

# Biotoxins, vision, inflammatory cytokines and hypothalamic hormones in primary care medicine

From Post-Lyme Syndrome to Sick  
Building Syndrome, a new paradigm for  
medically uncertain symptoms

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# Biotoxin-Associated Illnesses

- ▶ Potential for exposure to biologically produced neurotoxins
- ▶ Multiple symptoms, multiple organ systems
- ▶ Deficits in visual contrast sensitivity (VCS)
- ▶ Role of pro-inflammatory cytokine (PIC) responses to biotoxins
- ▶ Control of PIC by activation of adipocyte PPAR gamma
- ▶ Impact of PIC on hypothalamic proopiomelanocortin (POMC) pathway

# Biotoxin/illness mechanisms

- ▶ Importance of leptin, agonist and monitor
- ▶ Leptin receptor is primordial cytokine receptor
- ▶ Melanocyte stimulating hormone (MSH) in POMC
- ▶ MSH deficiency has multiple downstream hormonal and cytokine effects
- ▶ Genetic basis of susceptibility, HLA DR by PCR unique triplets as markers of illness
- ▶ Cholestyramine as a biotoxin binder: the first step
- ▶ Multiply antibiotic resistant coagulase negative Staph in biofilms, opportunistic hemolysin former

# Complexity of Biotoxin Illnesses

- ▶ Genetic basis of susceptibility
- ▶ Unique grouping of symptoms, not unique to organism
- ▶ Sources of symptoms include toxins, cytokines, hormones, secondary colonizers
- ▶ Without clearing all, little improvement is seen

# Organisms studied causing human illness

- ▶ Dinoflagellates: *Pfiesteria*, *Chattonella verruculosa*, *ciguatera*
- ▶ Fungi: *Stachybotrys*, *Aspergillus*, *Penicillium*, *Cladosporium*, *Chaetomium*, *Acremonium* list reflects established neurotoxicity, others possible
- ▶ Blue-green algae: *Microcystis*, *Cylindrospermopsis*, *Anabaenopsis*, *Lyngbya*
- ▶ Spirochetes: *Borrelia burgdorferi*
- ▶ Apicomplexans: *Babesia microti*, *WA-1*, *CA-1*
- ▶ Gram positive bacteria: *Coagulase negative Staph*, *Bacillus anthracis*
- ▶ Arachnids: Brown recluse spiders

# Unknown biotoxin, but illness meets all other criteria



Chronic soft tissue injury  
Chronic fatigue syndrome\*  
Charcot-Marie Tooth

\*defined by HLA genotype

# Symptoms

- ▶ Fatigue, weakness
- ▶ Muscle ache, cramps, unusual pain (ice-pick, “lightning bolt”)
- ▶ Headache, can be confused with migraine
- ▶ Sensitivity to bright light, tearing (or lack of tearing), blurred vision, redness
- ▶ Chronic sinus congestion, cough, short of breath
- ▶ Abdominal pain (often labeled IBS), diarrhea, often secretory
- ▶ Joint pain, enthesopathy, morning stiffness; migratory, rarely true arthritis

# Symptoms

- ▶ Cognitive impairment, recent memory, assimilation of new knowledge, abstract handling of numbers, word finding in conversation, confusion, difficulty sustaining concentration, disorientation, "brain fog"
- ▶ Skin sensitivity to light touch
- ▶ Mood swings, appetite swings, sweats, often at night, difficulty with temperature regulation
- ▶ Numbness, tingling, often non-anatomic, vertigo, metallic taste
- ▶ Excessive thirst, frequent urination, sensitivity to static shocks (doorknobs, car handles, light switch plates, kisses)
- ▶ Impotence, menorrhagia

# Visual Contrast Sensitivity Requirements

- ▶ Visual acuity 20/50 or better, monocular testing
- ▶ 70 foot-lamberts
- ▶ 18 inches for VCS
- ▶ 14 inches for visual acuity



# Visual Contrast Sensitivity as a Neurological Test

- ▶ Sinusoidal bars on gray background
- ▶ 1.5, 3, 6, 12, 18 cycles/degree of visual arc
- ▶ Intensity reduced by .15 log units from one column to next
- ▶ Magnocellular and parvocellular fibers
- ▶ Inverted U shape curve established in 2000 normal patients
- ▶ Deficits in all rows, greatest at 6 and 12 cycles/degree visual arc
- ▶ Eliminates near, far, color, peripheral, static, motion vision
- ▶ Binary output system

# Advantages of VCS testing

- ▶ Portable
- ▶ Non-invasive
- ▶ Inexpensive
- ▶ Reproducibly reliable
- ▶ Shows changes from day to day correlating with exposure and RX
- ▶ Correlation with flow rates in capillaries of retina and neural rim of optic nerve

# Disadvantages of VCS

- ▶ Not specific for given biotoxin
- ▶ Confounding exposures, including solvents, metal fumes, petrochemicals
- ▶ History of use and abandonment as a measure of optical function

# Pro-inflammatory cytokine (PIC) responses to biotoxins

- ▶ TNF to *Borrelia* and multiply resistant CNS, especially MRCoNS
- ▶ IL-1 $\beta$  to dinoflagellates and fungi
- ▶ Mixtures for BG algae, apicomplexans
- ▶ IL-6, CRP are downstream events

# Additional parameters of PIC response

- ▶ Matrix metalloproteinase-9 (MMP9)
- ▶ Plasminogen activator inhibitor-1 (PAI-1)
- ▶ Insulin resistance, peripheral
- ▶ Leptin resistance, hypothalamic
- ▶ Phosphorylation of serine instead of threonine on receptor a shared mechanism



# PPAR gamma activation opposes PIC effects

- ▶ TNF rapidly downregulated
- ▶ PAI-1 lowered if no-amylase diet use (no wheat, rice, oats, barley, rye, bananas, vegetables that grow beneath the ground; no maltodextrins, no added sucrose or corn syrup) fewer than 5 servings/week
- ▶ Leptin rapidly lowered by PPAR gamma agonists
- ▶ MMP9 lowered rapidly by PPAR gamma agonists
- ▶ Organic anion transport protein system in bile canaliculi upregulated
- ▶ UCP 1, 2, 3 activated
- ▶ Fatty acid uptake increase, reducing insulin resistance induced by FFA

# PPAR gamma safe in non-diabetics

- ▶ No reports of hypoglycemia
- ▶ Liver function abnormalities reported in users of rosiglitazone (not pio, yet) rare
- ▶ 113 patients with Post-Lyme syndrome reported at ADA, 6/02
- ▶ 40 patients with refractory obesity reported at 83rd Endocrine Society, 6/01

# Proopiomelanocortin (POMC) pathway

- ▶ Leptin is agonist for receptor
- ▶ JAK mechanism to activate transcription of POMC
- ▶ Cleaved into B-endorphin and MSH
- ▶ MSH is 13 amino acid peptide, cleaved to 10 aa compound, ACTH
- ▶ Ventromedial nucleus of hypothalamus
- ▶ Importance of hypophyseal portal system
- ▶ Vulnerable to peripheral cytokines, de novo cytokines

# Alpha melanocyte stimulating hormone (MSH)

- ▶ Neuroendocrine, immune modulator
- ▶ Peripheral regulating effects on PIC production by macrophages
- ▶ PIC effects on keratinocytes
- ▶ Mucus membrane effects in nasal mucosa and small bowel
- ▶ Controls hypothalamic production of melatonin and endorphins (note importance of MSH deficiency associated with chronic pain and fatigue)
- ▶ Regulates pulsatile secretion of gonadotrophins
- ▶ Interaction with vasopressinergic neurons and ADH production
- ▶ Posterior and anterior pituitary effects

# Deficiency of MSH

- ▶ Fundamental importance to question, "How long does it take to feel better?"
- ▶ Leptin changes quickly; MSH much more slowly
- ▶ Monitoring response to therapy employs leptin
- ▶ Once deficiency of MSH is being corrected, other hormone pathways clear
- ▶ Replacement of androgens and ADH not necessary once POMC pathway "resets"
- ▶ Inability of pathway to make MSH is marked by refractory symptoms, refractory obesity and leptin resistance
- ▶ FDA IND # 63,993 replacement of MSH via nasal instillation for CFS
- ▶ Patented protocol

# Cholestyramine as a therapeutic agent

- ▶ Multiple side chains on styrene backbone with quaternary ammonium group
- ▶ Radius is approximately 1.4 Angstroms
- ▶ Positive charge
- ▶ Biotoxins studied have central molecular of shared anions, radius 1.4 Angstroms
- ▶ Likely electrostatic interaction
- ▶ Not absorbed
- ▶ Used as binder of cholesterol for over 40 years

# Cholestyramine as a therapeutic agent

- ▶ Many reported uses in toxicology, including PCB, dioxins, chlorothalonil (EPA recommended)
- ▶ Documented to bind to BG algae toxins, fungal toxins
- ▶ Use is associated with recovery from illness, improvement in VCS
- ▶ If hormonal pathways are excessively damaged, won't correct syndrome
- ▶ Won't eradicate coag neg Staph
- ▶ FDA letter of exemption 6/99
- ▶ Side effects of reflux, bloating, constipation predictable and treatable

# Who gets these illnesses

- ▶ 3/10 in a Pfiesteria bloom; 15/30 in a sick building; 3/8 eating the same ciguatoxin-contaminated fish; many other examples
- ▶ Factors not important: race, sex, age, duration of exposure (NOT dose related), underlying medication use, cigarette use, alcohol use, caffeine, decongestant, topical steroids (including nasal and pulmonary preparations), additional illnesses, including diabetes, heart disease, allergy, asthma
- ▶ Specific HLA DR genotypes uniquely associated with susceptibility
- ▶ Analyzed by PCR; transplant serologies of no significant use
- ▶ No crossover of susceptibility
- ▶ MSH deficiency is a confounder, as coag neg Staph common with low MSH in other biotoxin illnesses
- ▶ DRB1-14, DQ 5, DRB3-52B is a multi-susceptible genotype

# Baseline work-up

- ▶ History, including exposure, symptoms, confounders
- ▶ VCS testing
- ▶ EKG, PFT, urine SG and sediment
- ▶ Labs: HLA DR, MSH, leptin, ADH, osmolality, ACTH, cortisol, androstenedione, DHEAS, total testosterone, PAI-1, TNF, GGTP, comprehensive metabolic panel, CRP, CBC, MMP9. Save 2 SST tubes in 4 aliquots. Must draw cytokine analyses and spin down within 5 minutes; MSH requires chilled lavender tube, with Trasylol added. HLA is room temperature, all others freeze
- ▶ Deep aerobic nasal culture, sent to lab that specifically will do biogram and identify species. Don't just send to any lab! Esoterix is particularly experienced in isolation of MRCoNS.

# Importance of MMP9

- ▶ Delivers inflammatory elements across subintimal matrix
- ▶ Organ involvement highly associated with elevated MMP9, i.e. complete heart block in Lyme, demyelinating lesions in Sick Building (UBO on MRI might suggest MS, but it is not MS; conversely, some MS patients with multisystem involvement have SBS), inflammatory arthritis in Lyme and Sick Building, commonly found in “not-asthma” asthma
- ▶ Elevations seen acutely in Herxheimer reactions in Lyme
- ▶ Normal levels and multiple symptoms suggest lack of inflammatory component and major role for hormonal disruption; lower with pioglitazone
- ▶ Patients with bizarre neurologic events and high MMP9 quite commonly have colonization with coag neg Staph

# Coagulase negative Staph in nasal cultures

- ▶ Present in controls 25% of the time
- ▶ Controls with CNS have <2 antibiotic resistance in >98% of isolates
- ▶ Cases have 2 or more antibiotic resistances in > 95% of isolates
- ▶ Methicillin resistance is associated with greater number of antibiotic resistances and more refractory symptoms
- ▶ Organism is a colonizer: presence does not suggest infection/tissue penetration
- ▶ Organism is a biofilm producer
- ▶ Release of hemolysins across mucus membranes, invoking cytokine response of susceptible host felt to be pathogenic mechanism
- ▶ Bismuth compounds show promise as therapeutic agents

# Coagulase negative Staph and CFS

- ▶ Associated with CFS by Roberts, Butts and colleagues in Newcastle, Australia 1998. Not speciated, no biograms done, no cytokine assays done, no HLA DR
- ▶ Associated with CFS by Gottfried and Swedish group, treated with Staph toxoid. Not speciated, no biogram, no cytokine assays, no HLA DR done
- ▶ Current use of Staph Phage Lysate shows promise in low MSH patients with repeated isolation of CNS and refractory symptoms

# Application of basic biotoxin paradigm

- ▶ 381 patients with Post-Lyme Syndrome
- ▶ 103 patients in 43 buildings with resident indoor toxin forming fungi (ITFF)
- ▶ 21 patients in 5 buildings with ITFF, evaluated as a case-control and then prospectively, with monitoring of leptin, weight, VCS and symptoms
- ▶ 250 patients with ITFF exposure and endocrinopathies
- ▶ 484 patients with coag neg Staph, importance of MRCoNS and antibiotic resistances, large control group
- ▶ 36 patients with ciguatera
- ▶ 8 patients with BG algae exposure, including one hyperacute case

# Biotoxin paradigm studies

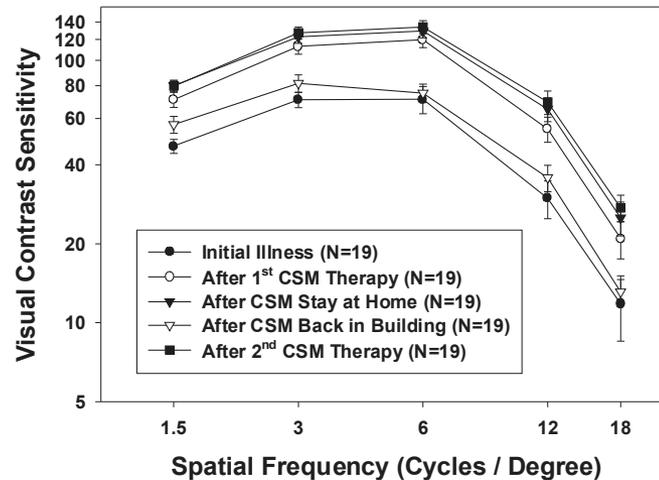
- ▶ 5 patients with PEAS (EHP 2001; 109: 539-545)
- ▶ 37 patients with residential and recreational acquisition of PEAS (EHP 2001; Special CDC Supplement 109(5))
- ▶ 10 patients with MMP9 and UBO on MRI of brain
- ▶ 3 patients with brown recluse bites
- ▶ 30 patients with Lyme and Babesia
- ▶ 580 patients with HLA DR by PCR and documented illness
- ▶ 750 patients with leptin/MSH

# Research for the future

1. Get the Sick Building and Lyme papers out
2. Correlate endocrinopathies of biotoxin-associated illnesses with risk factors
3. Follow MMP9 levels in UBO patients with respect to treatment and prospectively
4. Develop peer reviewed basis for recognition of MRCoNS as pathogen
5. VEGF, sphingomyelinase, genetic factors

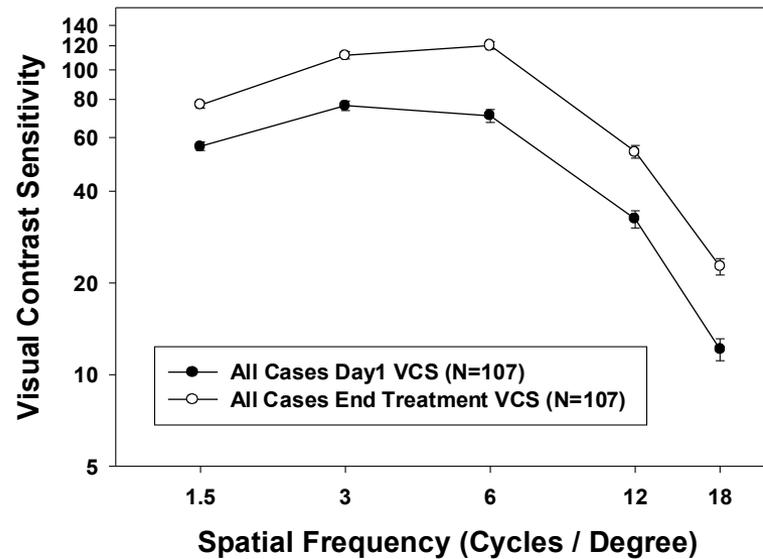
# SBS Paradigm

**Reacquisition of Sick Building Syndrome:  
VCS Deficit in Initial Illness,  
Resolution After Cholestyramine Therapy,  
Stable without Re-exposure,  
Deficit Reacquisition with Re-exposure,  
Second Resolution with CSM Therapy**



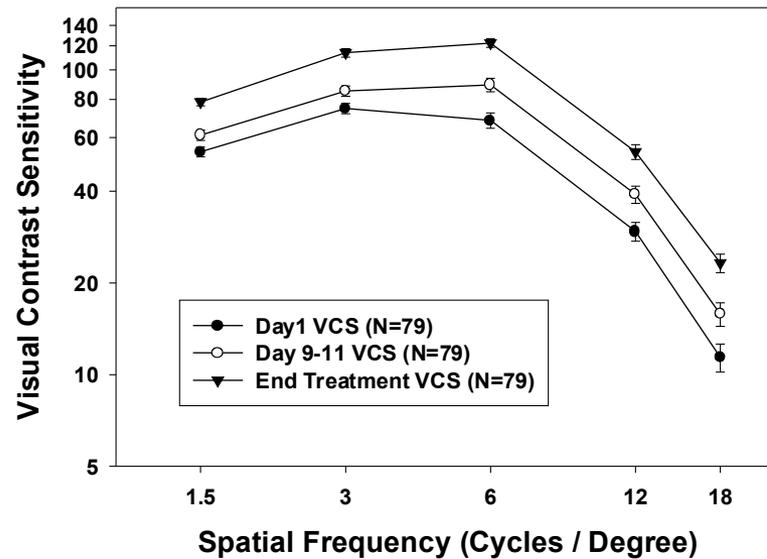
# VCS and Post-Lyme

**VCS in Post-Lyme: Day 1 (Begin Actos),  
Day 6 (Actos & Begin CSM) - Data Not Shown,  
Day 9-11 (Continue Actos & CSM) - Data Not Shown,  
End Treatment (4-8 Weeks)**



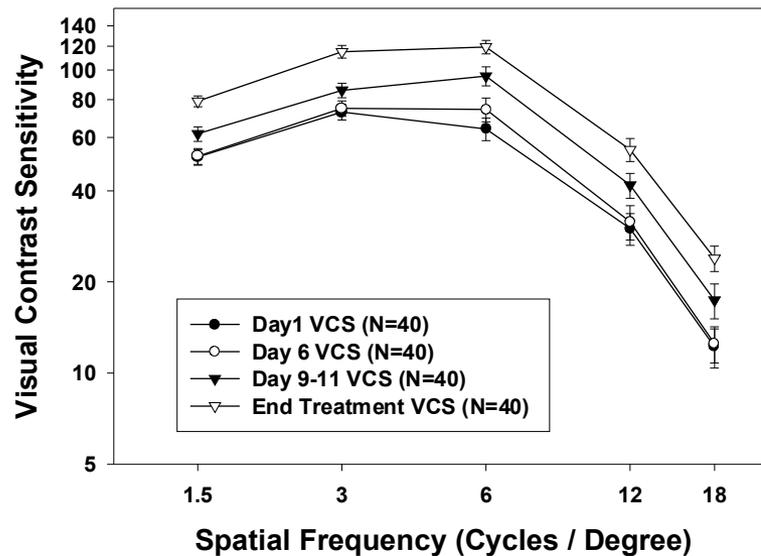
# TZD and VCS

**VCS in Post-Lyme: Day 1 (Begin Actos),  
Day 6 (Actos & Begin CSM) - Data Not Shown,  
Day 9-11 (Continue Actos & CSM),  
End Treatment (4-8 Weeks)**



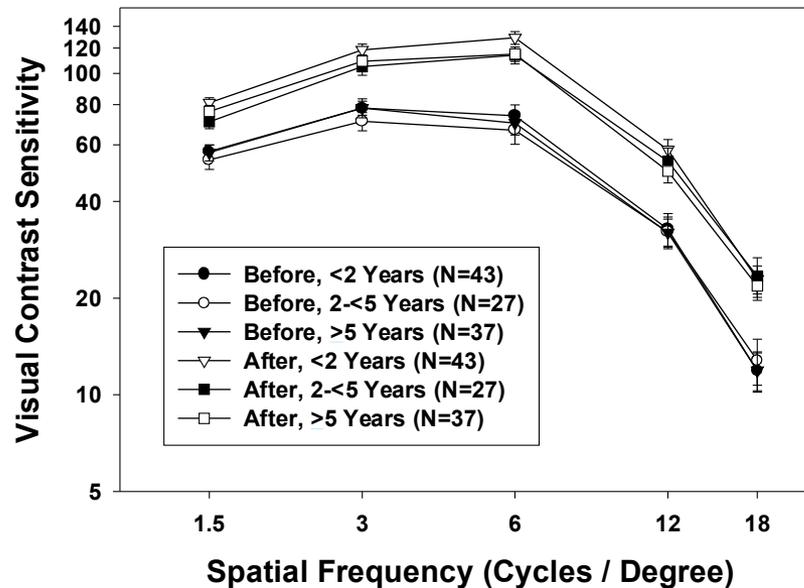
# VCS and Sequential Rx

**VCS in Post-Lyme: Day 1 (Begin Actos),  
Day 6 (Actos & Begin CSM),  
Day 9-11 (Continue Actos & CSM),  
End Treatment (4-8 Weeks)**



# Duration not Significant

## VCS in Post-Lyme: Before & After Treatment By Illness Duration - <2, 2-<5 and >5 Years



# Post-Lyme and Babesia

- ▶ 245-patient multisite clinical trial shows link to neurotoxins/proinflammatory cytokines
- ▶ Over 94% of patients had >50% reduction in symptoms
- ▶ All patients with symptoms refractory to standard and extraordinary antibiotic Rx
- ▶ Deficits in VCS and symptoms abate with cholestyramine
- ▶ Pretreatment TNF levels fall with activation of PPAR $\gamma$  using pioglitazone
- ▶ Babesiosis/Lyme patients, all VCS+, disproportionately represented in lower responders
- ▶ What is the mechanism?

# Results

## 12 week trial

- ▶ / ■ By week 6, no notable symptoms resolution or VCS improvement
- By week 9, “watershed” event, with increased symptoms, beyond which symptoms improved significantly, at weeks 8-9 trial (total 5-6 weeks active atovaquone).
- At completion
  - ▶ 16 had >50% reduction in symptoms
  - ▶ 5 had zero or one symptom
  - ▶ No relapse without reexposure
  - ▶ VCS scores significantly increased

# HLA and susceptibility

## **Mycotoxin illness**

	DRB1	DQ	DRB3	DRB4	DRB5
▶	17	2	52A,C		
▶	13	6	52A,B,C		
▶	7	2		53	
▶	7	9		53	

## **Post-Lyme susceptibility**

▶	15	6			51
▶	16	5			51

## **Coag neg Staph, includes MRCoNS**

▶	11	7	52B		
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