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# My summary of the 2007 IACFS Conference

## CARDIAC

1. Paul Cheney-Mayo Clinic

CFS patients have increased metHb, increase G6PD as a response to tissue hypoxia. They also have decreased cardiac output which is not just due to positional changes, i.e. worse while lying.

The cardiac index of CFS patients is so severe it falls between the value of patients with MI and those in shock!

CFS patients have congestive heart failure but mostly diastolic failure. The LV doesn't fill well and it squeezes really hard to get the blood out. (Probably much worse since CFS patients have a low blood volume).

2. Richard A Van Konynenburg (richvank@aol)

Estrogen increases oxidative stress thus explaining predominance of females.

Also reports studies by Cheney that 50-80% of 2,000 patients with CFS benefited from high doses of B12. Others found low B12and high homocysteine in the CSF of CFS pts. Also folininc acid improved energy in 81% pts. Other findings: elevated proinflammatory cytokines, Th2 shift, low NK cells, carnitine deficiency, gut problems.

Reduced glutathione seen in CFS and Chronic LD

Depletion of magnesium can cause mitochondria dysfunction, twitching, muscle pain, sleep problems and cardiac symptoms.

Loss of temperature regulation caused by low cardiac output which causes autonomic nerve dysfunction and decrease blood flow to the skin.

Lactulose breath test is abnormal indicating over growth also assoc. with low glutathione.

Weight gain results from inability to metabolize carbs nd fats normally because of blocks in krebs cycle due to decrease glutathione, carbs end up being cycled back as fat

Bottom line: supplement with B12, folinic acid, glutathione

3. Martin Lerner

States that all CFS patients have abnormal T waves. Inversions seen in 96%. Also have resting tachycardia. Cardiac bx show fibrosis, myofiber disarray and fatty infiltrates.

Did studies with Valacyclovere which were better for EBV but Valcyte better for CMV. Improved cardiac function as well as fatigue. Also 6 month studies.

Safety issues: drink 6-8 glasses of water a day. Monitor cbc and chem..

Another cardiac study: Javierre et al (Univ of Barcelona)

Workload is 52% higher in normals than CFS and oxygen uptake is 47.5% higher but similar duration

4. VA Spence (? Location)

CFS patients vs controls had higher CRP's, higher 8-iso-prostaglandin F2alpha which correlate with "arterial stiffness"

He questions the role of neutrophil elastase. Quotes article by Van Putte et al in Pediatrics 2005

## FATIGUE AND EXERCISE

5. Barry Hurwitz (University of Miami)

Documented low rbc and low blood volume in CFS. Also low rbc correlates with high IL6, ESR and CRP. Epogen did not improve clinical symptoms despite raising the rbc. Total tilt duration was not different between treated and controls but was different in those with the greatest increase in rbc, indicating a lower risk of syncope in that group.

6. Margaret Cicolella California

Abnormal ETT in CFS: decrease peak V02, atypical recovery response, post exertional malaise

Poster: Ruud et al –Rotterdam-rv@cvscentrum.nl

Prolonged physical performance improved aerobic capacity in normal people but resulted in a lower anaerobic threshold and a state of malaise that is comparable to overtraining

Poster: Mark Van Ness-Pacific fatigue lab, CA

Metabolic and immune response to exercise in CFS

Significant metabolic abnormalities in CFS: low peak workload, low peak ventilation, low peak oxygen consumption, low O2 consumption at anaerobic threshold

Poster: Alegre Martin-barcelona- email: 18502jam@comb.es

Activated elastase and monovytes RNAse, exercise induced decreased functional reserve, decreased peak aerobic power (can be cause of muscle symptoms)

Poster: Staci Stevens-Pacific fatigue lab

Post exertional malaise following exercise challenge. Fatigue, lightheadedness, vertigo, joint pain, muscle pain, cognitive dysfunction, headache, nausea, trembling, instability, sore throats and glands.

Poster: Konyenburg

Compelling evidence that glutathione depletion important part of pathogenesis of CFS

7. Garth Nicholson

Fatigue is caused by damage to the mitochondria thus impairing their ability to make ATP and NADH. Increased metHb is also a marker for oxidative stress.

Rx: NT Factor decreases fatigue by 35-45%

For cancer: Propax+NT Factor reduce chemo side effects by 70%

8. Teitlebaum (Annapolis Maryland)

CFS and FM pts have decreased ATP. Ribose increases tissue ATP.

Rx: 5g Ribose 3 times a day mixed with food or beverage improved sleep, energy. Mental clarity, pain and well being.

9. Ulf Hannestad-Brain amino acid dysfunction in CFS(Karolinska Institue)

Arginine-ornithine-putrescene-spermidine-spermine: latter two inhibit NK cells and T lymphocytes

Postulates that organisms could fuel the process by increasing ornithine decarboxylase

## SLEEP DISTURBANCES

10. Watanabe and Tajima:
Sleep disturbances which could potentially respond to:

CoQ10, Vitamin B1, Aloha Lipoic Acid, L-Carnitine

**11.**Dr. N. Porter (female)

**Defined 5 types of fatigue:**

**Wired (overstimulated)**
**Brain fog**
**Molasses (heaviness)**
**Flu**
**Post exertional**

12. Elizabeth Maloney (CDC)
CFS have high allostatic load predisposes to metabolic syndrome

due to mitochondrial dysfunction.

13. Joan Shaver (jshaver@uic.edu)
Sleep disorders in CFS. Also 10-15% of normal population have sleep disorders. Stages: 1: 5-10%, 2: 40-50% (light), 3&4; 20% deep/delta, REM 20-25%

Need to establish a routine. Initially sleep restriction, i.e. force patients to stay awake all day until bedtime. Restated that there is decreased growth hormone production in CFS during sleep (this was also documented in FM, as well as decreased exercise response in FM, i.e. normal pts increase GH after exercise, but FM pts failed to respond). In hyperactive people, need to find something that dampens their cognitive arousal. Dark also NB.

Her slides are phenomenal but didn't present all the data. Discusses overlap between FM and other syndromes. Neurophysiologic pathways. Genetic factors. Subgroups in FM. Causes of widespread hyperalgesia. Functional MR imaging comparing normal and FM brains. Awesome stuff!

GENERAL SLEEP CONCEPTS

RLS restless legs occurs before sleep

PLMS periodic limb movements occur during sleep

NM Nocturnal myoclonus

Dysania: foggy, stiff, sore in the morning

Alpha intrusion: "awake waves" that intrude during light sleep (stage 2)

UARS Upper Airway Resistance Syndrome. This is like a step down from sleep apnea. Associated with low PO2, fatigue, IBS etc. This syndrome DOES respond to CPAP whereas sleep apnea did not!

"Tired but wired"

## PAIN SESSION

14. Karen Berkley (Florida State Univ)

Talked about the "pain matrix" in the brain, and the fact that FM patients react differently to pain. Talked about estrogen playing a role in processing of pain at the spinal cord level. Female rats tolerated distension of the bladder and uterus differently depending upon the estrogen level.

## EPIDEMIOLOGY

15. Jin Mann S. Lin (cdc)

Looked at subgroups who do not fit criteria for CFS, called ISF. One third of ISF were similar to CFS but did not meet criteria for CFS.

16. Han Kang (DC VAH)

CFS in Gulf War Vets 10 years later. 5,000 gulf war vets vs. 3400 other vets: 5% GW vets had CFS in 1995 0.9% in other vets had CFS

After 10 years: another 8% GW vets had CFS

Of the ones who were positive in 1995, 71% were better after 10 years.

17. Rosemary Underhill (Kings College Hosp. in London)

CFS in offspring of mothers with CFS. 16% of kids had either CFS or CF.

24% mothers had at least one kid with CFS/CF

## BRAIN FUNCTION SESSION

18. Paul Nestadt (Sinai)

Neuroimaging looking at brain metabolites found that significantly higher lactate level in brain . Differences in hippocampal glutamate differentiated between CFS with and without depression. Also decreased NAA which can mean either decreased neuron density or decreased metabolism. They assume it is decreased metabolism. Also assume brain goes into anaerobic metabolism

19. Garcia Quintana (Brussels 18502jam@comb.es)

Brain SPECT in CFS: high prevalence of cortical uptake abnormalities in common areas. Correlates with markers: mostly RNAse, and less with elastase

Also did SPECT after stress test: exercise followed by frontal stimulation showed decreased uptake in all places but mostly wernicke region

20.Fumihara Togo (UMDNJ)

Accuracy rate of CFS same as controls when control for motor response time and information processing time

20. HIROHIKO KURATSUNE (BEST TALK OF CONFERENCE!)
Osaka City University School of medicine

"Brain Dysfunction is a key abnormality for understanding the state of chronic fatigue"

Ties together the concepts of stress, immune dysfunction, infections all impacting on brain function. Shows abnormal brain MRI's.

Correlates brain volume with performance status.

Shows abnormal SPECT scans in CFS. Looks at acetylcarnitine uptake in brains-also abnormal

Administered acetylcarnitine to rats and then ground up the brains to show metabolites in brain samples (not sure if this is part of the serum testing he does on patients)

Then shows reduced binding of 5-HTP in CFS brains

Next looks at PET scans: big difference between CFS and normal

Does a serum assay which differentiates normal from CFS (cant read slide but he identifies substances in serum not found in any normals)

Has awesome slide of the neuro-molecular mechanism leading to chronic fatigue...too complicated to explain

He is willing to collaborate and get serum samples from our patients.

## BEHAVIORAL INTERVENTIONS

Ellie Stein (Calgary, Canada) espc@shaw.ca CBT-cognitive behavioral therapy GET-graded exercise therapy

Both improve fatigue but exercise does not improve exercise capacity in CFS but less than half the studies show decrease in pain, mood or health in both CFS and FM.

CBT is not better than group programs.

## GENETICS

21. Garcia Fructuoso (Barcelona)

Showed very specific sets of SNP's in patients vs controls

22. Albright (Utah) Frederick.albright@utah.edu

Found that relatives of CFS patients with CFS had higher genetic relatedness than woyuld be expected. In Utah group, 13 had infectious onset and 11 had non infectious onset. Also states that estrogen improves symptoms (estrogen therapy and pregnancy)

23. AWESOME PAPER: BEGONA CASADA AND JAMES BARANIUK baraniuj@georgetown.edu

Proteomic biosignature of CFS in CSF

Unbelievable finding of completely unique markers in the CSF, completely absent from control group!!

Alpha 2 macroglobulin (anti-protease)
Orosomucoid 2 (anti-protease)
Keratin 16 (? Assoc with meningeal lining)

Pigment epithelial derived factor (assoc with vascular dysregulation, endothelial proliferation)

BEHAB (assoc with structural repair)

CDC-subspace clustering btl0@cdc.gov Clustering of SNPs mostly related to cortisol, dopamine, tryptamine

24. CDC- genetic markers-mor4@cdc.gov

Genetic markers for alzheimers, hypothalamic pituitary axis, glucocorticoid receptor, serotonin

Some genes correlated directly with specific symptoms.

25. Kerr et al (St Georges Univ of London)

Q Fever-DRB1-11-low gamma interferon and IL2

Parvo B19-DRB1-01/04-pos RF

7 genes upregulated in CFS: apoptosis, pesticides,mitochondrial,demyelination,viral binding sites

Has a nice diagram of causality regarding infections and CFS

## VIRAL SESSION

26. Toni Whistler (CDC, South African)

PIFS: Post Infectious Fatigue Syndrome

Q fever, Ross River syndrome, EBV in Australia

Selective expression of 256 genes involved in metabolic and regulatory pathways. Severity of acute infection correlated with progression to PIFS

27. Kogelnik et al (Stanford)

Valgancyclovere (Valcyte-Roche) in patients with high titers to HHV6 and EBV who had been sick for one year or more, treated for 6 months. 75% success rate. People went from 5-25% level of functioning to 70-90% level of functioning and

had sustained improvement. Patients felt worse in first 2 weeks (Herx-like reaction)

31. Japanese presenter-didn't get name.

HSV1 stimulated by UV light, hyperthermia and stress

HHV6A and B

B causes roseola infantum, becomes latent in macrophages in brain,causes febrile seizures if reactivated.

Can do PCR on saliva
Saliva HHV6 saliva viral load correlates with "hard work"
More HHV7 in CFS with psychiatric disorder

Herpes viruses all sit inside of macrophages in the parotid and salivary glands and remain latent until the immune system is challenged and then they reactivate.

Used "anti-fatigue substance" which substantially improved energy in these patients. This was D Ribose.

28. Ronald Glaser-Ohio State University

Chronic fatigue syndrome and viral latency.

"Stress is the confusion created when one's mind overrides the body's basic desire to choke the living daylights out of some jerk who desperately deserves it"

Stress increases cortisol releasing hormone which increases ACTH which stimulates increase in cortisol production

Also talks about immune cells (B and T lymphocytes) having receptors for glucocorticoids, serotonin, growth hormone, substance P, prolactin

Also looked at lymphocyte function in medical students before exams and after vacations. After vacation had 18,000 IFN U/ml, before exams went down to 888!! Also had reduced memory T cell response before exams, and reduced T cell killing by B cells before exams.

IN patients with normal immune systems you do not have to get a rise in titer when there is virus reactivation, however showed that med students had higher EBV VCA antibody titers, and higher herpes simplex I AB before exams than after vacation.

Also discussed grave concern about astronauts getting reactivation of EBV, CMV, Varicella Zoster when they remain in space for too long.

EBV EA roteins are made early in the infection and are proteins that do not require viral DNA. Viral proteins induce transformation of monocytes to macrophages.

EBV encoded dUTPase modulates immune function and induces sickness behaviour in mice.

Viral proteins induce TNF gamma and IL 6

29. Ablashi-HHV6 Foundation Santa Barbara, CA

Best assays for detecting reactivation of HHV6 and EBV.

Highly Elevated antibodies to EBV VCA and highly elevated antibodies to HHV6 are useful indicators of reactivated infection. EA IgG is best indicator. RNAse L Protein is a marker for active infection.

Two kinds of HHV6, A and B. A is neurotropic and B is not.

Other viruses implicated in CFS: stealth, enterovirus, foamy virus, parvovirus, hep C, Ross, Rubella, Coxsackie, Borna

Things that are anti-HHV6 are red marine dye, amantidine, lamictal.

30. Mary Fletcher -Miami VA Medical Center

Gulf War vets and CFS patients have increased CD26 and CD2 T cells but lower number of molecules per cell.

Neuropeptide Y released during stress in GW victims.

31. Gurbaxani-CDC

Elevated IL 6 in CFS. Supports the hypothesis that an ongoing pro-inflammatory response contributes to the CFS symptoms. Body Mass Index correlates with IL 6 levels.

32. Marshall Williams-Ohio State University

EBV encoded deoxyuridine triphosphate nucleotideohydrolase (dUTPase) is expressed during lytic and possibly during abortive reactivation and induces immune dysregulation and up-regulation of proinflammatory cytokines (TNF gamma, IL 1b, IL 6, IL8) Also inhibits T cell blastogenesis. Target cells are macrophages and dendritic cells. Induces "sick behaviour" in mice.

Looking at similar protein in HHV6.

Suggest that viral proteins responsible for more than just viral replication and play role in pathophysiology of infection. They enhance proliferation of infected B cells and activate endothelial cells

HHV6A activates latent EBV genomes in B cells!

33. Susan Levine-NYC

Looked at 20 CFS vs controls. 45% CFS showed activation of EBV (EA IgG). No controls.

35% CFS had high titers to HHV6. No controls.
EBV VCA and EA up in 30% CFS, 8% controls

Positive HHV6 antigen in 20% CFS, no controls

34. Modra Murovska-Riga Stradins University-Riga

Frequency of activation of both HHV6 and HHV7 higher in CFS patients

HHV6B variant predominant in CFS

Dual infection significantly decreased CD3+ and CD4+ cells

John Chia-EV Med Research, Lomita, CA IMPRESSIVE STUDY CFS associated with persistant enterovirus infection in the gut. Did biopsies and found positive staining for enterovirus in 80% of CFS patients! Only 5% positive for H. pylori. Found enterovirus RNA in 33% of biopsies, and confirmed infections with positive cultures.

35. Garth Nicolson-Insititute for Molecular medicine, CA

www.immed.org gnicolson@immed.org

Chronic bacterial co-infections in CFS and CFS subsequently diagnosed with Lyme disease

In Western US 9% of CFS patients have positive Lyme testing

Other bacteria: mycoplasma fermentans in 65%

36. Anthony Komaroff-Harvard medical School

Well documented that CFS develops in the wake of various infections: EBV, Parvo B19, Enteroviruses, Ross River Virus, Borrelia burgdorferi, Coxiella burnetti (Q fever), Mycoplasma species, HHV6.

The most robust immunological abnormalities found in CFS: activated CD8+, poorly functioning NK cells, novel 2-5A binding protein(low molecular weight 25A RNAse seen ONLY in CFS), dysregulated pro-inflammatory cytokines-these most likely the cause for many of the symptoms in CFS.

## TREATMENT STUDIES

1. IV Saline

Poster: Travis et al-pacific fatigue lab-Stockton, CA

1liter IV Saline improves physical functioning in CFS and improves peak V02, HR and BP I response to exercise.

2. Modafinil

Poster: Garcia Fructouoso-barcelona

Use of Madafinil on daytime hypersomnia effective but side effects in 65% (excitation symptoms)

3. NT Factor

Poster: Garth Nicolson-Lipid replacement and antioxidant therapy for restoring mitochondrial function in CFS

NT Factor replaces damaged mitochondrial lipids and resulted in increased functioning vs controls. Needs continuous use for benefit to be sustained.

4. Lactic acid bacteria

Poster: Sullivan-Karolinska Institute- Sweden

Lactic acid bacteria improve fatigue (cultura dofilus natural yoghurt, alra foods, Stockholm)

5. Methylphenidate

Poster: Daniel Blockmans-Belgium

Methylphenidate improved fatigue, concentration at 2x10mg a day

6. Pulse low dose IVIG/diet/exercise

Poster: Tae Park-Korea

IVIG 1g per week for 6 months with strict diet(organic food, no processed foods or sugars, no chocolate, no hot pepper), sleep (Klonipin), ample hydration and salt, and exercise control (no heavy lifting, no heavy house cleaning)showed significant improvement

IVIG improved sleep apnea

7. Tadalafil

Ritchie Shoemaker-MD ritchieshoemaker@msn.com

Tadalafil 20mg every 3 days for 5 doses reduced shortness of breath, improved exercise tolerance

8. B12, folinic acid, glutathione. CoQ10, Vitamin B1, Aloha Lipoic Acid, L-Carnitine
9. Valacyclovere which were better for EBV but Valcyte better for CMV. Improved cardiac function as well as fatigue. Also 6 month studies.
   Safety issues: drink 6-8 glasses of water a day. Monitor cbc and chem..

10. D Ribose

Rx: 5g Ribose 3 times a day mixed with food or beverage improved sleep, energy. Mental clarity, pain and well being.

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