Phospholipase A2
Inflammatory Trigger in Various Autoimmune and Neurological Disorders
Phospholipase A2 (PLA2)

- PLA2 is not only produced locally, but can be transported throughout the blood stream causing damage tissue damage elsewhere.

- PLA2 elevations are implicated in a wide variety of disorders:
  - Allergies, asthma, autoimmune disorders such as Rheumatoid Arthritis.
  - Autism-Spectrum Disorders
  - Brain trauma, i.e. concussion
  - Cancer
  - Cardiovascular disease
  - Chronic infections, i.e. clostridia, candida, Lyme
  - Inflammatory Bowel Disease, i.e. Chron’s
  - Neurodegenerative disorders, i.e. multiple sclerosis, Alzheimer’s
  - Mental health – bipolar, depression, schizophrenia
Phospholipase A2

Test | Units Per Creatinine | Patient Value
--- | --- | ---
Phospholipase A2 | 1.500 | Elevated

Secreted Phospholipase A2 (sPLA2) has been implicated in many diseases because of its role in inflammation and host defense. sPLA2 is found in many mammalian tissues as well as insect and snake venom (Nicolas et al, 1997). sPLA2 catalyses the release of arachidonic acid and is involved in the production of prostaglandins for inflammation (Sawada et al, 1999). sPLA2 is present in connection with multiple diseases including rheumatoid arthritis, sepsis, psoriasis, pancreatitis, cancer, Crohn’s disease, and multiple sclerosis (Furakoshi et al, 1993; Green et al, 1991; Lilja et al, 1995; Mourier et al, 2008; Pinto et al, 2003;
**Phospholipase A2**

<table>
<thead>
<tr>
<th>Test</th>
<th>Patient Value PLA2 Activity / Creatinine</th>
<th>Mean</th>
<th>Normal</th>
<th>Elevated</th>
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<tr>
<td>Phospholipase A2</td>
<td>1.361</td>
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<td>0.5</td>
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- Requisition #:  
- Patient Name:  
- Patient Age: 25  
- Sex: F  
- Physician Name: NO PHYSICIAN  
- Date of Collection: 4/4/2015  
- Time of Collection: Not Given  
- Print Date: 4/6/2015
**Phospholipase A2 (PLA2)**

- Phospholipases are a group of enzymes that catalyze (release) fatty acids leading to elevations of inflammatory mediators called Eicosanoids (thromboxane, leukotriene, prostaglandins).
- A2 phospholipase is named because of its specific function at the second functional group on a phospholipid molecule.
Phospholipids

• Building blocks of the cell membrane
• Provide the barrier between the inside and outside of the cell.
• Helps maintain the cell membrane with regards to ion channels, receptors, transport proteins, and enzymes which all function to maintain normal cellular function.
Phospholipase A2

Phospholipids (lecithins)

CDP-Choline
Vitamin E
Omega-3

Lysolecithin

Free Fatty Acid
Including Arachidonic Acid

Prostaglandins, Leukotrienes, and other Eicosanoids

Arachidonic Acid

Fatty Acid Removed by PLA2
Phospholipase A2 (PLA2)

- PLA2 is present in human tissue
- When activated by infection (ex: bacteria, i.e. clostridia, candida) PLA2 releases a cascade of chemical events that helps to damage the cell membranes of invading pathogens:
  - Damage cell membranes
  - Denatures proteins
  - Disrupts cellular function
- The problem is surrounding tissue can become damaged as well (collateral damage).
- Bee stings and poisonous snake venom contain PLA2
In the development of Alzheimer's disease, the abnormal PLA₂ levels appear to be related to oxidative signaling pathways involving NADPH oxidase and production of ROS species that lead to impairment and destruction of neurons and inflammation of glial cells.” (Bill Shaw, Ph.D)

Direct and Indirect activation of microglia leads to cell damage.
Neurobiol Dis. 1996; Cytosolic phospholipase A2 (cPLA2) immunoreactivity is elevated in Alzheimer's disease brain. Stephenson DT, et. al.

- Phospholipase A2 (PLA2) is the key enzyme that initiates the arachidonic acid cascade, which leads to the generation of multiple eicosanoid products. Many of these products are believed to play an important role in the inflammatory process. Activation of PLA2 is observed under pathological conditions where inflammation is present. Cytosolic PLA2 (cPLA2) is activated by very low levels of calcium and is thought to control receptor-mediated eicosanoid production and to participate in intracellular signal transduction processes. In view of the presence of numerous inflammatory mediators and acute phase proteins in the Alzheimer's disease (AD) brain, localization of cPLA2 in AD brain was evaluated and compared to that observed in nonneurologically diseased controls. In this study, a monoclonal antibody raised against cPLA2 was used to immunostain tissue sections of human cerebral cortex. Five AD cases and six neurologically normal cases were evaluated in the occipital cortex and the cerebellum. Two of the AD cases were also examined in other cortical regions. Granular-like staining with anti-cPLA2 was found to be associated with astrocytes in the cortex of both control and AD cases. Colocalization with GFAP confirmed that cPLA2 immunoreactivity is associated almost exclusively with protoplasmic astrocytes. Staining was abolished when sections were labeled with antibody that had been preadsorbed with purified cPLA2. In AD brain, cPLA2 immunoreactive astrocytes were greater in number and more intensely stained than those in control cases. cPLA2 immunoreactivity was virtually absent in the cerebellium of AD and control cases, despite the presence in this region of diffuse amyloid in two AD cases and amyloid angiopathy in a third case. In the cortex, cPLA2 immunoreactive astrocytes were detected in regions that contained numerous A beta deposits.

The finding of elevated levels of cPLA2 immunoreactivity in AD brain supports the hypothesis that there is an active inflammatory process occurring in AD.

“Patients with both regressive autism and classical autism/Asperger's syndrome (ASP) had significantly higher concentrations of RBC type IV phospholipase A2 compared to controls. However, patients with autism/ASP, who had taken EPA supplements, had significantly reduced PLA2 concentrations compared to unsupplemented patients with classical autism or ASD.”
Lipid Signaling Pathology in Autism

Comprehensive Guide to Autism

• 2014, pp. 1259-1283

• Lipid Signaling in the Pathology of Autism Spectrum Disorders
• Restores brain levels of Phosphatidylserine, Phosphatidylcholine and Sphingomyelin – *all important for function of neurons and the myelin sheath.*

• Increases brain levels of neurotransmitters like acetylcholine (for memory), dopamine (for fine motor control and mood), and norepinephrine (for mental energy).
Cytidine 5-diphospho-choline (CDP-choline) – *precursor to phospholipid production*

- 500-4000 mg per day dosing range in patients with a variety of disorders such as Parkinson's disease, memory disorders, vascular cognitive impairment & dementia, senile dementia, schizophrenia, Alzheimer's disease, head trauma, and ischemic stroke.

- A trial in patients with Alzheimer's disease indicated that citicoline (1,000 mg/day) is well tolerated and improves cognitive performance, cerebral blood perfusion, and the brain bioelectrical activity pattern.

- **In autism, start with lower dosage, i.e. 250mg daily (range – 250mg to 750mg daily).**

- No side effects were noticed at the lower doses of CDP-choline and only some mild gastrointestinal symptoms were found using higher doses. No abnormal blood chemistry or hematology values were found after the use of CDP-choline.

www.nbnus.com

Strong Inhibitor of PLA2
Dedicated to investigating the diagnosis and treatment of medical issues related to neurological inflammation, immune dysfunction and microglia activation in autism.
Neuroinflammation

Neuroinflammation

Glia

COX-1
COX-2

COX-1
COX-2

Myeloid cells,
lymphocytes

Growth
factors,
cytokines

NSAIDs

Neurodegeneration

γ-secretase

Aβ
Daniel’s Story
(as discussed from the SCIA organization)

Before Autism

With Autism

Autism Free

Integrative Medicine Academy
Daniel’s Story

• Born 2004 – neurotypical development (attentive, responsive to name, normal eye contact) until 18 months.

• Words began approximately 1 year of age

• At 18 months:
  • Stopped responding to name
  • Deterioration in health began
  • Developed vitiligo (autoimmune skin disorder where pigment is changed or lost via pigment cell damage).
Daniel’s Story

• At 30 months his autism became severe following a ‘viral’ infection.

• At 4 years of age developed another ‘viral’ infection with persistent high fever.

• Began to administer Ibuprofen – noticed better awareness, was calmer, and saying more words.

• SPECT scan performed – indicated BRAIN INFLAMMATION was likely contributing to autistic symptoms (at least suspected).
NOT actual scans of Daniel
Daniel’s Story

• Parents began research into brain inflammation and discovered the connection to microglia activity.

• Realized that previous use of Ibuprofen helped with Daniel’s awareness, calmness, etc.

• Began treatment course for chronic viral and fungal infections, as well as administering Ibuprofen, along with high bacteria count probiotics to offset any potential gastrointestinal (GI) side effects of the medication

• Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are notorious for causing GI distress.
Daniel’s Story

• After 3 years of anti-inflammatory and immune therapy (i.e. low dose naltrexone) Daniel progressed off the autism-spectrum to a neurotypical healthy kid.
  • Daniel no longer needs medication to stay healthy
  • Vitiligo went away, along with environmental allergies, recurrent yeast, bacterial, and viral infections.
  • Graduated from speech therapy (had severe speech impairment).
  • Currently is physically active, plays sports, very social, does well in school, and is a popular with other children.
SCIA Treatment Protocol - Overview

For more specifics please refer to the information at SCIA website – www.stopcallingitaudism.org:

• Acquire lab testing as outlined in the next slide before implementing therapy.

• Every 6 weeks, while on therapy, repeat blood chemistry (metabolic panel) and blood count (aka. CBC w/Differential).

• Every 6 months while on therapy repeat comprehensive immune panel.
# SCIA Recommended Labs

<table>
<thead>
<tr>
<th>Quest Diagnostics Lab Test Codes</th>
<th>LabCorp Lab Test Codes</th>
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</thead>
<tbody>
<tr>
<td>6399 Complete Blood Count (CBC)</td>
<td>005009 CBC With Differential</td>
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<tr>
<td>10231 Comprehensive Metabolic Panel</td>
<td>322000 Comprehensive Metabolic Panel</td>
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<tr>
<td>7197 Immune Panel (Lymphocyte Subset Panel 1)</td>
<td>505370 T- and B-Lymphocyte/NK Cell Profile</td>
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<tr>
<td>34184 Natural Killer Cell Functional Assay</td>
<td>910032 Natural Killer Cell Functional Assay</td>
</tr>
<tr>
<td>15435 Immune Cell Function (Cell Mediated Immunity Assay)</td>
<td></td>
</tr>
<tr>
<td>809 Sedimentation Rate (ESR)</td>
<td>005215 Sedimentation Rate-Westergren</td>
</tr>
<tr>
<td>4420 C-Reactive Protein, Quantitative</td>
<td>006627 C-Reactive Protein, Quantitative</td>
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<tr>
<td>7083,542 Quantitative Immunoglobulins (IGG, IGA, IGM, IGE)</td>
<td>002295 Immunoglobulins A/E/G/M, Serum</td>
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<td>30666 Herpes Simplex Virus Types 1 &amp; 2, IgG</td>
<td>164905 Herpes Simplex Virus Types 1 &amp; 2, IgG</td>
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<td>34282 Human Herpesvirus 6 Antibodies, IgG</td>
<td>161075 Human Herpesvirus 6 Antibodies, IgG</td>
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<td>403 Cytomegalovirus (CMV) Antibodies, IgG</td>
<td>006494 Cytomegalovirus (CMV) Antibodies, IgG</td>
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<td>6421 Epstein-Barr Virus Antibody Panel</td>
<td>096230 Epstein-Barr Virus (EBV), IgG</td>
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<td>964 Measles Antibodies, IgG</td>
<td>096560 Rubella Antibodies, IgG</td>
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<td>8624 Mumps Antibodies, IgG</td>
<td>096552 Mumps Antibodies, IgG</td>
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<tr>
<td>10268 Rubella Antibodies, IgG</td>
<td>006197 Rubella Antibodies, IgG</td>
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<tr>
<td>265 Anti-Streptolysin O Antibody (ASO)</td>
<td>006031 Antistreptolysin O (ASO) Antibodies</td>
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</table>

The laboratory companies above are used to help doctors identify the lab tests from the most common reference labs – Lab Corp and Quest. Physicians or patients may choose a different lab company that identifies the various markers too. Test numbers may change without notice.
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) - *Ibuprofen*

- NSAIDs and probiotics help to reduce nitric oxide and inhibit microglia activation.
- Ibuprofen or Dexibuprofen (*general form of Ibuprofen overseas*) is the NSAID of choice for SCIA protocol.
- **Dosages are prescription strength** (must be obtained from a physician).

*DO NOT* self-administer over-the-counter NSAIDs at prescription dosage to child without the assistance of a physician (*SCIA statement*).
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) – Ibuprofen

- Dosage recommendation for Ibuprofen is 20-22mg/kg 3 times per day strictly given with meals.
- Dosage recommendation for Dexibuprofen is 12-17 mg/kg 3 times per day strictly given with meals.
- The NSAIDs are administered for the first 10 days of each month.
- If child cannot swallow pills it can be compounded to 300mg/5ml.
- Ibuprofen Dosing Example: 40lbs child = 18kg (40 ÷ 2.2 = 18 kilograms). Take 18 kg x 20 - 22 = 360mg – 400mg dose given 3 times daily = total 24 hour dose of 1080mg to 1200mg.
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) – Ibuprofen

• Generally, Ibuprofen is dosed (approximately) 7.5mg to 10mg/kg every 6 to 8 hours for general purposes of fever and pain. The dosage of Ibuprofen recommended in the SCIA program felt to be more beneficial for inhibiting microglial activation is slightly over twice the amount over the over-the-counter dosage.

• **MUST take NSAIDs with food.** Ibuprofen can cause stomach irritation, ulceration, abdominal pain, nausea, itching skin, vomiting, unusual bleeding or bruising, heartburn and others.

  **MUST have repeat blood chemistry (metabolic panel) looking at electrolytes, kidney and liver function, as well as complete blood count every 6 weeks if doing high dose Ibuprofen.**

• If child on seizure medication need to check with prescribing physician or pharmacist for any potential interactions with NSAID therapy.
NSAIDs and Microglia Activation

What does scientific evidence show?

NSAIDs use in humans has been associated with decreased numbers of activated microglia (Bendlin BB, Newman LM, Ries ML, Puglielli L, Carlsson CM, Sager MA, Rowley HA, Gallagher CL, Willette AA, Alexander AL, Asthana S, Johnson SC. NSAIDs may protect against age-related brain atrophy. Front Aging Neurosci. 2010, 3;2. pii: 35.)

Ibuprofen (in vitro) has been shown to modulate production of Nitric Oxide (Vandivier, et. al – Journal of Pharmacology, 1999, vol. 289, no 3.)

Sustained NSAID use appears to decrease the prevalence of Alzheimer’s Disease, and lessens its severity, and slows progression of disease. Alzheimer’s is associated with microglia activation.
Probiotics work to colonize the gastrointestinal tract with beneficial bacteria.

- They adhere to mucosal lining of the intestines and promote a barrier to opportunistic bacteria, yeast, and various toxins.
- High dose probiotics have been associated with decreasing inflammation in the intestines and prevent GI side effects from NSAIDs.

- **Look to have 200 billion organism count given twice daily on empty stomach before prescription dose NSAIDs are implemented.**

- Tolerance to high dose probiotics can take some time, i.e. one week. Sometime high dose probiotics will cause loose stools.
Science Behind Probiotics and GI Tract


Ibuprofen Trial

• In many cases doing a trial of over-the-counter (OTC) Ibuprofen for 10 days works well to see if further testing and intervention is worthwhile.

• Administer Ibuprofen (Motrin) at an OTC dose three times daily for 10 days:
  • Have at least a moderate dose probiotic in place (20 billion organisms twice daily).
  • MUST take Ibuprofen with food
  • Have parents monitor positive changes such as improved behavior, less hyperactivity, better eye contact, increased language, etc.
  • Stop the Ibuprofen and contact doctor immediately if problems such as vomiting, bloody stools, and aberrant behaviors occur.
Ibuprofen Trial

• If clinical improvements are seen – improved behavior, less hyperactivity, better eye contact, increased language, etc. – then:
  • *Run blood work for liver function, kidney function, and rest of SCIA blood testing suggestions, and consider proceeding with higher dose cyclical administrations of Ibuprofen over the next 2 to 3 months or longer.*
  • *If none or only mild improvements are seen, you can double the dose of the Ibuprofen for an additional 10 days (after at least a 2 week break) to see if positive benefits can be recognized.*
Thank You

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