Neuropsychiatric symptoms in patients with illness acquired following exposure to WDB are associated with structural abnormalities: a volumetric MRI study using NeuroQuant

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Co-authors

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James Ryan PhD, Proteogenomics
Dennis House, CRBAI
Before I start

• Thanks to David Ross MD of Virginia Neuropsychiatry Institute and Virginia Commonwealth University

• Mentor

• Provider of academic papers

• Author of NeuroQuant slides used
Goals for today

• Ideally, this talk will let you put together data on inflammatory responses and brain structural data to improve patient care

• Realistically, you need to know that the proteomics/diagnostics used for years are now joined by a new generation of test results
The Biotoxin Pathway

In genetically susceptible people, biotoxins bind to pattern receptors, causing continuing, unregulated production of cytokines.

- **Biotoxin (HLA susceptible)**
- **Increased Cytokines**
- **Increased Leptin**
- **Nerve cell/axon**
- **Dendritic Cells**
- **Surface Receptors** (Toll; C-type lectin; mannose & others)
- **Hypothalamus**
  - **Reduced MSH**
  - **Leptin receptor**
  - **VIP**
  - **AVP**
- **Immune System Symptoms**
  - Patients with certain HLA genotypes (immune response genes) may develop inappropriate immunity. Most common are antibodies to:
    - Gliadin (affects digestion)
    - Cardiolipins (affects blood clotting)
  - Treg cells: Pathogenic T cells
- **Inflammation-related symptoms**
  - High levels of cytokines produce flu-like symptoms: Headaches, muscle aches, fatigue, unstable temperature, difficulty concentrating and more. High levels of cytokines also result in increased levels of several other immune-response related substances, including TGF B-1, MMP-9, IL-1B, and PAI-1. MMP-9 delivers inflammatory elements from blood to brain, nerve, muscle, lungs, and joints. It combines with PAI-1 in increasing clot formation and arterial blockage.
- **Resistant Coag-negative Staph Bacteria**
  - Colonies of MARCoNS with resistance to multiple antibiotics may develop in biofilm or mucus membranes. The bacteria produce substances that aggravate both the high cytokine levels and low MSH levels.
  - Reduced ADH
    - Reduced MSH can cause the pituitary to produce lower levels of anti-diuretic hormone (ADH), leading to thirst, frequent urination, and susceptibility to shocks from static electricity.
  - Reduced Androgens
    - Reduced MSH can cause the pituitary to lower its production of sex hormones.
- **Sleep Disturbance**
  - Production of melatonin is reduced, leading to chronic, non-restorative sleep.
- **Chronic Pain**
  - Endorphin production is suppressed. This can lead to chronic, sometimes unusual, pain.
- **Gastrointestinal Problems**
  - Lack of MSH can cause malabsorption in the gut, resulting in diarrhea. This is sometimes called “leaky gut” and resembles (but is not) celiac disease. IBS is often present.
- **Reduced MSH**
  - White blood cells lose regulation of cytokine response, so that recovery from other illnesses, including infections diseases, may be slowed.
- **Changes in Cortisol and ACTH levels**
  - The pituitary may produce elevated levels of cortisol and ACTH in early stages of illness, then drop to excessively low levels later. (Patients should avoid steroids such as prednisone, which can lower levels of ACTH)
  - Reduced ADH
- **Split Products of Complement Activation**
  - C4a: capillary hypoperfusion
  - C3a: bacterial membranes
- **High cytokine levels in the capillaries attract white blood cells, leading to restricted blood flow, and lower oxygen levels. HIF stimulates VEGF and TGF B-1. Reduced VEGF leads to fatigue, muscle cramps, and shortness of breath (may be over-ridden by replacement with erythropoietin). TGF B-1 changes cell type and interacts with Treg cells.**
- **Removal from the body**
  - In most people, biotoxins are either removed from the blood by the liver or attached by the immune system, broken down, and excreted harmlessly. In people who don’t have the right immune response genes, however, biotoxins can remain in the body indefinitely.

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### Biotoxin symptoms

- Fatigue, weak
- Ache, cramps
- Unusual, sharp, claw, electrical
- Light sens, red, blurred, tearing
- SOB, cough, sinus
- Abdominal pains, secretory diarrhea
- Joints, AM stiff
- Exec cognitive memory, concen, word, assimilation, confusion, disorien
- Mood, appetite, sweats, temp reg
- Thirst, pee, shocks
- Numb, tingle, taste
- Vertigo, tremor, skin
Cognitive and neurologic symptoms in WDB patients

- We call the illness CIRS-WDB*
- Systemic inflammatory responses
  - Blood brain barrier effects well shown
  - Illness only seen in organs with blood flow
- Innate immune activation clear
- Absence of regulatory neuropeptides
- TH17/TGF beta-1/T reg imbalance incredibly common

* Treating physicians expert report 7/2010; POA
Add to the list

- Absence of executive inhibition
- Tics
- Atypical seizures
- OCD
- What looks like depression
- What looks like anxiety/panic
- ALL REPORTED IN CAUDATE NUCLEUS ATROPHY SYNDROMES
How do I know these so many neuropsychiatric symptoms are inflammatory?

• Seen in cases
• Not seen in controls
• Differences are $p < 0.001$
• Abate with Rx only (not self-healing)
• Recur with relapse (prospective!!)
• Genomics (mRNA and MicroRNA)
• TGF beta-1, VEGF, MMP9, C4a key
How does a “Neuro-Naysayer” know otherwise?

- Data on thousands of patients affirms
- Data on treatment of thousands of patients affirms
- No data from anyone (ever) to deny
- No research (ever) to deny
- All the Naysayer has are empty words; no data, no research, no prospective studies
- Countless mRNA markers affirm
- US Patent 8/21/2012
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<th>Cyano</th>
<th>WDB-1</th>
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</table>
Chronic cognitive abnormalities in CIRS-WDB patients

• Executive cognitive functions
  – Recent memory
  – Concentration
  – Word finding; assimilation of new
  – Confusion
  – Disorientation

NOT SPECIFIC FOR A GIVEN BIOTOXIN ILLNESS
No differences between CIRS-WDB and other biotoxin illnesses

- Mold (think water-damaged buildings)
- Dinoflagellates (Pfiesteria, ciguatera, Chattonella, ?? Karenina)
- Apicomplexans (Babesia, Sarcocystis and Eimeria)
- Cyanobacteria (Microcystis, Lyngbya, cylindrospermopsis)
Sx CLUSTER ANALYSIS

- Fatigue
- Weak, assimilation, aching, headache, light sensitivity
- Memory, words
- Concentration
- Joint, AM stiff, cramps
- Unusual skin sensations, tingling
- Shortness of breath, sinus
- Cough, thirst, confusion

- Appetite, body temperature regulation, urinary freq.
- Red eyes, blurred vision, sweats, mood, ice-pick pains
- Abdominal pain, diarrhea, numbness
- Tearing, disorientation, metallic taste
- Static shocks, vertigo
8 clusters are only seen in biotoxin illnesses to date

- History must be taken by the health care provider
- No check lists
- No self reporting
- Use techniques of attorneys: multiple re-asking of same question to confirm reliability of history
## Logistic Regression Model - 8 Factor Score

### Combining Symptoms: Predicting Membership in the Group of Cases or Controls

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<th>PREDICTED CONTROLS</th>
<th>PREDICTED CASES</th>
<th>ROW TOTAL</th>
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<td>COLUMN TOTAL</td>
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<td>278</td>
<td>521</td>
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</table>

### Percent Agreement

- **98.85%**

### Agreement Odds

- **515/521**

### Disparities

- **6**

### Standard Deviation

- **0.47%**

### Agreement Limits

- **Lower Confidence Limit = 97.03%**
- **Upper Confidence Limit = 99.76%**

### Confidence Limits

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<th>2-tailed Z at ( \alpha=0.05=1.960 )</th>
<th>% Agreement</th>
<th>Disparities</th>
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<td>Lower Confidence Limit=</td>
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<td>Upper Confidence Limit=</td>
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### Significance Test of Agreement

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<td>Pearson</td>
<td>497.264</td>
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Biotoxins are ionophores

- Forget relying on antibody testing if epitope separation isn’t confirmed
- Move from cell to cell
- Very small, many less than 1000 daltons
- Secreted against a gradient into bile by organic anion transport system (OATP)
- News: OATP is also found along blood brain barrier!!
Back to the brain

- Are executive symptoms telling us about abnormal brain structures?
- Brain physiology?
- What we need is a dynamic imaging study that correlates with symptoms and physiology!
- And we have one: NeuroQuant
NeuroQuant

• Volumetric study of 11 brain regions
  – Can expand to 15
  – Changes over time key
• FDA approved in 2007
• Software added to MRI of brain
• Takes 10 minutes
• Reproducibly reliable
• Controls data sets available
What do changes from normal in NeuroQuant mean?

- Changes in volume
  - Interstitial edema will increase
  - Atrophy or pruning will decrease
- Analyzed sequentially
- Correlate with clinical studies
- Correlate with genomics!
- We can link mRNA to changes in brain volumes with changes in clinical status
Review: what is the blood brain barrier?

- Endothelial cells and tight junctions
- Basement membrane
- Pericytes
- Astrocytes
- "The fence and the gate"
- Breached by VEGF, MMP9
- TGF beta-1 dual role
BLOOD BRAIN BARRIER

Adapted from: Karen Francis, Johan van Beek, Cecile Canova, Jim W. Neal and Philippe Gasque, The Blood Brain Barrier. Expert Reviews in Molecular Medicine, Vol 5, 23 May, 2003
BLOOD BRAIN BARRIER

MMP9
VEGF
+ fluid
plasma proteins

TGF beta-1 → Gene Expression → GFAP

Adapted from: Karen Francis, Johan van Beek, Cecile Canova, Jim W. Neal and Philippe Gasque, The Blood Brain Barrier. Expert Reviews in Molecular Medicine, Vol 5, 23 May, 2003
What are we talking about when we say brain fog?

- Executive cognitive disruption from neuronal dysfunction?
- What injures the neuron? Toxin, infection
- How about pressure up or down?
- How about loss of dendritic connections ("pruning")
- Atrophy
Work with C4a and epo says the injury isn’t permanent

- 2006 study, CFS in Fort Lauderdale
- Certainly high C4a associated with high lactate = capillary hypoperfusion
- Correction of lactate resolved “fog”
- Of 8 measurements on MRS, cases were 5.2 before and 1.2 after
- Controls were 0.9
Dendritic pruning

• Hot topic in neurology
• Ranges from PTSD to MS
• Loss of volume with pruning and then replacement of lost volume with correction of inflammation
• Plasticity of dendritic connections
• What do we know about remodeling?
Glial fibrillary acidic protein

- Release from astrocytes after TGF beta-1 stimulation
- Effects can come from luminal and abluminal sides of BBB!
- Suppression neuronal re-growth
- Suppression reformation of axonal connections
Atrophy

- Loss of neuronal tissue
- Atrophy is permanent unless it is actually dendritic pruning
- How can one tell?
- MRS, NAA and creatine help
History of Structural Brain Imaging

- 1970s: Computerized tomography (CT) scans
MRI scan

A patient undergoing an MRI examination of the head.
MRI in TBI

• Summary of MRI brain volumetry through 2000
  • Traumatic brain injury causes brain atrophy.
  • Brain volumetry was performed by human operator with computer assistance.
  • Brain volumetry took about 15 hr per subject/MRI.
  • Brain volumetry was confined to research settings.

References

FreeSurfer Methods
Segmentation and Volumetry
FreeSurfer Methods

a) Inflation and spherification

b) Mapping to common space and comparison to brain atlas

c) Return with brain regions mapped
Typical MRI Slice
Segments Differentiated
History of Structural Brain Imaging

- 1970s: CT scans
- 1980s: MRI scans
- 1990s: Brain volume measurement
- 2000s: Automated brain volume measurement
  - FreeSurfer
  - ADNI
- 2007: NeuroQuant®
History of Structural Brain Imaging

- 2007: NeuroQuant®
  - Developed by CorTechs Labs
  - Based on FreeSurfer
    - Computer-automated analysis of brain MRI volume
  - Commercially available
  - FDA-approved method

References


NeuroQuant® Segmented Brain Image
History of Structural Brain Imaging

• 2007: NeuroQuant®
  • FDA-approved method
    • Cleared for marketing by the US FDA [510(k) K061855] as a medical device to measure brain MRI volume in human subjects
    • Highly reliable with the earlier approach based on computer-assisted, manual identification of brain regions
    • “Brain ruler”

Reference
http://www.cortechs.net/products/neuroquant.php
NeuroQuant® Standard Report
Page 1

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### MORPHOMETRY RESULTS

![Brain images](image)

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<th>Volume (cm³)</th>
<th>% of ICV (5%-95% Normative Percentile)</th>
<th>Normative Percentile</th>
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### AGE-MATCHED REFERENCE CHARTS

- **L & R Hippocampus**
  - ![Chart](chart)
  - Total Volume (% of ICV) vs Age (Years)
  - 95%, 75%, 50%, 25%, 5% percentiles

- **L & R Inferior Lateral Ventricle**
  - ![Chart](chart)
  - Total Volume (% of ICV) vs Age (Years)
  - 95%, 75%, 50%, 25%, 5% percentiles
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<td>4.11</td>
<td>66.08</td>
<td>4.16</td>
<td>-1.25</td>
</tr>
</tbody>
</table>

*The Asymmetry Index is defined as the difference between left and right volumes divided by their mean (in percent)
Reliability of NeuroQuant®

- NeuroQuant is reliable with FreeSurfer (Kovacevic, Rafii et al. 2009).
- NeuroQuant® is reliable with a computer-supported manual technique using NeuroMorphometric software (Brewer, Magda et al. 2009).
- The segmentation error rate of NeuroQuant® was found to be very low (9 out of 822) (Heister, Brewer et al. 2011).

Reference
Experience with NeuroQuant® at the Virginia Institute of Neuropsychiatry

- Quality control
  - Prior to data collection, communicate with radiology center
  - NeuroQuant® software automatically checks several parameters
  - Visual inspection of each set of segmented brain images
  - Inspection of the numerical and statistical results of the analyses
# Radiologist vs. NeuroQuant®

<table>
<thead>
<tr>
<th></th>
<th>N positive/ Total N</th>
<th>% positive for atrophy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiologist atrophy</td>
<td>2/20</td>
<td>10%</td>
</tr>
<tr>
<td>NQ Extended atrophy</td>
<td>10/20</td>
<td>50%</td>
</tr>
</tbody>
</table>

Paired sign test, test statistic $M = -4.00$, $P=0.02$

Reference
## VIN Research: Test-retest Reliability

<table>
<thead>
<tr>
<th>Brain region</th>
<th>Intraclass correlation coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total intracranial volume, Brain parenchyma, Cerebrospinal fluid,</td>
<td>0.95 – 1.00</td>
</tr>
<tr>
<td>Forebrain parenchyma, Cortical gray matter, Cerebral white matter, Lateral ventricle, Inferior lateral ventricle, Caudate, Hippocampus, Cerebellum, Brainstem, Fourth ventricle</td>
<td></td>
</tr>
<tr>
<td>Thalamus, Amygdala, Exterior cerebrospinal fluid</td>
<td>&gt;.90</td>
</tr>
<tr>
<td>Putamen</td>
<td>&gt;.85</td>
</tr>
<tr>
<td>Third ventricle</td>
<td>&gt;.80</td>
</tr>
<tr>
<td>Pallidum</td>
<td>&gt;.75</td>
</tr>
<tr>
<td>Ventral diencephalon</td>
<td>&gt;.35</td>
</tr>
</tbody>
</table>

Test-retest reliability for NeuroQuant® volumetric measures were mostly excellent.

Reference:
Community Acceptance of NeuroQuant®

• NeuroQuant® is currently used in at least a dozen clinics and radiology centers across the USA:

<table>
<thead>
<tr>
<th>West</th>
<th>East</th>
</tr>
</thead>
<tbody>
<tr>
<td>Santa Rosa Imaging Center</td>
<td>Lenox Hill Radiology &amp; Medical Imaging</td>
</tr>
<tr>
<td>3536 Mendocino Ave., Suite 280</td>
<td>Associates</td>
</tr>
<tr>
<td>Santa Rosa, CA 95403</td>
<td>61 East 77th Street, New York, NY 10075</td>
</tr>
<tr>
<td>Dr. James Brewer</td>
<td>East River Medical Imaging, PC</td>
</tr>
<tr>
<td>University of California, San Diego</td>
<td></td>
</tr>
<tr>
<td></td>
<td>519/523 East 72nd Street, New York, NY 10021</td>
</tr>
<tr>
<td>San Joaquin Community Hospital</td>
<td>Advanced Radiology</td>
</tr>
<tr>
<td>2615 Chester Avenue, Bakersfield,</td>
<td>888 Bestgate Rd, Ste 101, Annapolis 21401</td>
</tr>
<tr>
<td>CA 93301</td>
<td>Washington Radiology Associates</td>
</tr>
<tr>
<td>Liberty Pacific Advanced Imaging</td>
<td>2141 K St. NW, Washington, DC 20037</td>
</tr>
<tr>
<td>16130 Ventura Blvd., Suite 100,</td>
<td></td>
</tr>
<tr>
<td>Encino, CA 91436</td>
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<table>
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<th>South</th>
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<tbody>
<tr>
<td>Virginia Institute of Neuropsychiatry</td>
</tr>
<tr>
<td>364 Browns Hill Court, Midlothian,</td>
</tr>
<tr>
<td>VA 23114</td>
</tr>
<tr>
<td>Center for Neurorehabilitation</td>
</tr>
<tr>
<td>Services</td>
</tr>
<tr>
<td>10710 Midlothian Turnpike, Suite 125, Richmond, VA 23235</td>
</tr>
<tr>
<td>MRI CT Diagnostics</td>
</tr>
<tr>
<td>4668 Pembroke Blvd, Virginia Beach,</td>
</tr>
<tr>
<td>VA 23455</td>
</tr>
</tbody>
</table>
Acknowledgements

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Megan DeSmit, B.S.
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Virginia Institute of Neuropsychiatry
NQ algorithm

Cases versus control

- Look at differences between cases and controls
- Assign point value to 50%-99% of difference=1 and ≥100% =2
- Add the differences for controls; none are > 3
- Add the differences of cases; none < 4
Creating the mold NQ Index (MNQI)

- Now look at the sum of abnormalities for each measure between cases and controls
- Select top five $> 3.0$
- Return to the top five
- Create scoring on the top five
- Stratify scores by illness type
For CIRS-WDB, the five areas are not seen in any other illness to date

- Forebrain parenchyma increased
- Cortical gray increased
- Hippocampus increased
- Caudate decreased
- Pallidum increased
Scoring system 0, 1, 2

- Forebrain $\geq 31.7 \text{ and } 32.3$
- Cortical gray $\geq 16.4 \text{ and } 17.0$
- Hippocampus $\geq .28 \text{ and } .30$
- Caudate $\leq .24 \text{ and } \leq .23$
- Pallidum $\geq .066 \text{ and } \geq .071$
No other combination like this in neurology known

- Selective increase in multiple areas
- Reduced lateral ventricle size
- Reduced caudate size but no other grey matter or basal ganglia
- Role of BBB in edema? Corrected by Rx illness
- Caudate atrophy responds slowly to VIP and nothing else to date
MNQI values in two cohorts

- Controls 2.5 and 1.9
- Untreated cases 6.6 and 6.4
- Partially treated cases 4.0 and 3.8
- Treated cases 2.0 and 2.1
- Relapse 7.0 and 6.5
- Cohort 1 N= 19
- Cohort 2 N= 65
Edema?

- BBB leak?
- Reduced albumin?
- Dehydration preventing measurement of edema
- Is edema macroscopic i.e. seen on MRI?
So what is going on?

• Microscopic interstitial edema means loosening of BBB
• Caudate atrophy is not permanent!
• Pruning!
• How do we say that pallidum increases and caudate decreases yet no other posterior gray is altered
• Diffuse gray reduction is typical of MS, other CNS illnesses (Huntington’s chorea and PSTD)
BBB

- VEGF increases capillary permeability
- So does MMP9 and OATP
- TGF beta-1 has dual role (what a surprise); can stiffen tight junctions and reduce inflow
Inflammation effects-1

- Loosening of blood brain barrier permits intrusion of peripheral elements into CNS
- Major players are TGF beta-1, VEGF, MMP9
- C4a is less of a problem
• The new buzz phrase is “TH17/Treg imbalance”

• Rising TGF beta-1 will direct T regs into tissue to suppress inflammation if there is ROR receptor present but if not, and IL-1, IL-17, IL-23 are, the T regs are converted into pathogenic T cells that make more TGF beta-1
Inflammation effects-3

- The T reg imbalance can be from systemic T regs (thymus derived)
  - CD4+CD25++127 lo/-
- Or it can be from acquired T regs
  - CD4+CD25++

The days of looking at CD4+CD25+ are over (that was last years buzzword)
What do I need to know to treat?

• No single attack corrects BBB or pruning
• Multiple sequential steps based on BT pathway
• Relapse with re-exposure wreaks havoc with sequential intervention
A bit of review

- We are looking at specific brain areas as targets of inflammatory processes
- We cannot forget that similar kinds of changes in tissues are ongoing
- We know a lot or about peripheral innate immune abnormalities
Innate immune effects are systemic

- Pre-formed proteins, ready to go
- Pattern receptors pick up foreign signals
- Activation is instantaneous
  - Imagine *what turns off* such activation
- Initiates the formation of antibodies, in a different type immune response called acquired immunity
- The names of innate immunity might be new: cytokines, complement, VEGF, TGF beta-1, MMP9, CD4+CD25++ (cellular)
Innate immunity isn’t new

• It was 1989 at the CSH Symposia
• Charles Janeway, looking at immunology, predicted an expansion of insight in innate immunity
• 1972 Lewis Thomas talked about the peculiar over-reaction of the host to toxins, thinking of bacterial toxins
• 1985 first description of TNF
• By 2000, over 50,000 papers published
• 2011 Nobel Prize, Bruce Beutler, Scripps
Defining what is wrong brings effective treatment

- Lowering levels of inflammagens: C3a, C4a, MMP9 and TGF beta-1
- Correct hormonal dysregulation
- Deal with auto-immunity
- Improve capillary hypoperfusion
- Eradicate commensal staphs
- Correct cellular immunity
Table 4b. Distribution of Case Definition Parameters

<table>
<thead>
<tr>
<th>Number of parameters met by each test subject</th>
<th>Number of test subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
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<tr>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
</tr>
</tbody>
</table>

- CC Cases
- Controls
Treatment steps

VIP

TGF beta-1
- Correct C4a
- Correct C3a
- Correct VEGF
- Correct MMP9
- Correct ADH/osmolality

Correct androgens
Correct antigliadin
Eradicate MARCoNS
CSM/Welchol
Remove from exposure
Look for the final common pathway

• Abnormalities in innate immune responses (non-specific for cause)
• Call it the host response
• Incredible amplification of multiple pathways following initiation
• CHRONIC INFLAMMATORY RESPONSE SYNDROMES!
CIRS is systemic, interacting

- No way to say just one lab as source of fatigue, cognitive abnormalities, joints, respiratory problems
- All of the putative diagnoses have the same final common pathway
- You will see the same combo of multisymptom illness and labs
- Differential diagnosis key
CIRS-1

• Once you see it once your life as a physician will be changed forever
• Lack of regulation of inflammation
• Enhanced innate inflammatory parameters (C4a, TGF beta-1, MMP9 and more)
• Hormonal dysregulation
• Hypoxia from capillary hypoperfusion
• And now T regs too
CIRS-2

- Colonizing commensal MARCoNS
- Von Willebrand’s factor-66% abnormal: Acute reactants? NO
- Autoimmunity like crazy! AGA, ACLA, ANA, ANCA, actin
- Cellular immunity: TGF beta-1
- Activated complement split products (C3a, C4a)
VEGF

- Vascular endothelial growth factor
- Responsive to hypoxia inducible factor; feedback from TGF beta-1
- Increases O2 and increases new blood vessel formation
- Judah Folkman and anti-angiogenesis knew about VEGF
VEGF 2

- Blockade of VEGF a big deal in chemotherapy now; most effective at VEGF + receptor tumors
- But low VEGF is the norm in the worst biotoxin people
- Sure some U-shaped skew but low VEGF means cell-based starvation
Capillary hypoperfusion

- Bottom line is decreased delivery of nutrients and oxygen into capillaries
- ABG won’t help; I don’t see where venous gases have academic basis in these illnesses
- Use VO2 max from PST
- Use lactate in MR spectroscopy
VO2 max

- Disability uses this measure a lot
- Look for over 35 in healthy younger person; nomograms available
- 12 ml/kg/min is stage 4 CHF
- So many have VO2 max < 20
- Conversely training to raise VO2 max that doesn’t go beyond anaerobic threshold works in biotoxin people
Raising VO2 max shows benefit

- Correcting VEGF must happen
- Anaerobic threshold is measured
- At exercises start low, go slow
- Defined exercise EVERY DAY
- Bike, treadmill; work up to 15’
- Add floor; build up to 15’; then free
- Go back to first defined work, increase sequentially
Post-exertional malaise

- Measure VO2 max in pulm stress test
- It will be low
- What about glycogen in exercise
  - Remarkably inefficient glucose burn
- No O2; no efficiency
  - Can’t say this is mitochondrial illness!
- Fat storage (look at leptin)
- Protein burning (alanine and glutamine)
TGF beta-1

- Will have its own section
- Here is the key advancement in assessment of inflammatory illness
- Lung symptoms? Ask re TGF beta-1
- Neuro problems? Ask re TGF beta-1
- Autoimmune? Ask re TGF beta-1
- Learning disability? MS? TM? Same
TGF beta-2

- First found to have increased tissue effect in those with mutate fibrillin-1
- Then the switch to plasma measures
- Normal is < 2380; over 5000 I worry
- Over 10,000 essentially guaranteed restrictive lung disease, tremor, cognitive issues and joint problems
TGF beta-3

- Must be double spun plasma
- Platelet contamination common
- If result over 40,000, not properly handled
- Always have second specimen saved
- Cambridge runs the assay
### MR spectroscopy

- **3 Tesla coil; single voxel**
- **Frontal lobes and hippocampi**
- **Same spots! Measure same compounds**
- **High lactate (> 1.29) too high**
- **Ratio of glutamate to glutamine \((G/G)\) < 2.19 too low**
MRS-2

- Change in cognition is a tip-off
- Reversal of high lactate reverses suppressed G/G
- And Voila! Reversal of cognitive too
- Key concept is that the cellular neuronal mechanisms are not permanently injured
VIP-1

- Vasoactive intestinal polypeptide
- Neuroregulatory
- Agonist in suprachiasmatic nucleus
  - Primarily olfactory!
- Binds to membrane receptors
- Activates cellular regulation
- Downregulates cytokines (MMP9)
VIP-2

- Downregulates MASP2
- Restores balance of Vitamin D3
- Downregulates aromatase
- Up-regulates VEGF
- Warning re lipase
- Main effect immediately is endorphin
- Followed by lowering PASP in exercise
PASP and VIP

• 50 mcg QID corrects paradoxical rise in PASP in exercise in days, not weeks, with durable effects with titration to BID and over time: off!

• So many people aren’t diagnosed with acquired PASP even if they have stress echo: must measure TR!

• Don’t accept “normal”
Looks like asthma, but isn’t

- Measure PASP in exercise
- Should not rise more than 8 mm Hg
- Source of palpitations and SOB
- Won’t get better with beta-2 agonists
- Don’t forget EMT and TGF beta-1
- Remodeling in heart, CNS, liver
- Fibrotic change
VIP-3

- Immunoregulatory aspects
- Drives up CD4+CD25++
- Here is link from neuropeptides to humoral factors to T-cell physiology
- Role of downregulation of TGF beta-1 has no obvious upper limit in its application
What you need to know

- Symptoms must be there
- Labs must be there to show what is
  - And labs must show what is not
- Differential diagnosis must be there
- The labs will show you the way
  - Start looking at innate immunity as a target
  - Start looking at targets that you can fix
  - Fix the targets; watch the illness disappear
  - Wait for relapse
Here’s my treatment message

- Look for environmental exposures
- Establish a decent baseline of results of innate immunity testing
- Look for biofilm formers; they must go!
- Treat the inflammatory physiology
- What do you have left?
- What happens when the injured patient is exposed next week? Repeat illness!
For more information:

www.survivingmold.com
www.chronicneurotoxins.com
Surviving Mold  December, 2010
Lose the Weight You Hate  2002, 2005