**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 on their surface. Through interactions 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 effective T cells upon re-exposure to their cognate antigen, thus providing the immune system with “memory” against subsequent infections. Memory T cells contain 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** (also known as suppressor T cells). These are crucial for the maintenance of immunological tolerance. Their main role is to shut down T cell-mediated immunity toward the end of an immune reaction and to suppress autoimmune reactions 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 lethal autoimmune diseases.

- **Natural Killer T cells** - Bridge the adaptive immune system with the innate immune system. NKT cells recognize glycolipid antigens presented by a molecule called CD1d, rather than HLA. 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

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**THE CELLULAR IMMUNE SYSTEM**

> Helper T cells - CD4+ T cells activate B cells and macrophages and present antigens to T cells.

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**GENETIC SUSCEPTIBILITY - HLA GENES**

- Human leukocyte antigen (HLA) genes play a critical role in the development of autoimmune diseases.

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Dr Nancy O’Hara

**Immunological Disease & Autism (PANDAS)**

**Nancy O’Hara, MD**

www.ihealthnow.org

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**Immune and Inflammatory Dysfunction in Autism**

August, 2011

Sydney, Australia

MINDD

Nancy O’Hara, M.D.

**THE CELLULAR IMMUNE SYSTEM**

> Helper T cells - CD4+ T cells activate B cells and macrophages and present antigens to T cells.

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**GENETIC SUSCEPTIBILITY - HLA GENES**

- Human leukocyte antigen (HLA) genes play a critical role in the development of autoimmune diseases.
Developmental Immunotoxicology (DIT)

Adverse effects from the environment, nutrition, maternal health, infections and radiation, and genetics on the development of the immune system. Programming results in infants during critical periods of development that have long-term effects, pregnancy-based experiences determine the health of the baby.

Fetal Origin 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.


Ø Th1/Th2 skewed immune system
Ø Deficiency of T regulatory cells
Ø Dysregulation of inflammatory cells
Ø Hyperinflammation
Ø Damage to a variety of systems and tissue
Ø Impaired maturation of dendritic cells
Ø Immunosuppression
Ø Autoimmunity
Ø 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

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

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. 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.

IMMUNE DEFICIENCY

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

All frequently sick kids deserve an evaluation for immunodeficiency.

DEVELOPMENTAL IMMUNOTOXICOLOGY EFFECTS

Ø Th1/Th2 skewed immune system
Ø Deficiency of T regulatory cells
Ø Dysregulation of inflammatory cells
Ø Hyperinflammation
Ø Damage to a variety of systems and tissue
Ø Impaired maturation of dendritic cells
Ø Immunosuppression
Ø Autoimmunity

IMMUNOPATHOLOGY

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

HYPERSENSITIVITY/ALLERGY

Ø High IgE (atopy)
  - Measured by RAST or skin testing
  - In neurotypical kids untreated allergies can cause poor memory, concentration, and sleep.
Ø 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 (Crittenden 2006)
  - Increases in IgG2 and IgG4 subclasses (Croonenberghs 2006, Enstrom 2008)
  - Hyperimmune response to measles vaccine antigen (Singh 2003)
Ø A history of allergies in mom during pregnancy increases the risk of autism over 2-fold (Croen, 2008)
Ø Children with autism have more food allergies than controls (Lucarelli, 1996)
Immune and Inflammatory Dysfunction in ASD

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

Autoantibodies to Self and Brain

Myelin basic protein
Serotonin receptors
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)

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

Swedo et al, Clini Pediatr, 2004

Overall 50% improvement with treatments for PANDAS

Snider et al., 2005  Biol Psychiatry 57(7):788-92

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

Stricker-Pecora, Susan Fosher, Majid Afnan, Susan Hamburger, Stephanie, and Leonard

Overall 50% improvement with treatments for PANDAS
PANDAS – TREATMENT

www.pandasnetwork.org

Ø Probiotics
Ø Kyolic
Ø Salubrion Mycena Boudierii/Alkalization/Charcoal

Ø Antibiotics

Ø Ativan (1.2 mg orally administered monthly)
Ø Penicillin, Dimenhydrinate

Ø Antimicrobial Folliculitis (Barbae, Meeth)

Ø Oral mucosal immunoglobulin (IVIG in oral formulation: Bahrkeidis et al, 2006)
Ø Imunization/Modulation (March et al, Arch Ped Adol Med, 2004)

Ø Oral immunoglobulins (IVIG in oral formulation: Bahrkeidis et al, 2006)
Ø Transfer factor/alkalinization/charcoal

Ø Antibiotics (Snider et al, Biol Psychiatry, 2005)

• IM Bicillin (1.2 million units per month—perhaps monthly)
• Penicillin, Omnicef, Zithromax
• Antibiotic prophylaxis with Penicillin or Zithromax

Ø Antimicrobial Herbs (Berberine, Neem)

Ø Antiinflammatory herbs (Mushroom extracts, plant sterols)

Ø Minocycline (NIH study at 1.4 mg/kg, max of 50 mg bid; teeth discoloration)
• Actos (PPAR agonist inhibits NF kappa B induced inflammation; Boris et al, J Neuroinflamm., 2007)
• Spironolactone (Aldosterone, potassium sparing diuretic inhibits TNF-alpha; Bradstreet et al, Med Hypothesis, 2006)

Ø IVIG and plasmapheresis (Snider LA, Swedo SE, Mol Psych, 2004)

Further Testing

Ø Selective IgA Testing

• If +, can exclude IgA from IVIG
• Safety proceed without risk of anaphylaxis

Ø CaM Kinase testing

• If +, steroids
• If positive response to steroids than more likely to respond well to IVIG (1 gm/kg over 2 days)

Ø Sydenham’s chorea (SC)

• Immune mediated cross-reactive anti-strep Ab response against basal ganglia (Cunningham, Clin Microbiol, 2000)

Ø PANDAS

• Ab mediated cell signaling
• Strep Ab induce CaM kinase III activation in neuronal cells
  • (Kirvan et al, J Neuroinflamm., 2007)

INFLAMMATION

Ø CBF

• Elevated TNF-alpha in CBF (Chez 2007)
• CBF and serum markers of inflammation in autism (Zimmerman 2005)

Ø 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 (Chashou 2006)
• Neuronal modulation by vago sympathetic nervous system receptors (Pavlov, 2003)
• Galantamine and nicotine effect microglial activation

Cytokine profiles in the duodenal LPL

Autistic
Normal

www.mindd.org

Mind Foundation
Healthy cells for Life

International Forum on Children 2011
13-14 August 2011
Australia Turf Club
Randwick, Sydney

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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 (Bablotta, 2005)

Proinflammatory response to dietary proteins (Iyomichi, 2004)

Reflex esophagitis, Chronic gastritis, Duodenitis (Horvath, 1999)

Lymphocytic colitis, mucosal gamma delta cell density, basement membrane thickness increased, CD8(+) gut epithelial dysfunction (Puliano, 2004)


Elevated levels of urinary and blood neopterin (Messahei 1998, Sweeten 2001)

Biomarkers 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, GCSF), 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.

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 diseases such as AD, Parkinsons, ALS, HIV).

Autopsy brains of 11 autistic individuals, CSF analysis from live autistic children.

Demonstrated an active neuroinflammatory process in the cerebral 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 TGF-beta, derived from neuroglia.

CSF also showed marked increase in proinflammatory cytokines and growth factors.

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 diseases such as AD, Parkinsons, ALS, HIV).

Autism is a neuro-immune-inflammatory condition, caused by environmental factors in the presence of genetic susceptibility.
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**

- Prenatal Exposures – vaccines, infections, meds, stress…
- History of Regression after Vaccines
- Eczema, Allergic Rhinitis, Asthma
- Chronic Tonsillitis, Adenoiditis, Otitis
- Seasonal Regression in Symptoms
  - Cold sores, Warts, Molluscum Contagiosum ...
- Frequent Bacterial Infections
  - Otitis, Sinusitis, ...
- Chronic Diarrhea

**Options**
- Complete Blood Count
- Total Immunoglobulin Profile
  - (total IgE, IgM, 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
- IgG ELISA testing for inhalants, food, and mold
- Celiac Panel
- CRP, Sed Rate, Platelet Count
- Fecal calprotectin or lysozyme
- Vaccine titers
- C3D

**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...)

**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 flavonoids.
- Limit processed and preserved foods; organic is best.
- Avoid excitotoxins (ex. Caffeine, MSG, NutraSweet, red/yellow food dyes, nitrates, sodium glutamate, artificial flavors and preservatives).
- 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. Avoid plastic water bottles.
- Eliminate sea food.
- Add whole foods (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 asthma
  - 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, Borrelia...

NUTRIENTS: IMMUNOREGULATION

- Zinc
- Selenium
- Vitamin A
- Vitamin B16
- Vitamin B12
- Vitamin C
- Vitamin D3 - modulates Th1 response, decreases autoimmunity
- Vitamin E
- Folate


ANTI-INFLAMMATORY AGENTS

- Herbs
  - Boswellia, Green Tea, Nettles, Slippery Elm, Cal’s Claw,
  - St John’s Wort, Goldenseal, Echinacea, Ginseng, Echinacea, Ginger, Garlic, Echinacea, Ginseng,
- Bioflavonoids (catechins, kaempferol, quercetin, rutin).
- Antioxidant rich fruits and vegetables, and nutrients
  - Glutathione

ANTI-INFLAMMATORY AGENTS: MEDS

- Antihistamines
  - Singulair (montelukast)
  - Cromolyn sodium
  - Allergy desensitization (SQ, sublingual…)
  - Sulfasalazine, Pentasa (mesalamine)
  - Spironolactone (aldactone)
  - Actos
  - Minocycline
  - Namenda
  - Steroids
  - NSAIDS
  - Antihistamines – Claritin, Singulair, Zyrtec
  - Anti-Seizure Meds – Lamictal, Depakote
  - Cholinergic agonists
  - Phosphatidyl Choline, Phosphatidyl Serine,
- Potassium sparing diuretic
- Aldosterone antagonist
- Has anti-inflammatory/immunomodulatory effects potentially through lowering of aldosterone (Ahokas 2003)
- Inhibits TNF-alpha, IL-1 beta, granulocyte macrophage colony stimulating factor and lymphotixin in arthritis trials (including RIA) (Sandheit 2000)
- Trial dose is 2-3 mg/kg/day
- May help socialization, motivation, mood
  - Protocol: oral or transdermal 3mg given at night between 9-11 pm

SPIRONOLACTONE

- Potassium sparing diuretic
- Aldosterone antagonist
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- Inhibits TNF-alpha, IL-1 beta, granulocyte macrophage colony stimulating factor and lymphotxin in arthritis trials (including RIA) (Sandheit, 2000)
- Trial dose is 2-3 mg/kg/day
- May help socialization, motivation, mood
  - Protocol: oral or transdermal 3mg given at night between 9-11 pm

ACTOS

- Peroxisome proliferator-activated receptor agonist
- Inhibits NFKB induced inflammation (Wan, 2008)
- Inhibits IL-8, IL-6, IL-8 and MCP-1 expression in monocytes and lymphocytes (Shang, 2008)
- Modulates microglial and astroglial cell activation by toll-like receptors (Gurtley, 2008)
- Lower IL-2, IL-6, IL-8 and MCP-1 expression in monocytes and lymphocytes (Shang, 2008)
- Modulates microglial and astroglial cell activation by toll-like receptors (Gurtley, 2008)
- Controls Th1 type inflammation in Crohn’s disease (Schafer, 2008)
- May help socialization, motivation, mood
**Immune and Inflammatory Dysfunction in ASD**

- IVIG
- Oral immunoglobulins
- Transfer factors
- Colostrum
- Low dose Naltrexone
- Lactoferin
- 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
  - Pre-depaminergic
  - Affect NMDA receptor
  - Has anticholinergic side effects

**Markers of HBOT on immune dysfunction in autism**

<table>
<thead>
<tr>
<th>Marker</th>
<th>Autism Finding</th>
<th>HBOT Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-10</td>
<td>[Ashwood and Anthony, 2004]</td>
<td>[Buras, 2006]</td>
</tr>
<tr>
<td>HSP-90</td>
<td>[due to increased antibodies to HSP-90]</td>
<td>[Thom, 2002]</td>
</tr>
<tr>
<td>Lymphocytic activity</td>
<td>[Shibli, 1977]</td>
<td>[Lee, 1993]</td>
</tr>
<tr>
<td>T-helper cells</td>
<td>[Warren, 1986]</td>
<td>[Nyland, 1989]</td>
</tr>
<tr>
<td>Serum IgA</td>
<td>[Gupta, 1996]</td>
<td>[Nyland, 1989]</td>
</tr>
<tr>
<td>Serum IgE</td>
<td>[Lucarelli, 1995; Gupta, 1996]</td>
<td>[Olszanski, 1992]</td>
</tr>
</tbody>
</table>

**Effects of HBOT on inflammatory markers in autism**

<table>
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<tr>
<th>Marker</th>
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<th>HBOT Effect</th>
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<tr>
<td>TNF-α</td>
<td>[Yonouchi, 2004; Ashwood, 2004]</td>
<td>[Yang, 2006; Weisz, 2006; Benson, 2003; Yang, 2001; Shiratsuchi, 2005]</td>
</tr>
<tr>
<td>IL-1β</td>
<td>[Yonouchi, 2001]</td>
<td>[Yang, 2006; Benson, 2003]</td>
</tr>
<tr>
<td>IL-6</td>
<td>[Yonouchi, 2004; Vargas, 2005]</td>
<td>[Weisz, 1997]</td>
</tr>
<tr>
<td>IL-10</td>
<td>[Ashwood, 2004]</td>
<td>[Buras, 2006]</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>[Ashwood, 2004]</td>
<td>[Granowitz, 2002]</td>
</tr>
<tr>
<td>Neuroinflammation</td>
<td>[Vargas, Purba, 2005]</td>
<td>[Vlodavsky, 2006]</td>
</tr>
</tbody>
</table>

**HBOT**

- 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

- Chronic viral and fungal infections
- TH1 to TH2 shift
- Increased autoimmunity and allergy

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