



Treatment of Chronic Inflammatory Response Syndrome.

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Do you suffer from chronic unexplained illnesses? Take multiple medications for widespread symptoms that are treated symptomatically without a succinct diagnosis? Fibromyalgia? Chronic fatigue, brain fog, autoimmune disorders, shortness of breath with no reason, unusual skin sensations, diarrhea, just multiple, multiple symptoms across many body systems that just do not add up? Did these symptoms all kind of just start happening in a certain time period? Have you been diagnosed with Adrenal Fatigue, leaky gut, food sensitivities, POTS syndrome, Pulmonary Hypertension, interstitial Lung Disease, new onset asthma for really no reason? Neurological symptoms that you really have but have been written off as a psychological etiology as the evaluating physician cannot believe the symptoms? Is there a single entity that may tie all these symptoms together? Maybe so.

Because all of the usual tests that physicians know to run are usually normal. Let me tell you, I have been seeing a lot of abnormal tests these days now that I know what tests to check!

I have been practicing Integrative and Functional Medicine since 2007. Internal Medicine since 1991. I will tell you that I have seen all of the above and have missed the unifying diagnosis more than I would like to admit. Because, none of this was known when I went through medical school or residency at one of the most prestigious programs in the country. Emory University ranked #7 when I did my residency in Internal Medicine.

Over 2018-2019, especially an intensive course November-December 2019 I have become much more aware of that potential "missing link" that may tie many of these symptoms into that "entity".

I am also very lucky to be associated with two very astute Nurse Practitioners that have studied and understand this phenomenon as well as described below.

History:

The chronic inflammatory response syndrome is an illness pioneered by Dr. Ritchie Shoemaker. In 1997 patients in Maryland were exposed, during a fish killing caused by a dinoflagellate called pfiesteria, came down with a multisystem illness. This was dominated by muscular symptoms, confusion and diarrhea along with others. To treat the patient's diarrhea, Dr. Shoemaker gave them cholestyramine, which is a drug developed for treatment of cholesterol, however, had an off-label use for diarrhea. The patient's diarrhea got better but also there multi system symptoms. This began Dr. Shoemaker's desire to delve further into this illness and see why cholestyramine helped so many. Approximately 20% of these patients. However, went on to develop chronic illness. This has now been ascribed to a defect in the major histocompatibility complex that 20-25% of the population has. Usually when our body is exposed to a pathogen, it deals with it in a rather quick way with what is called our innate immune system. After this, however, the "picture" of that pathogen is handed off to the second and more broad-spectrum aspect of our immune system called the adaptive immune system. In patients that go on to develop this chronic disease, these are the ones that have the defect in the major histocompatibility complex discussed above.

What was found. However, pfiesteria is not the only one thing that could initiate this process. Pfiesteria is a biotoxin, there are many, many other biotoxin's that can trigger this abnormal response.

Consider the following potential biotoxin sources and differential diagnosis:

- CIRS-Water Damaged Building (WDB):

-Up to 80 % of buildings are water damaged (WDB). Source of exposure is through inhalation of molds such as *Chaetomium globosum*, *Aspergillus penicilloides*, *Aspergillus versicolor*, *Stachybotrys chartarum*, *Wallemia sebi*, *Actinomyces*. Also consider bacteria, toxic byproducts, antigen, /or inflammagens that trigger systemic inflammation and the innate immune system via pathogen-associated molecular patterns and danger associated molecular patterns. A WDB must meet the criteria of potential exposure to water damage, or documented growth of microbes as evidenced by visible mold, mold odors, or commercial mold specie testing such as ERMI or HERSMI2. Humans with an exposure to a suspected WDB must display symptoms defined in peer reviewed studies, and they must improve with treatment guidelines from peer reviewed studies.

- CIRS-Post Lyme Syndrome (PLS): a source of biotoxin is skin disruption.

- CIRS-Arachnids: Recluse spider: a source of biotoxin is skin disruption.

- CIRS-Apicomplexans: *Babesia* spp., *Sarcocystis*.

-Has there been or is there now a documented bite, exposure, potential for exposure, assess travel patterns and high risk locations for tick borne illness

- CIRS-Possible estuarine associated syndrome (PEAS): Pfiesteria (dinoflagellate) source of exposure is water, aerosol, ingestion.
- CIRS-Ciguatera: Gambierdiscus (dinoflagellate).
- CIRS-Cyanobacteria: Microcystis, Lyngbya, Cylindrospermopsis, Anabaenopsis .
- Heavy Metal exposures (amalgams, occupational, recreational).
- Chemical Exposures (occupational, recreational).

-Look to a timeline that coincides with the occupation, a move, recreational activities that relate to metal and chemical exposures.

- Post traumatic Stress Events (mark on a timeline).
- Traumatic Brain Injury (mark on a timeline).

This abnormality in the innate immune system causes significant inflammation in the brain, leading to many downstream negative effects. There are numerous other diagnoses that patient have such as POTS, chronic fatigue, fibromyalgia, memory loss, joint pains, shortness of breath, pulmonary hypertension, frequent urination, abdominal pain and diarrhea and there also are unusual electrical type symptoms that many people have. Many patients have also been diagnosed with chronic fatigue syndrome, attention deficit disorder, hypochondriasis, posttraumatic stress disorder, allergies, anxiety, depression, or just faking it.

In summary, if a patient has widespread otherwise unexplained symptoms, has seen multiple providers without adequate answers, is on multiple medications for multiple different diagnoses other than the usual hypertension, diabetes, etc., this patient likely should be evaluated for chronic inflammatory response syndrome.

And, even if the exposure goes away, the syndrome may continue because of this upregulation in the immune system going on unchecked.

I know, I have been there, even though practicing functional medicine, I have missed this syndrome. In retrospect, many times.

It is important to seek a practitioner out that is familiar with this because through the work of Dr. Shoemaker and Dr. Heyman as well as others, this now is a disease with a potential cure, certainly a significant improvement in overall symptoms.

Overall, there are 37 different symptoms ascribed to this, but have been grouped into the 13 cluster groups as below:

1. Fatigue.
2. Weak, assimilation, aching, headache, light sensitivity.
3. Memory, word finding
4. Concentration
5. Joint, morning stiffness, cramps.
6. Unusual skin sensations, tingling
7. Shortness of breath, sinus congestion.
8. Cough, thirst, confusion.
9. Appetite swings, body temperature regulation.
10. Red eyes, blurred vision, sweats, mood swings, ice pick pains.
11. Abdominal pain, diarrhea, numbness
12. Tearing, disorientation, metallic taste.
13. Static shocks, vertigo

If you have 8 or more of these, only need one in the cluster, there is a 95% chance that you have this illness. If so, go to survivingmold.com and take the VCS, visual contrast sensitivity test. If this is failed, there is a 98.5% chance that you are dealing with this.

During your initial evaluation. You will need a complete history and physical examination along with the usual labs to rule out other diagnoses. After this, specialized testing will be done that takes a look at these major histocompatibility complex that was discussed above. Numerous other markers of neuro inflammation will be tested along with clotting studies and other markers of inflammation which will be followed during the treatment course to ensure normalization.

A list below includes lab abnormalities along with how some of the things that these potential abnormal labs affect us: Do not proceed with any supplements listed, this for information only and patients will have specific instructions at time of treatment.

CIRS LABS

VCS:

Best test of functional vision.

Diagnostic at baseline essential for follow-up. Especially hyperacute.

Correlates with measures perfusion. Neurologic function nerves/vision. Elimination near, far, static, motion, peripheral vision.

MMP-9 Range: Less than 385

Delivers inflammatory elements out of blood, across two endothelial membranes, across basement membrane into subintimal space of tissue (brain, nerve, muscle, lung, blood). Hence, can see widespread destruction.

If elevated over 500, take omega-3 4.2 g per day for one-month (875/675) TID. Start this 5 days before starting cholestyramine or WelChol.

If MMP 9 greater than 600, check a PAI-1 as well.

Bridges BBB. Breaks down connective tissue.

ACTH/Cortisol Abnormal in approximately 60% of patients

ACTH Range: 8-37

Cortisol AM Range: 4.3-22.4

Absolute or relative ACTH dysregulation may be seen:

Absolute high: ACTH greater than 45 or cortisol greater than 21

Absolute low: ACTH less than 5 or cortisol less than 4

Relative: ACTH was less than 10, when cortisol was less than 7, Two-tiered test

Relative: ACTH was greater than 15 when cortisol was greater than 16. Two-tiered test.

Basis is not adrenal insufficiency or Cushing's. Basis is disruption in Melanocortin physiology.

Risk of suppression of ACTH is dramatically increased in CIRS because of low MSH.

If MSH low, one cannot rely on ACTH stimulation test.

Correct the source of low cortisol or low ACTH first

Rarely is prescription needed.

Coming off cortisol is hard for those with low MSH.

Oral steroids relatively contraindicated. Liberal Rx for prednisone, Medrol dose packs, Depo-Medrol should be avoided.

ADH/Osmolality Abnormal in approximately 80% of patients

Range: ADH 1-13.3 pg/ml

Range: Osmolality 280-300

dysregulation's

Absolute high: ADH, greater than 13, or osmolality greater than 300

Absolute low: ADH less than 5 or osmolality less than 275

Relative: ADH was less than 2.2. When osmolality was 292-300, 2 tiered test

Relative: ADH was greater than 4 when osmolality was 275-278

ADH (Anti-diuretic Hormone) stimulates cells in renal tubules to reabsorb free water in response to rising osmolality (saltiness) of blood. Low MSH is associated with blunted ADH response to rising osmolality = loss of free water. Dysregulation of ADH/Osmolality is quite common (80% in low MSH) with intravascular dehydration as a concomitant. Salt may be excrete to skin causing "static shocks", pee shocks.

Chronic migraines in CIRS is usually ADH dysregulation.

POTS (Postural Orthostatic Tachycardia Syndrome) usually is increased PASP (Pulmonary Artery Systolic Pressure) and ADH dysregulation

Treatment with DDAVP 0.2 mg QOHS, monitor osmolality and electrolytes in 10 days.

Patients with acquired von Willebrand bleeding need to carry DDAVP with them when they travel.

Record daily weights. Look for nocturia and polyuria to stabilize in one week.

MSH Range: 35-81

Anti-inflammatory, neuro regulatory peptide hormone.

Involved in weight, appetite, mood, circadian rhythms, mucous membranes defenses, pulmonary responses, blood-based immunocyte responses, gut tight junctions. (Don't say leaky gut in face of low MSH.)

Rx: **VIP intranasal** 50 mcg/ml. Normal dose 4 times a day; 120 doses per month equals 12 mL. Use micro doses for chemical and food sensitive. Macro dose for serious illness. Mandatory completion of protocol before starting. Must have normal visual contrast sensitivity, normal nasal culture, normal hertsmi-2 (or ERMI). Normal lipase and normal GGTP. Regular monitoring mandatory.

Antigliadin antibodies. Range: 0-19

If elevated, gluten-free diet. 3 months and recheck.

MSH regulates tight junctions in gut.

If Serum positive, check TTG-IgA to r/o celiac disease.

Androgen deficiency. Is present in about 40% of patients

Challenge with DHEA 25 mg by mouth 3 times a day for one month. Measure DHEA and estrone at baseline and in one week. Then wait 1 week and show stability.

Aromatase challenge: Give DHEA 25 mg 3 times a day for 1 week. Baseline estrone and estradiol. Testosterone, DHEA and androstenedione. If testosterone goes up and estrogens stay low, aromatase okay. If testosterone goes down and estrogens go up, aromatase activity is up. Do not use aromatase inhibitors in low MSH patients.

Usually stabilize on their own.

Leptin Recalcitrant weight gain.

Range: 0.5–13.8 men

Range: 1.1–27.7, women

C3a Quest: Range: 55–486

High-dose statin, Zocor, 80 mg daily for one month, usually indicates there is a bacterium in the blood, actinomycetes? Lyme?

C4a: Quest: Range: 0–2830

Highly involved with **mast cell activation syndrome**. Dermatographia is C4a in action.

Putative anaphylatoxin. activates mast cells and basophils, increases smooth muscle contraction, vascular permeability, release of chemotactic factors. Systemic responses follow activation. Associated with cognitive defects, restrictive lung disease, hypersensitivity pneumonitis, multisystem, multi symptom illness, dominated by chronic fatigue. Re-exposure. **Brings a rise in C4a within 4 hours in patients exposed to toxigenic fungi, 12 hours after tick bite and Lyme patients.** Elevated levels of C4a are durable even though C4a is short-lived.

Produced by MASP2; can auto-activate.

High dose fish oil (875/675) TID.

VIP may lower this as well.

VEGF: Range: 31–86.

Low VEGF should be correlated with suppressed VO2 max.

Ignore high levels until plasma levels greater than 600. Then consider octreotide scan looking for APUDoma tumor.

Increases oxygen delivery on capillary basis. Increases new blood vessel growth. In CIRS, 1/3 low, 1/3 normal, 1/3 high.

Capillary hypoperfusion/hypoxia stimulates VEGF. Rising VEGF stimulates TGF beta-1, TGF beta-1 suppresses VEGF. Can be overridden by ongoing exposures. Bartonella not a player in any VEGF trend.

Persistent low VEGF rare in older, worse when in younger.

Prescription same Omega's (875/675) TID as for MMP 9, omega-3 4.2 g per day.

If no response, move on quickly to VIP.

TGF beta-1 Range: less than 2380, greater than 5000. Symptoms appear, greater than 10,000, restrictive lung disease. Correction of fibrosis in lung, skin, liver is an important benefit of lowering TGF beta-1.

Might be the single most important proteomic test. Pleiotropic: pro and anti-inflammatory.

Fibrosis everywhere. tremor, cognitive issues, joint symptoms may occur. Sends T-regs into tissue, interacts with tissue ROR to suppress inflammation, but if ROR low, T-regs can be plasticized into T-effector cells-increased inflammation.

Especially important in interstitial lung disease. Role in aneurysm. Plasma higher in hypermobile.

Treatment is losartan, VIP.

VIP (Vasoactive Intestinal Polypeptide) Range: 23–63

First found in intestine, 75% of receptors, however, are in the lung. Anti-inflammatory, immune-regulatory. Treatment with VIP is excellent for pulmonary hypertension, primary and acquired.

Hopkington Drug, Hopkington, Ma.

Treatment is best monitored by GENIE. Level in plasma have nothing to do with level of VIP receptor 2. Targeting PASP is a reasonable surrogate.

After several months, the need for 4 times a day dosing can be eased to twice a day.

VIP intranasal 50 mcg/ml. Normal dose 4 times a day; 120 doses per month equals 12 mL. Use micro doses for chemical and food sensitive. Macro dose for serious illness. Mandatory completion of protocol before starting.

With Multinuclear atrophy on NeuroQuant, however may need 12 sprays/day

VWF von Willebrand's factor (clotting) may be abnormal in as many as 60% of patients

Factor VIII, von Willebrand's antigen, ristocetin associated cofactor

Values may be low (acquired vWF) –(bleeding) or high (clotting), Pulmonary embolus, PICC line clotting. Greater percent high in Post-Lyme than mold.

For low, bleeding, nasal... DDAVP, usually only one tablet needed to stop hemorrhagic episode.

NeuroQuant MRI:

Another very important consequence of these actions are the effects on the brain causing either atrophy (shrinkage) or swelling (edema) to 11 areas of the brain. Interestingly, the work of Dr. Shoemaker and Heyman is showing improvement in these areas with treatment protocols. This is the NeuroQuant MRI, which is a noncontrast MRI of the brain. The images are then measured with special software to show the areas that are either smaller or larger as above.

Significant findings differentiating disease pattern:

CIRS-WDB: Forebrain parenchyma increased, cortical gray increased, caudate decreased.

Post Lyme's: Small putamen, large right thalamus.

Automated report on surviving mold, download report.

Lateral ventricle. Newly added

6 Months of VIP after steps 1 through 11 of protocol improved volumes. Minimum dose 12/day for 6 months.

Encourage all to test. This also has different patterns based on whether this is a post Lyme patient versus a water damage to the building versus other reasons. It is giving information that we are not able to see on any lab tests.

GENIE:

In addition, we are now using transcriptomics, your blood is drawn under very strict parameters and then is sent to the lab. This is looking at how the immune system is being regulated, whether certain genes are upregulated or down regulated due to the disease process. This is also been shown to change in the positive way after treatment. It also gives us a lot of information regarding what aspects of the immune systems are upregulated more than others and again, is showing very specific findings that direct us to the underlying process and how to address this.

All of the above is in general regarding the illness. Following this, an 11-step protocol that must be followed in order is begun.

Remove from exposure, then

1. Cholestyramine/WelChol

CSM 4 g 4 times a day, or Welchol 2 tabs BID, continued until able to pass VCS

2. Eradicate MARCoNS

Everyone needs testing. Microbiologydx.com

EDTA 2% both nares TID one month or may use EDTA/Ag. Shoemaker currently uses only EDTA 2%.

After 2 weeks of EDTA–Ag, resolution of the worst gene suppression. Staying on this is acceptable. Keep dogs out of bed. Avoid antifungals at all cost.

EDTA 2% both nares TID one month Or may use EDTA/Ag. Shoemaker currently uses only EDTA 2%.

MARCoNS (Multiple Antibiotic Resistant Coagulase Negative Staphylococci) is an antibiotic resistant staph that resides deep in the nasal passage of 80% of people with low MSH (Melanocyte-Stimulating Hormone), those suffering from Biotoxin Illness and other chronic inflammatory illnesses CIRS (Chronic Inflammatory Response Syndrome) and CFIDS (Chronic Fatigue and Immune Dysfunction Syndrome). This percentage increases when the person has also been treated with antibiotics for a month or more. Once they have taken up residence, MARCoNS will further lower MSH (MARCoNS make hemolysin that cleave MSH rendering it inactive), increases cytokines, and lower T-reg cells resulting in Chronic Fatigue symptoms of body aches and debilitating exhaustion. MARCoNS is not an infection but a commensal colonization that can become an infection. These bacteria send chemicals into the blood (exotoxins A and B) that increase inflammation and by cleaving MSH causes a further decrease of MSH levels, which in turn creates more inflammation.

Document clearing with repeat cultures.

3. Correct Antigliadin

If elevated, gluten-free diet for 3 months and then recheck.

4. Correct androgens

Challenge with DHEA 25 g by mouth 3 times a day for one month. Measure DHEA and estrone at baseline and in one week. Then wait 1 week and show stability.

Aromatase challenge: Give DHEA 25 mg 3 times a day for 1 week. Baseline estrone and estradiol. Testosterone, DHEA and androstenedione. If testosterone goes up and estrogens stay low, aromatase okay. If testosterone goes down and estrogens go up, aromatase activity is up. Do not use aromatase inhibitors in low MSH patients.

Usually stabilize on their own.

5. Correct ADH/osmolality

Treatment with DDAVP 0.2 mg QOHS, monitor osmolality and electrolytes in 10 days. Then go to nightly and titrate as needed.

Patients with acquired von Willebrand bleeding need to carry DDAVP with them when they travel.

Record daily weights. Look for nocturia and polyuria to stabilize in one week.

6. Correct MMP9

If elevated over 500, take omega-3 4.2 g per day for one-month (875/675) TID. Start this 5 day before starting cholestyramine or WelChol.

Consider low amylose diet

- a. Correct VEGF
Omega (875/675) TID
7. Correct C3a
High dose statin, Zocor 80 mg/day one month, also look for organisms that may be causing this to go up. C4b-2A attaches to organisms and cause cleavage fo C3 to C3a
8. Correct C4a
Omega 875/675 TID
9. TGF beta-1
Losartan 25-50 mg BID, VIP if failing to resolve
10. VIP
Treatment is best monitored by GENIE. Level in plasma has nothing to do with level of VIP receptor 2. Targeting PASP is a reasonable surrogate.
After several months, the need for 4 times a day dosing can be eased to twice a day.
VIP intranasal 50 mcg/ml. Normal dose 4 times a day; 120 doses per month equals 12 mL. Use micro doses for chemical and food sensitive. Macro dose for serious illness.
Mandatory completion of protocol before starting. Must have normal visual contrast sensitivity, normal nasal culture, normal hertsmi-2 (or EMI). Normal lipase and normal GGTP. Regular monitoring mandatory.
Lipase and GGTP.
With MCS (multiple chemical sensitivities), Micro-dose VIP titration

Other medical issues, frequent in the population, very much so in chronic inflammatory response syndrome and potentially reversible are discussed below:

Pulmonary Hypertension:

PASP >30 resting is Pulmonary hypertension, if not get stress echo, push to 90% predicted HR, then recheck TR, rise over 8 mm Hg is positive.

Treatment: When ready for VIP (lipase normal, BCS normal, MARCoNS absent, HERTSMI-2 < 11, GGTP normal), use 1 spray 4 times a day intranasally, ramp up over 1 week, for 30 days. After 30 days, repeat resting echo. If pulmonary artery systolic pressure not decreasing, increase PIP to 2 sprays 4 times a day. Verify target reached after a total 60 days with third echo.

POTS:

Volume depletion.

ADH/osmolality dysregulation.

Elevated pulmonary artery systolic pressure.

Reduced stroke volume and reduced venous return to left atrium

Rare to find benefit from Florinef in CIRS.

Any tricuspid regurg greater than 2.5 is a problem. If so, verify. D-dimer is okay, maybe venous Doppler, Always do comprehensive von Willebrand profile.

Verify low MSH, no MARCoNS, normal HERTSMI-2

If not: DDAVP QOHS 5 doses, verify correction and no low sodium. Verify no low osmolality. Advance to daily DDAVP, titrate to safety.

Now, add VIP. 50 mcg/0.1 ml. Test dose, redraw in 15 minutes, verify TGF beta-1 does not rise greater than 33% which would indicate ongoing exposure. Ramp up with dilute doses if multiple chemical sensitivities, food intolerance. Monitor pulmonary artery systolic pressure in one month.

NeuroQuant shows unusual hippocampal enlargement.

Pediatric associated neuropsychiatric syndrome (PANS)

Significant overlap with CIRS.

Cholestyramine for one month, usually all that is needed.

Hypometabolism:

This is essentially Universal with chronic inflammatory response syndrome. What the new data has found is that mitochondrial DNA in the nucleus of the cell goes into a very suppressed state, causing what is called the cell danger response. Mitochondrial function declines in an effort to shield itself from the "outside enemy".) Treatment of this syndrome helps to restore mitochondrial function back closer to normal. This is also why many patients with this have the complaint that they eat nothing but still gained weight.