Neuroinflammation: Can this Potential Cause of Cognitive Decline be Reversed in Individuals with FASD?

Rod Densmore, M.D., Father of a young adult who has FAS

Concurrent Session D6
Fifth National Biennial Conference on Adolescents and Adults with Fetal Alcohol Spectrum Disorder: *It's a Matter of Justice*

Friday, April 20th 2012
Welcome to my world!

• Thanks for your interest

Biases:

• **Practical/real tools:** Dad, Primary Care Clinician (not researcher), author of DVD series/book: *FASD Relationships*, husband of Shannon, OT with Sensory Processing Training

• **Advocacy:** Member: BC Provincial Family Council for Child & Youth Mental Health, Past Member: BC Provincial FASD Action Fund Advisory Committee
Don and Val Massey (2009) ...cognitive decline in young adults with FASD?

- In a subset of patients with FASD repeatedly tested over time...newly-emerging concept of (premature) neurocognitive decline

Don says that he first coined the term "developmental dementia" about 15 years ago to describe the young adults he and his wife Val were assessing. They developed their theory of (premature) cognitive decline to explain their observations of progressive deterioration of brain function in some of their patients.

Rod’s idea:

**Excessive Neural Inflammation?**

Ref: Kendall-Tacket K. 2010.
Neuroinflammation

It is now well documented that neuroinflammation is actively involved in neurological diseases and disorders, like Alzheimer’s disease (AD), amyotrophic lateral sclerosis, depression, epilepsy, multiple sclerosis and Parkinson's disease


Particularly, in AD, there is a correlation between local inflammation, and presence of amyloid plaques and neurofibrillary tangles

Ref: Sivaprakasam K. 2006
<table>
<thead>
<tr>
<th>Dr Stirling Clarren: neuroinflammation in FASD? (Feb 2012)</th>
<th>Almost no autopsies of older patients... absence of evidence, not denial the of concept re: neuroinflammation's role</th>
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<td>Dr. Joanne Weinberg: is she aware of articles re: neuroinflammation in FASD? Any evidence of elevated levels of neuroinflammatory markers in FASD? (Feb 2012)</td>
<td>“Funny you should ask....we are currently conducting a series of studies to examine exactly this question in our rat model....we have a strong hypothesis that inflammatory markers will be elevated...this article describes what we are doing now....”</td>
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- **Background:** children with FASD have impaired immunity—e.g. increased incidence of bacterial infections, lower eosinophil, neutrophil and gammaglobulin levels and reduced mitogen-stimulated increases in leukocytes. Rodent models of PAE are similar; also, their immune deficits are exacerbated by chronic intermittent stress.

- **Observation:** Increased TNF-alpha, Il-6 and IL-1Beta levels in prenatally alcohol–exposed (PAE) rodents versus controls

- **Result:** PAE females had a more prolonged course of disease and greater severity of inflammation compared to controls. Also, PAE females showed immune changes before any clinical signs of disease were apparent

- **Conclusion:** prenatal alcohol exposure has both direct and indirect effects on inflammatory processes, altering both immune and HPA function, and likely, the normal interactions between these systems.
Is there another condition associated with early development of dementia?


“….in Alzheimer Disease many cytokines have been found to be altered. Among these, the most common are *IL-1beta, IL-6, TNF-alpha and TGF-Beta*”
2012 UBCO Research Rodeo winner: Jocelyn Madiera

Gold Compounds and Your Brain: Auranofin as Neuroprotective and Anti-Neuroinflammatory Molecule.

“Neuroinflammation is a causative factor of Alzheimer Disease, Parkinson Disease and even Fetal Alcohol Syndrome”

Announced on CBC Radio Afternoon Show March 8, 2012,

Also available at: https://news.ok.ubc.ca/2012/03/09/philip-ainslie-named-ubcs-okanagan-campus-researcher-of-the-year/Research Rodeo winners
Auranofin

- Gold Compound used in rheumatoid arthritis, psoriatic arthritis, pemphigus (autoimmune blisters)
- Canadian Brand Name: Ridaura®
- The exact mechanism of action: unknown; gold is taken up by macrophages which results in inhibition of phagocytosis; also alters immunoglobulins. Additionally, complement activation is decreased, prostaglandin synthesis is inhibited, and lysosomal enzyme activity is decreased.
- May be associated with significant toxicity involving dermatologic, gastrointestinal, hematologic, pulmonary, renal, and hepatic systems; patient education is required.
- Adapted from: “Auranofin” UpToDate Desktop 19.1, 2011
“chronic ethanol activates microglial cells and stimulates the secretion of pro-inflammatory cytokine TNF-alpha, which participates in mediation of ethanol’s apoptotic action. In fetal microglia cultures ethanol increased the release of pro-inflammatory cytokines TNF-alpha, IL-6, and IL-1beta.”

Ref: Boyadjieva NI, Sarkar DK. 2010
Jocelyn Madeira

• 3 days of alcohol exposure (at 29-32 weeks) resulted in considerable white matter damage in developing sheep fetuses. TNF-alpha, IL-1 beta and IL-6 BLOOD levels were not elevated.


“a compelling body of evidence documents that obesity, MDD, and BD all represent conditions of chronic low-grade inflammation. Inflammation... can arise from several mechanisms including mitochondrial dysfunction, reactive oxygen species, endoplasmic reticulum stress, insulin resistance and adipokine dysfunction. MDD, BD and obesity are also associated with elevated levels of inflammatory markers such as tumor necrosis factor alpha, C reactive protein, and inflammatory cytokines such as IL-1, IL-2 and IL-10”

MDD=Major Depression, BD= Bipolar Disease
Can (a blood test for higher amounts of) neuroinflammation chemicals predict disease??

- **Stress is Visible**: Objective assessment of stress based on multiple cytokines in plasma, workshop presented by Atsuo S, et al. at 2011 American Psychiatric Assoc. Annual Conference

Autism

• A review of research trends in physiological abnormalities in autism spectrum disorders: immune dysregulation, inflammation, oxidative stress, mitochondrial dysfunction and environmental toxicant exposures

Ref: D A Rossignol et al. 2011.

“The strongest evidence was for immune dysregulation/inflammation and oxidative stress, followed by toxicant exposures and mitochondrial dysfunction.”
Autism

• http://www.cbc.ca/natureofthings/episode/autism-enigma.html#
Traumatic brain injury

- Neurotransmitter-mediated excitotoxicity causing glutamate, free-radical injury to cell membranes
- Electrolyte imbalances
- Mitochondrial dysfunction
- Inflammatory responses
- Apoptosis
- Secondary ischemia from vasospasm, focal microvascular occlusion, vascular injury
- These lead in turn to neuronal cell death as well as to cerebral edema and increased intracranial pressure that can further exacerbate the brain injury. This injury cascade shares many features of the ischemic cascade in acute stroke.

Ref: Phan N. 2011.
Mechanisms of Alcohol-mediated CNS Teratogenesis  
(permission: de la Monte, S. 2010)

Chronic in Utero Alcohol Exposure

- Mitochondrial Dysfunction
- DNA Damage
- Lipid Peroxidation
- Pro-inflammatory Cytokines

- oxidative
- Insulin/IGF Resistance

- Gene Expression
- Cholinergic Homeostasis
- Energy Metabolism
- Neurotropins

Apoptosis

- Neuronal Growth & Migration
- Neuronal Plasticity
- Learning and Memory
The brain is protected (by the BBB) from excessive inflammation

• Endothelial cells lining the capillaries of the central nervous system (CNS) help to form the blood-brain barrier (BBB) protective physical barrier that maintains neural homeostasis in the brain. This blood-brain barrier (BBB) blocks uncontrolled passage of molecules. To meet the high metabolic needs of the CNS tissue, efficient transport of nutrients from the blood into the CNS and rapid efflux of toxic metabolites out of the CNS is required.

• CNS astrocytes secrete the glycoprotein Sonic hedgehog (Shh) to induce and maintain the BBB and also to limit access of the immune system to the CNS during mammalian embryogenesis and adulthood.

Ref: Engelhardt B, et al. 2011
The Hedgehog Pathway Promotes Blood-Brain Barrier Integrity and CNS Immune Quiescence


The blood-brain barrier (BBB) is composed of tightly bound endothelial cells (ECs) and perivascular astrocytes that regulate central nervous system (CNS) homeostasis.

We showed astrocytes secrete Sonic hedgehog and that BBB ECs express Hedgehog (Hh) receptors, which together promote BBB formation and integrity during embryonic development and adulthood.

We also demonstrated a critical role of the Hh pathway in promoting the immune quiescence of BBB ECs by decreasing the expression of proinflammatory mediators and the adhesion and migration of leukocytes.

Overall, the Hh pathway provides a barrier-promoting effect and an endogenous anti-inflammatory balance to CNS-directed immune attacks, as occurs in multiple sclerosis.
Sonic Hedgehog Signaling Pathways and FASD

• Alcohol reduces key signaling components of the Hedgehog signaling pathway (such as the Shh molecule).

• If Shh molecule levels are restored experimentally, alcohol-induced craniofacial anomalies are reduced because apoptosis of neural crest cells is reduced.

Ref: Lombard Z et al. 2007
The Hedgehog Pathway helps the BBB
Keep “Spazz” Chemicals out of the Brain!

Endothelial cells (lining capillaries) and astrocytes (next to capillaries) form the BBB

**Astrocytes** secrete **Sonic hedgehog** and **Endothelial cells** express **Hedgehog receptors**, which together form a strong BBB in the fetus, child and adult

Hedgehog receptor pathways keep the immune system from spazzing in the brain by **decreasing the expression of proinflammatory mediators** and **keeping unwanted white blood cells out**.

Rod’s speculation: If the Hedgehog pathway is dysregulated (as in FASD) Brain-directed immune attacks, like multiple sclerosis could be more common
My Patient, Susan

- 23-yr-old, 3 kids, FASD
- Age 15: “stroke” left side partial paralysis X 3 weeks but CT and blood tests negative (a time of parental rejection/ultimatums)
- Age 22: speech, memory, ataxia, ICU for breathing, MRI=Multiple Sclerosis (MS) (A time of leaving husband and then forced removal of kids)
- MS clinic (thus far) ignores my input re how FASD could exacerbate MS, MCFD hard to convince that stress directly* exacerbates MS

Our immune system  Johnston RB. 2011.

Part 1: Innate—from birth

• Physical barriers: skin, membranes
• Enzymes: e.g. tear/saliva lysozyme
• Phagocytes (neutrophils, monocytes, macrophages)
• Inflammation-related serum proteins (e.g., complement, C-reactive protein, lectins)
• Cell receptors that sense microorganisms and signal a defensive response (e.g., Toll-like receptors)
• Cells that release cytokines and inflammatory mediators (macrophages, mast cells, natural-killer cells)
Our immune system  Johnston RB. 2011.

Part 2: Learned/ adapted as a result of exposure to microorganisms (days-weeks)

- **T lymphocytes**: regulate T and B cells, help B cells make antibodies, effectors of antigen-specific cell-mediated immunity (virus, cancer, graft rejection)

- **Antigen Presenting Cells**: e.g. Dendrite cells Initiate T cell responses, express molecules needed for activation of CD4+ T Cells
Overview of CD4+ T cell activation

• Naive T cells reside in spleen, lymph nodes, and Payer's patches in the intestine.
• Dendrite cells capture and process antigen from peripheral sites. They then migrate into lymph nodes and develop into mature antigen presenting cells.
• Antigen recognition triggers a complex cascade of intercellular membrane glycoprotein contacts, and intracellular biochemical signals.
• The T cell- other cell interaction is modulated by alterations in the expression of surface molecules and cytokine secretion by both cells.
• Specific characteristics of the cytokine milieu and the combination of signals results in either activation or polarization of the T cell.
T cells are the effectors of antigen-specific cell-mediated immunity (CMI). CMI is important in the elimination of cells infected with pathogens (e.g., viruses, mycobacterium, and some bacteria) and neoplasm's. CMI also causes graft rejection.

- T cell responses are initiated by antigen presenting cells, primarily dendrite cells. T cells are critical in the regulation of both humeral (antibody) and cellular effectors mechanisms. Antibody responses to the vast majority of antigens require T cell help.
I just need a mum! My patient, Debbie, 32 (Pain processing #1)

- L pelvic pain (ovarian cysts)...could not function
- Pain and inflammatory cytokines:
  1) Parental rejection/invalidation: shaming and shunning pushes the buttons of our stress response system more strongly than any other toxic stressor. *Rejection shakes our core.*

Ref: Goldman D. 2006. p231
I just need a mum! (Pain processing #2)

2) Does social rejection increase *pro-inflammatory products*?

**YES!** Ref: De Han M, et al. 2009. up 511

3) “If we block release of *pro-inflammatory products* by reducing activation of spinal cord gill cells virtually every animal model of enhanced pain is prevented”

Ref: Adder R, et al. (editors) 2007. up 405
Social rejection-caused increases of proinflammatory products

- In addition to HPA activation, stress activates innate immune responses including the release of proinflammatory cytokines.

** Kamanda T, et al. 2007. (**MAPK is dysregulated in FASD)
Dr Ab Chudley: specific genes of 3 Critical Pathways are likely to influence **risk of developing** FASD

- **Transforming growth factor-beta:** regulates *immune system*, neuronal growth and migration, axon growth and cell adhesion

- **Mitogen-activated protein kinase:** (when alcohol dysregulates...) changes in cell growth and migration

- (Alcohol reduces activity of key parts of the...) **Hedgehog signaling pathway such as the Shh molecule**...restore Shh= reduce alcohol-induced craniofacial anomalies via reduced apoptosis of neural crest cells
Allostasis

• Allows us to respond to changing conditions
• Mediators: stress hormones, the immune system, neurological responses....
• Result (over time).... a new “stable” state
Allostasis

E.g. Abuse

XS adrenaline, cortisol, CRH, inflammatory cytokines

suppression of Natural Killer T cells

Less immune surveillance of infections and cancer!

Adverse Cholesterol, B.P., insulin resistance, (over)activation of immune system

Heart disease, diabetes, allergies

This new allostatic state SUCKS!
So how do we decrease inflammation?

- Omega 3’s
- Adequate (high quality) sleep
- Exercise
- ASA
- Statins
- Minocycline
Omega 3’s

**EPA** - eicosapentaenoic acid  **DHA** - docosahexaenoic acid

- lower triglyceride levels
- antinflammatory (↓ proinflammatory cytokines and...)
- antiarrhythmic
- immune enhancing
- nerve cell stabilizing
- ↓ clot formation

**EPA** - more evidence of effectively reducing depression and anxiety
Tends to be stimulating

**DHA (D for Dopey)**
Tends to be sedating

Flaxseed is **ALA** = 1/9 the bioavailability so not optimal)
Omega 3 doses

• “Doses of EPA + DHA averaging 3.5-4.3 grams per day improve disease activity and reduce symptoms in Rheumatoid arthritis, Inflammatory Bowel diseases and asthma” Ref: Kendall-Tackett.2010. p92

• “Doses of EPA up to 2 grams per day are effective for Depression; DHA is not helpful for depression by itself, but can be used in addition to EPA” Ref: Kendall-Tackett K. 2010. p 224

• “It seems a dose of 3 grams/day of EPA + DHA is effective for ADHD” Ref: Amen DF. 2008.

• “We have XS omega 6 + 9 in our diets already” Ref: Weil A. 2006
• Omega 3 given to rat model of Bipolar
• As fragility and destruction of mitochondrial membranes progressed...so did bipolar symptoms
• Omega 3 reduced membrane problems and this reduced bipolar symptoms

Ref: Young LT. 2008.
Dr. Young’s mental health model

Windsor Station

Victoria Station
**My favorite FASD or PTSD stress slide**

**To Settle Alarm (Bruce Perry)**

<table>
<thead>
<tr>
<th>Thinking</th>
<th>Abstract</th>
<th>Concrete</th>
<th>“Emotional”</th>
<th>Reactive</th>
<th>Just Reflexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mental State</td>
<td>Calm</td>
<td>Alert</td>
<td>Alarm</td>
<td>Fear</td>
<td>Terror</td>
</tr>
<tr>
<td>Word Use</td>
<td>“New” ideas</td>
<td>Follow rules</td>
<td>Less words</td>
<td>Few words</td>
<td>No words</td>
</tr>
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- Regular, Rhythmic, Age-appropriate, Fun, Engaging Activities
- Stress, Frustration
SLEEP ARCHITECTURE

Stages: I II III IV

- non-REM “is idling brain in moving body” (Wm. Dement)
- dreams here = like thoughts, as through solving problems

Rapid eye movement (REM): as night progresses

“active hallucinatory brain in paralyzed body” (Dement)
- dreams more bizarre

| I II III IV | I II III IV | I II III IV | I II III IV |

“cycle” (5-6 cycles / night)
Disrupted Sleep

• E.g. Obstructive Sleep apnea...increases TNF-alpha and IL-6...effective treatment decreases these inflammatory markers

• E.g. Primary Insomnia...increases TNF-alpha and IL-6 (=reason for daytime fatigue?)

• Depression...increased time to get to sleep...elevated IL-6

Ref: Kendall-Tackett K. 2010. p 60
$E=mc^2$ means energy and matter are kind of the same.

- Depression \(\leftrightarrow\) Reduced Slow wave sleep
- Depression \(\leftrightarrow\) Diabetes
- Depression \(\leftrightarrow\) Chronic Pain

Depression/ Reduced slow wave sleep/ Diabetes/ Chronic pain are also very closely interrelated...all are affected by....?

Ref: Goumeniouk A. 2011.
Slow Wave Sleep (SWS) (III and IV)

• As SWS decreases, depression increases
• Exercise helps increase SWS, so do other effective treatments of depression
• If need be: mirtazepine or trazodone help SWS
• Mirtazepine can be assoc with wt. gain
• Trazodone is seldom assoc with wt. gain and is usually ok even in sleep apnea (if used cautiously)

Ref: Goumeniouk A. 2011
References


Johnston RB. 2011. An overview of the innate immune system. UpToDate Desktop 19.1 Medical Reference


References


