Appendix A
Presentation 1 – Benjamin Natelson

WRIISC Welcomes You

Good News!

We were officially informed two weeks ago that our application to establish a post-doctoral program in war-related illness was approved for two fellows

Road to the WRIISC

- 1974-1996 >> continuous MR funding in experimental behavioral medicine
  - Stress and serious medical illness
- 1989 >> started CFS Center at UMDNJ
  - Began unfunded pilots
- 1990 RFP to establish CFS CRCs
- 1991-2004 continuous funding (2 recompetes)
  - More than 125 papers published in this time

Road to the WRIISC

- 1993 >> RFP to establish CEHRs
- 1994-1999 NJ Gulf War Research Center
  - $500,000 + one FT MD for research only
  - 18 month recompetition process
  - Approved!! VACO decided not to refund!!!!
- 2000 >> Congress mandated WRIISCs
  - Modeled after GRECCs
    - $1,100,000 start up; $1,500,000 out years
      - Research only one of 4 equally important missions
      - Increased funding never given
    - Minimal research support (two 2-yr pilots)

WRIISC Construction Plan

- Included funds to set up "Restricted Living Center"
  - Allows environmental control
- Useful for research in small groups working in small spaces
  - Confinement (Tank Crews, POWs)
  - Military con-ops
  - Civilian first responders
  - Submariners
  - Astronauts on Mars mission
- Its existence will make us one of a kind for research funding opportunities

WRIISC Mission

- Clinical – Evaluate veterans with complex, hard to explain medical complaints
- Education – Educate veterans and health care professionals about medically unexplained fatigue and pain
- Risk Communication – Improve communication between veterans and health care professionals about medically unexplained symptoms; provide information on war related exposures
- Research – Develop comprehensive research program to understand/treat war-related illnesses

The Gap and Some Solutions

- Consequences of last minute funding cut
  - No treatment possible
  - No funds for veteran travel
  - Inadequate infrastructure to recruit subjects and support research
- Some possible solutions
  - Establish mini-grant program with $30K per year
  - VACO support of veteran travel
  - Ideas from you about how to find healthy controls

VA Research and the Doctor Today

- Physician-Scientist, a dying breed
- VA career development program, a life preserver for the academic physician
  - Guaranteed protected research time
- Huge changes in past 18 months
  - Heightened scrutiny and oversight; concerns about publicity; huge paperwork burden w/no support
  - Inadequate salary support (AI pays 5/8 of a salary)

CFS/FM in Civilians

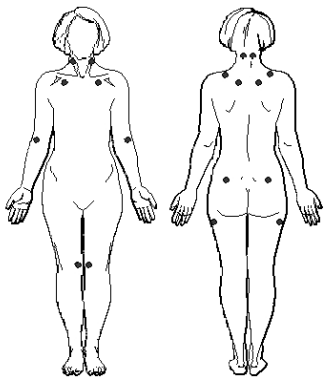
1988 & 1994 CFS Case Definitions

- 1988 - ↓ in activity by at least 50%
- 1994 – "substantial" decrease in activity
- Minor symptoms
  - Rheumatological; infectious; neuropsychiatric
- Exclusions
  - Obesity; any medical cause of fatigue
  - Bipolar; eating disorder; schizophreniform; alcohol or drug abuse

1994 Prevalence: ~0.4% of general population F>M

Minor Criteria to Diagnose CFS

1988	1994
sore throat	✓
tender lymph glands	✓
myalgia	✓
arthralgia	✓
unrefreshing sleep	✓
headache	✓
cognitive problems	✓
↑ Sx after exertion	✓
weakness	no
fever/chills	no

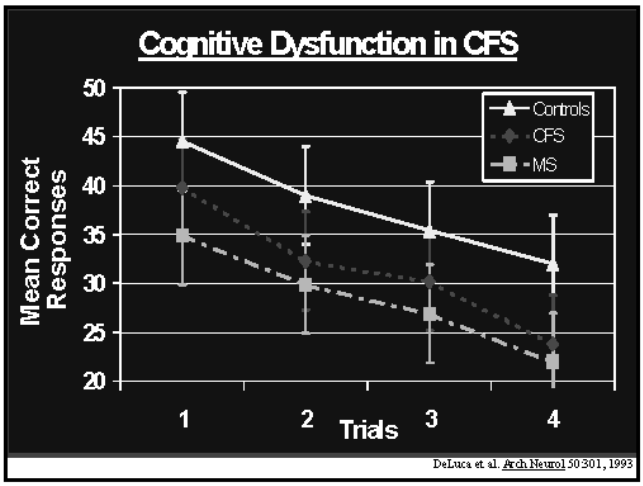


Rates of Comorbid Diagnoses

	CFS	CFS/MCS	CFS/FM	CFS/FM/MCS
Dx				
IBS	4/26 (15%)	2/11 (18%)	12/32 (38%)	10/18 (56%)
No Psych	35/62 (56%)	14/31 (45%)	17/44 (39%)	4/26 (15%)

Our Primary Hypothesis

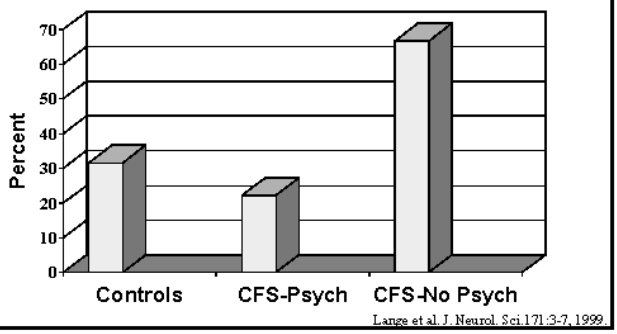
Some CFS patients may have an occult encephalopathy despite having no neurological findings other than occasional balance problems



Brain MRIs in CFS

- Do MRIs on CFS and sedentary controls
- Test hypothesis that the patients with no Axis I pathology will be the group with the highest frequency of brain MRI abnormalities

Percent of subjects with brain MRI abnormalities



Lange et al. J. Neurol. Sci.171:3-7, 1999.

Conclusions

- Stratification of CFS subjects is important to understand pathophysiology of illness
- CFS subjects without concurrent Axis I psychiatric disorder show significantly more
  - small abnormal MRI signal changes in subcortical white matter of frontal lobes

Supports conclusion that some CFS patients may have underlying encephalopathy

Where to go from here?

Examination of spinal fluid

Results

- LPs successfully done on 13 controls
  - None had protein >40 or > 3 WBCs/HPF
- LPs were successfully done on 39 CFS
  - 11 had elevated protein (≥ 45 mg/dl)
  - 4 had increased numbers of WBCs (> 5/HPF)
- Thus 39% of taps were outside of nl range!!

CFS Abnormality & Psychopath

- Of 28 CFS patients whose spinal fluid was normal – 8 had depression within a month of the psychiatric diagnostic interview (i.e., 29%)
- Of 15 CFS with spinal fluid abnormalities, none had current major depression ($p < .04$)
- However there were no differences in life time depression or in overall Axis I Dx

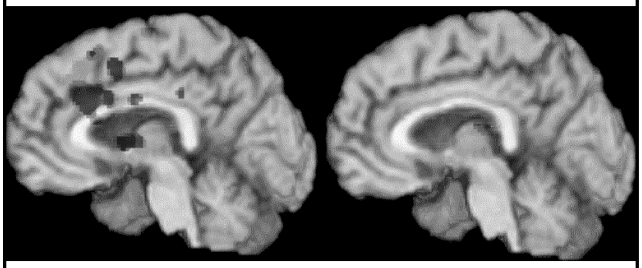
Conclusion

- Nearly 2/5 of all CFS patients tapped had spinal fluids outside of laboratory norms
  - Supports our inference that some patients with CFS have an occult encephalopathy
    - One confounding variable is drugs -- ???
  - We again found most CFS abnormalities in the group with no psychopathology
    - Continues to support our stratification strategy
  - Illness onset a predictor of pro-inflammatory IL-8

Use fMRI to Assess Brain Activity

- fMRI assesses Hb-O_2/Hb ratios to provide an indirect measure of neuronal activity
- This technique allows one to "see" the brain during various tasks and states
  - Study 1: Brain activation during warm and painful stimuli
    - FM and controls
  - Study 2: Brain activation during PASAT, a complex attentional task
    - CFS and controls with normal cognitive function

Warm non-painful stimulus



FM Group | Control Group

Cook et al., J. Rheumatology, in press.

What These Studies Tell Us

- FM patients feel warm "as if" it were hot
- CFS patients process information "as if" it were substantially harder than it really is
- The two studies suggest that CFS/FM brain requires additional neural resources to deal with mental processes that we take for granted
  - Is this the process responsible for mental fatigue?

A primary brain problem or not?

Look at the heart and determine if abnormalities exist and, if present, if they relate to any index of brain dysfunction

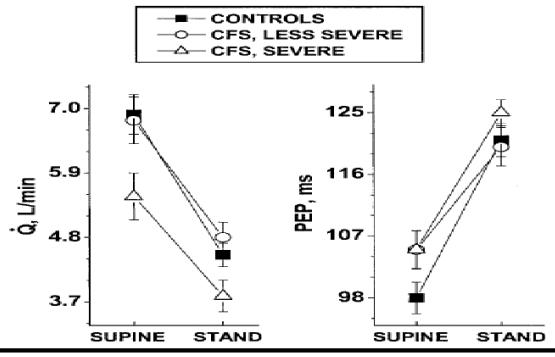
Non-Invasive CV Evaluation

• Assessed heart rate, blood pressure, and stroke volume in 17 CFS patients and 24 sedentary controls while supine, standing, and sitting

• Used impedance cardiography used to measure stroke volume -- an index of cardiac blood flow

Peckerman et al. *Am J Med Sci, 326:55, 2003*

Cardiac Output in CFS



Suggests that cardiac function is not normal – at least in the most severely affected patients

Research Question

Are CNS lesions secondary to perfusion problem or primary?

Conclusion

Data collected to this point supports our major hypothesis that CFS is for some a neurological disorder

Overlap with Sjögren's Syndrome

- Complaints of sicca common in CFS
  - May in part be due to use of TCAs
- Presence of Sjögren's antibodies very rare
- Lip biopsy is definitive way to Dx Sjögren's
  - We inquired about sicca, did Schirmer's tests, and biopsied 18 healthy controls and 25 CFS

Overlap with Sjögren's Syndrome

Gland Pathol Score	25 CFS Subjects				18 Controls	
	+ Symptom of Mucosal Dryness		– Symptom of Mucosal Dryness		– Symptom of Mucosal Dryness	
	Low Schirmer	Normal Schirmer	Low Schirmer	Normal Schirmer	Low Schirmer	Normal Schirmer
Normal	0	0	0	0	0	1
<1	2	3	0	12	1	16
≥1	8	0	0	0	0	0

Sirois et al. J Rheum 28:126, 2001