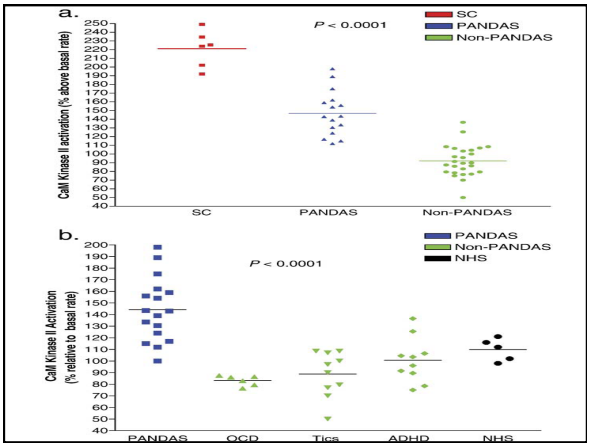
PANDAS – TREATMENT

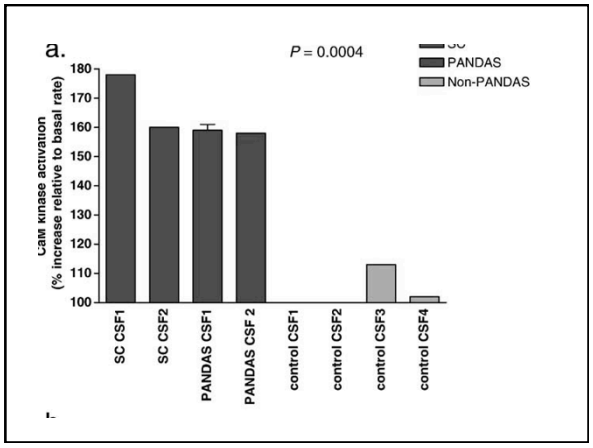
www.pandasnetwork.org

- Probiotics
- Xylitol
- Saccharomyces Boulardii/Alkalinization/Charcoal
- Antibiotics (Snider et al, *Biol Psychiatry*, 2005)
  - IM Bicillin (1.2 million units-perhaps monthly)
  - Penicillin, Omnicef, Zithromax
  - Antibiotic Prophylaxis with Penicillin or Zithromax
- Antimicrobial herbs (Berberine, Neem)
- Immune Modulators (March et al, *Arch Ped Adol Med*, 2004)
  - Oral immunoglobulins (IVIG in oral formulation; Schneider et al, 2006; Handen et al, 2009)
  - Transfer factor/colostrum
  - Mushroom extracts/plant sterols
  - Minocycline (NIH study at 1.4 mg/kg, max of 50 mg bid; teeth discoloration)
  - Actos (PPAR agonist inhibits NFKappaB induced inflammation, (Boris et al, *J Neuroinflam*, 2007))
  - Spironolactone (Aldosterone, potassium sparing diuretic inhibits TNF-alpha, (Bradstreet et al, *Med Hypoth*, 2006))
  - IVIG and plasmaphoresis (Snider LA, Swedo SE, *Mol Psych*, 2004)

Further Testing

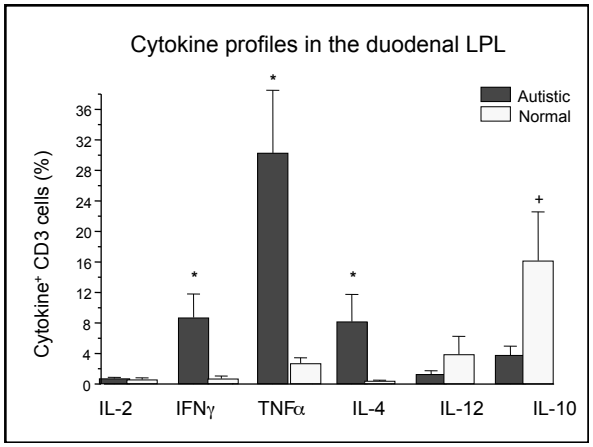
- **Selective IgA Testing**
  - If +, can exclude IgA from IVIG
  - Safely proceed without risk of anaphylaxis
- **CaM Kinase testing**
  - If + -> steroids
  - If positive response to steroids then more likely to respond well to IVIG (1 gm/kg over 2 days)
- **Sydenham's chorea (SC)**
  - Immune mediated cross-reactive, anti-strep Ab response against basal ganglia (Cunningham, *Clin Microbiol*, 2000)
- **PANDAS**
  - Ab mediated cell signaling
  - Strep Ab induce CaM kinase III activation in neuronal cells
    - (Kirvan et al, *J Neuroimm*, 2006)





INFLAMMATION

- **CSF**
  - Elevation of TNF-alpha in CSF (Chez 2007)
  - CSF and serum markers of inflammation in autism (Zimmerman 2005)
- **Blood**
  - Elevated levels of peripheral blood monocytes and neopterin (Sweeten 2003)
  - Elevated proinflammatory macrophage metabolites such as nitric oxide (Sweeten 2004)
  - Immune dysregulation leads to oxidative stress (Chauhan 2006)
  - Neuroimmodulation thru vagus nerve and nicotinic acetylcholine receptors (Pavlov, 2003)
  - Galantamine and nicotine effect microglial activation



INFLAMMATION:GASTROINTESTINAL

- Increased pro-inflammatory cytokines – LP, TNF alpha, IFN gamma, B cells and decreased IL 10 in GI mucosa (Ashwood, 2004, 2006)
- Crypt cell proliferation , IgG deposition, C1q (Torrente, 2002)
- Ulceration of the epithelium (Balzola, 2005)
- Proinflammatory response to dietary proteins (Jyonuchi, 2004)
- Reflux esophagitis, Chronic gastritis, Duodenitis (Horvath, 1999)
- Lymphocytic colitis, mucosal gamma delta cell density, basement membrane thickness increased, CD8(+), gut epithelial dysfunction (Furlano, 2004)
- Eosinophilia in association with gluten sensitivity (Ashwood 2003, 2004) with a decrease in eosinophilic infiltrated on biopsy on children on a gluten-free diet. (Ashwood 2003, 2006)

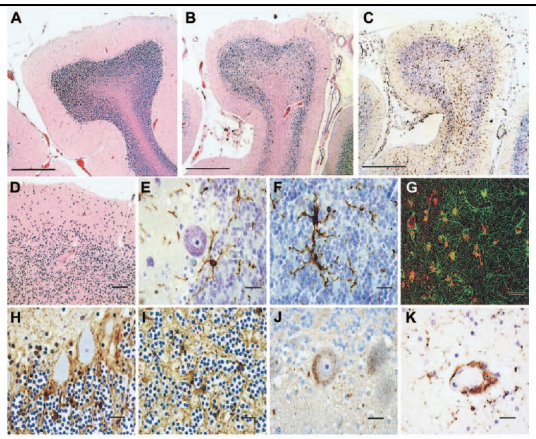
INFLAMMATION: BRAIN

- Elevated levels of urinary and blood neopterin (Messahei 1998, Sweeten 2001)
  - Biomakers of immune activation involving cellular immunity particularly related to T-cell activation of macrophages by IF-gamma
- Glial fibrillary acidic protein (GFAP) is a CSF marker for activation of microglial and astrocyte cells and is elevated in children with autism (Rosengren 1992)
- GFAP levels high in postmortem analysis of cerebellum in brains of autistic individuals (Laurence 2005)
- TH1 shifting in brains of autistics (Li 2009)
  - Elevated proinflammatory cytokines (TNF-a, IL-6, GM-CSF), TH1 cytokine (IFN-gamma) and chemokine (IL-8).
  - Th2 cytokines (IL-4, IL-5, IL-10) not elevated.
  - Increase innate and adaptive immune response thru the Th1 pathway, suggesting brain inflammation and autoimmunity.

Neuroglial Activation and Neuroinflammation in the Brain of Patients with Autism

Diana L. Vargas, MD,[1,2] Caterina Nascimbene, MD,[1–3] Chitra Krishnan, MHS[1] Andrew W. Zimmerman, MD,[1,4] and Carlos A. Pardo, MD[1,2,5]

- Autopsied brains of 11 autistic individuals, CSF analysis from live autistic children.
- Demonstrated an active neuroinflammatory process in the cereberal cortex, the white matter and notably the cerebellum associated with a patchy loss of purkinje cells
- Showed marked activation of microglia and astroglia
- Showed high levels of proinflammatory cytokines MCP-1 and TARC and the anti-inflammatory cytokine TGFB1, derived from neuroglia.
- CSF also showed marked increase in proinflammatory cytokines and growth factors.



Vargas Findings & Conclusions

- The purkinje cells in the cerebellum seem to be the largest target.
- The injury to the purkinje cells is ongoing suggesting an active, chronic process not a single developmental hit.
- Study showed marked activation of microglia and astroglia.
- There is chronic, sustained activation of the innate immune system in the brain without a secondary adaptive immune response (this is seen in other neurodegenerative disease such as AD, Parkinsons, ALS, HIV).
- Autism is a neuro-immune-inflammatory condition, caused by environmental factors in the presence of genetic susceptibility

IMMUNE DYSREGULATION

- Elevated IL-2 (Singh 1991)
- Elevated IL-12 and IF-gamma (Singh 1996)
- Elevated TNF-alpha, IL-1b and IL-6 (Jyonouchi 2001)
- Elevated MCP-1, TGF-beta1 in brain tissues and MCP-1, IL-6 in CSF (Vargas 2005)
- Elevated IL-13 and IF-gamma, decreased IL-10, abnormal cell mediated immunity (Molloy 2006)
- Decreased IL-26 (Enstrom 2008)
- Abnormal T-cell subsets, decreased NK cells, abnormal cytokines, Th2 skewing (Zimmerman, 1998; Gupta, 1996)

IMMUNE DYSREGULATION

- Over activity of the immune system, especially the innate system along with dysregulation of the adaptive system manifesting with inflammation in the blood, GI tract, and brain.
- Immune dysregulation leads to:
  - Chronic inflammation in brain and mucosal tissues (especially gut)
  - Autoimmune reactions
  - Frequent infections, especially of GI tract, sinuses, throat and ears.
  - Allergic and sensitivity reactions to food and common environmental allergens.

Immunological Findings in Autism, Panja 2005

HISTORY - IMMUNE

- Prenatal Exposures-vaccines, infections, meds, stress…
- History of Regression after Vaccines
- Eczema, Allergic Rhinitis, Asthma
- Chronic Tonsillitis, Adenoiditis, Otitis
- Seasonal Regression in Symptoms
- Frequent Viral Infections
  - Cold sores, Warts, Molluscum Contagiosum…
- Frequent Bacterial Infections
  - Otitis, Sinusitis, …
- Chronic Diarrhea
  - Gastroenteritis
- Food Sensitivities/Allergies
- Rare Fever or even rarely ill, better with fever
- Family History of Autoimmunity

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PHYSICAL

- Poor growth – height, weight
- Pale skin, spider veins, long eyelashes
- Skin rash, sand paper skin, eczema, warts, molluscum contagiosum
- Dilated pupils, lack of eye contact, divergent gaze, poor visual tracking
- Allergic shiners, Nasal crease, Mouth breathing
- Nails – spots, ridges, fungus
- Coated tongue or thrush
- Enlarged tonsils
- Lymphadenopathy
- Spleen tenderness
- Abdominal bloating

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OPTIONS

- Complete Blood Count
- Total Immunoglobulin Profile
  - (total IgE, IgM, IgA, IgA and IgG subclasses)
- T Lymphocyte Panel
- Natural killer cell function
- ASO titer, AntiDNase B antibody
- Autoantibody tests (e.g. myelin basic protein antibodies, brain endothelial antibodies)
- Secretory IgA in stool
- Urinary neopterin, biopterin levels
- IgE RAST or skin testing
- IgG ELISA testing for inhalants, food, and mold
- Celiac Panel
- CRP, Sed Rate, Platelet Count
- Fecal calprotectin or lysozyme
- Viral titers
- Vaccine titers
- C3D
- Strep pneumococcal serotypes

AVOID ENVIRONMENTAL TRIGGERS

- 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 retardant materials, use organic bedding.
- Use fluoride-free toothpaste. (Xylitol)
- Use stainless steel, ceramic, glass or cast iron cookware, avoid aluminum and non stick.
- Use an air purifier, especially in the bedroom.
- Avoid prolonged exposure to EMFs.
- No plastic furniture or flooring. (polyvinyl chloride).
- Use aluminum-free baking powder, deodorant. Do not cook in aluminum foil or drink from aluminum cans.
- Avoid use of herbicides or pesticides, on lawns, garden, home or on pets.
- Use natural shampoos, soaps, lotions, make-up, lipstick
- Avoid highly allergenic substances.(pollution, cigarette smoke, dust mites…

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AVOID DIETARY TRIGGERS

- Casein-free/Gluten-free/Soy-free Diet Trial for 3-6 months.
- Eliminate allergenic foods and rotate sensitive foods.
- Avoid sugar and refined starch, replace with whole grains
- Maximize antioxidants, phytonutrients, and flavinoids.
- Limit processed and preserved foods; organic is best.
- Avoid excitotoxins (ex. Caffeine, MSG, NutraSweet, red/yellow food dyes, nitrites, sulfites, glutamates, propionates, benzoates).
- Limit intake of phenolics (apples, grapes, strawberries…).
- Drink plenty of filtered water.
- Never microwave in plastics or Styrofoam, do not store food in plastic or foil, or cook on Teflon coated pans. Avoid plastic water bottles.
- Eliminate seafood.
- Add good fats (olive, coconut, flax). Avoid hydrogenated and trans fats and esterified fats.
- Buy hormone-free, antibiotic-free, organic meat and eggs.
- Add fermented foods (cabbage, coconut kefir, kombucha,…).

MIND THE GUT

- Probiotics
  - Probiotics induce the production of Treg cells
  - Treg cells are key to immune regulation
  - Hygiene Hypothesis: allows priming of Treg cells, decreased allergy and atopy
  - Probiotics upregulate IL-10
  - Prime the mucosal immune system to maintain SIgA and balance T helper cell response.
- Treat Pathogens
  - Clostridia
  - Yeast
  - Strep
  - Parasites
  - Virus
  - Mycoplasma, Borrellia…

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NUTRIENTS: IMMUNOREGULATION

- Zinc
- Selenium
- Vitamin A
- Vitamin B6
- Vitamin B12
- Vitamin C
- Vitamin D3- modulates Th1 response, decreases autoimmunity
- Vitamin E
- Folate

Maggini, S., et al., Br J Nutr, 2007. **98 Suppl 1**: p. S29-35.

ANTI-INFLAMMATORY AGENTS

- Herbs
  - Boswellia, Green Tea, Nettles, Slippery Elm, Cat's Claw, DGLicorice, Aloe, Ginger, Garlic, Echinacea, Ginseng, …
- Bioflavinoids (carotenoids, catechins)
  - Curcumin, Hesperidin, Pycnogenol, Quercetin and Rutin.
- Antioxidant rich fruits and veggies, and nutrients
  - Glutathione
- Omega 3 and Omega 6(DGLA) EFAs
- Cholinergic agonists
  - Phosphatidyl Choline, Phosphatidyl Serine,

Aggarwal, B.B. and K.B. Harikumar, *Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases.* Int J Biochem Cell Biol, 2009. **41**(1): p. 40-59.

ANTI-INFLAMMATORY AGENTS: MEDS

- Antihistamines
- Singulair (montelukast)
- Cromolyn sodium
- Allery desensitization (SQ, sublingual…)
- Sulfasalazine, Pentasa(mescalamine)
- Spironolactone (aldactone)
- Actos
- Minocycline
- Namenda
- Steroids
- NSAIDS
- Cholinergic agonists –Galantamine, Nicotine, Vagal Nerve Stimulation (VNS)
- Anti-Seizure Meds – Lamictal, Depakote
- Chelators

SPIRONOLACTONE

- **Potassium sparing diuretic**
- **Aldosterone antagonist**
- **Has antiinflammatory/immunomodulatory effects potentially through lowering of aldosterone (Ahokas 2003)**
- **Inhibits TNF-alpha, IF-gamma, IL-6, granulocyte macrophage colony stimulating factor and lymphotoxin in arthritis trials (including JRA)(Bendtzen 2003)**
- **Bradstreet, J.J., et al., Spironolactone might be a desirable immunologic and hormonal intervention in autism spectrum disorders. Med Hypotheses, 2007. 68(5): p. 979-87.**
- **Trial dose is 2-3 mg/kg/day**
- **Safest to follow electrolytes routinely (looking for elevated potassium) although risk is low if kidneys are normal**
- **Rare side effects may also include androgen-blocking effects (gynecomastia, breast tenderness)**

ACTOS

- **Peroxisome proliferator-activated receptor agonist**
- **Inhibits NFkappaB- induced inflammation (Wan 2008) Lowers IL-2, IL-6, IL-8 and MCP-1 expression in monocytes and lymphocytes (Zhang 2008)**
- **Modulate microglial and astroglial cell activation by toll-like receptors (Gurley 2008)**
- **Primary use is for Type II Diabetes. Off-label use with other autoimmune conditions in experimental trials.**
- **Can prevent MS relapses in experimental models (Peiris 2007)**
- **Decrease airway inflammation in asthma by upregulating IL-10 (Kim 2005)**
- **Controls Th1-type inflammation in Crohns(Schaefer 2005)**
- **May help socialization, motivation, mood**

- Protocol: oral or transdermal 3mg given at night between 9-11 pm

IMMUNE MODULATION

- IVIG
- Oral immunoglobulins
- Transfer factors
- Colostrum
- Low dose Naltrexone
- Lauricidin
- Alpha and beta glycans
- Plant Sterols
- Mushroom extracts
- IP-6
- Antivirals
- Hormones (secretin, oxytocin)
- HBOT

IVIG

- Intravenous immunoglobulin (human-derived)
- Low dose 400-500mg/kg every 4 weeks for true immunodeficiency
- Hi dose 750-1000mg/kg every 4 weeks for autoimmune, such as PANDAS
- Several small studies have been done in autism with mixed results (Gupta 1996, Pliopys 1998, Delguidice-Asch 1999, Boris 2006)
- Expensive, invasive and hard to get insurance coverage
- Contraindication: low IgA
- Side effects: anaphylaxis, headache, fever

ANTIVIRALS

- **Valtrex(valacyclovir)**
  - Herpes family (HSV1, HSV2, Varicella, EBV, CMV, HHV6)
  - Affect adenosine pathways
  - Not effective for RNA viruses (like measles, rubella)
  - 3 month trial of 250mg bid/tid
- **Amantadine**
  - Antiviral for influenza
  - Pro- dopaminergic
  - Effects NMDA receptor
  - Has anticholinergic side effects

Effects of HBOT on inflammatory markers in autism

Marker	*Autism Finding*	*HBOT Effect*
TNF-α	↑ [Jyonouchi, 2001; Ashwood, 2004]	↓ [Yang, 2006; Weisz, 1997; Benson, 2003; Yang, 2001; Shiratsuch[1], 2005]
IL-1β	↑ [Jyonouchi, 2001]	↓ [Yang, 2006; Benson, 2003]
IL-6	↓ [Jyonouchi, 2001; Vargas, 2005]	↑ [Weisz, 1997]
IL-10	↑ [Ashwood, 2004]	↓ [Buras, 2006]
IFN-γ	↑ [Ashwood, 2004]	↓ [Granowitz[2], 2002]
Neuroinflammation	↑ [Vargas; Pardo, 2005]	↓ [Vlodavsky, 2006]

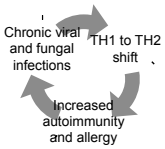
Effects of HBOT on immune dysfunction in autism

Marker	*Autism Finding*	*HBOT Effect*
IL-10	↓ [Ashwood and Anthony, 2004]	↑ [Buras, 2006]
HSP-90	↓ (due to increased antibodies to HSP-90) [Evers, 2002]	↑ [Thom, 2002]
Lymphocytic activity	↓ [Stubbs, 1977]	↑ [Lee, 1993]
T-helper cells	↓ [Warren, 1986]	↑ [Nyland, 1989]
Serum IgA	↓ [Gupta, 1996]	↑ [Nyland, 1989]
Serum IgE	↑ [Lucarelli, 1995; Gupta, 1996]	↓ [Olszanski, 1992]

HBOT

- *Hyperbaric treatment for children with autism: a multicenter, randomized, double-blind, controlled trial.* (Rossignol et al, BMC Pediatr, 2009, 9(1): p. 21).
  - 62 children, 6 sites, ages 2-7 yrs old
  - "soft" chambers, 1.3 atm, concentrated air (24% oxygen) vs. room air (21% oxygen), slightly pressurized (1.03 atm), one hour at pressure, twice a day, 5 days per week for total of 40 dives.
  - Outcome measures: CGI, ABC and ATEC
  - Found statistically significant improvements in overall functioning, receptive language, social interaction, eye contact and sensory/cognitive awareness.

Immune Dysregulation



Some Guiding Principles

What does each child need to:

- Get
- Get rid of
- Treatment pyramid
  - Dietary interventions
  - Correct nutritional deficiencies
  - Treat gastrointestinal problems
  - Treat immune issues