Stanford Myalgic Encephelomyelitis 2014

## Approach to the Medical Care of a ME/CFS Patient: Medical Interview and Diagnostic Pitfalls
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Note: This isn't a transcription, but rather, primarily I captured the slides, plus some of the comments I felt were interesting. I think it is far better to watch & listen to the video yourself than to read these notes! (The notes below while quite accurate were not carefully checked. If you have a question, watch the video.)

Note: Dr. Komaroff talks at times about "proving" things. Generally, this is incorrect usage. In science, while you can "disprove" things, we generally don't say were "proved" something. Rather, we say things like "provides (overwhelming) support for X". This has to do with the logic of the scientific method (if you're interested in more detail about this, do some searches on google)

**Goals**
Distinguishing chronic fatigue (CF) from CFS
Differential diagnosis of chronic fatigue
Most important ?s on history
Physical examination
Biology of CFS
Lab tests in CF & CFS
Treatments for CFS

**CFS: Who**
Age: Mid-30s (5-65 years)
Sex: 65% female
Socioeconomic: Middle class but more common among African American/Latino on population-based surveys
Education: 50% college grads in office-based samples
Severity: 50% intermittently bedridden/shut-in
Average duration: 14 years (4-36 years) in our patients

**Sudden onset**
78% of patients, CFS started suddenly, usually with a "flu", "virus", "bad cold"
- Sore throat
- Cough
- Rhinorrhea
- Swollen glands
- Myalgias
- Fever
- Headache
- Diarrhea

**Post-exertional malaise**
Even after modest exercise
- Fatigue gets much worse 81%
- All muscles become weak 47%
- New/worse difficulty concentrating 50%
- New/worse sore throat 33#
- New/worse adenopathy 28%
- New worse fevers 23%
- Never had before CFS 71%

**Physical exam abnormalities uncontrolled studies (examiner was not blind to patient status)**
- Posterior cervical adenopathy 35-45%
- Falls on Romberg test 10-20%
- Impaired tandem gait 20-25%
- Impaired serial 7s 30-40% (subtracting from 100 by 7s)

SF36 Health status subscale scores (graph): CFS vs. Comparison groups (Komaroff et al. Am J Med 1996; 101:281)

**Prospective studies of prognosis**

CFS cases from population-based cohort followed 3 years
- Relapsing and remitting course
- Slight improvement in symptoms/function, but not employment, over time but only 10% total remission
- 23% alt diagnoses (e.g., sleep disorders)
- Nisenbaum. BMC Health Qual Life Outcomes 2003; 1:49

Are there objective biological markers that are abnormal in CFS?
Do we understand the pathogenesis of CFS?

**Biology of CFS**

**Why isn't CFS "just" depression?**

Differences in objective neuroendocrine studies of hypothalamic function
- Downregulation of HPA axis in CFS – opposite of what is seen in depression

Treatment with SSRIs does not cure CFS
Several nervous system & immunological findings seen in CFS & not depression
Formal psychiatric assessment finds that fewer than half of patients have ever suffered an episode of major depression (in most of those, the depression developed after onset of CFS)

**HPA abnormalities in CFS**

| | | |
|---|---|---|
| ACTH release after stimulaton | CFS: decrease | Depression: increase |
| Prolactin release after stimulation | CFS: increase | Depression: decrease |

Sharpe, M, et al, BMJ 1997;315:164 & other cites

**Evidence of CNS involvement in CFS (preponderance of evidence in concord)**
- Neuroendocrine dysfunction: Impairment of multiple HP axes (involving cortisol, prolactin, & growth hormone) and 5HT system
- Cognition: Impairment of info processing speed, memory, and attention – not explained by concomitant psychiatric disorders
- Autonomic dysfunction: impaired sympathetic & parasympathetic function, 30-80%
- MRI: punctuate areas of high signal in white matter
- SPECT: areas of reduced signal (not clear whether due to refused perfusion or cellular metabolic)
- EEG abnormalities: increased sharp/spike waves, distinctive spectral coherence pattern

**MRI/SPECT studies in CFS**

Majority of studies with majority of patients have found differences

Lactate in spinal fluid in CFS (in vivo proton MR spectroscopy)
- Mathew SJ et al. MNR Biomed 2008 (DOI 10.1002/nbm.1315)

Higher lactate levels in CFS pts compared to patients with anxiety & healthy controls

Autonomic abnormalities in CFS: Results of studies
- Majority of studies (20.5 vs. 7.5) with majority of patients (767 vs 263) have found differences

Molecular sensors of fatigue & pain
- Ion channel receptors
- Adrenergic receptors
- Immune molecules

Fatigue & pain sensing molecues: normals vs. CFS, post exercise
- Light, AR. J Pain 2009, 10, 1099
- White AT Psychosom Med 2012; 74, 46)

Very different patterns between normals vs. CFS

**Summary: The brain in CFS**

Many different techniques for looking at the brain; all say something is wrong

They do not say that the problem is permanent or progressive
The cause of the problem remains obscure: infection of the brain and nervous system, or an immune system attack on parts of the brain, are reasonable but unproven possibilities

**Studies of the immune system (most robust findings listed below)**

CD8 + cytotoxic T cells bearing activation antigens
Landay AL, Levy JA. Lancet 1991: 338, 702
Barker E, Landay AL, Levy JA Clin Infect Dis, 1994, 18, Sf36
Poorly functioning natural killer (NK) cells
Caliguri M, Komaroff AL, Ritz J Immunol 1987; 139, 3306
Klimas NG et al. J Clin Microbiol, 1990 28; 1403
Herberman, R. et al. Clin Immunol 1993; 69; 253
Upregulation of the 2,5A system (triggered primarily by viral infection)
Suhardolnik RJ et al. Clin Infect Dis 1994; 18-S96 (not sure of sp of last name)
De Meirleir K, et al. Am J Med 2000; 108:99-105
Increased production of pro-inflammatory cytokines
Patarca R. Ann NY Acad Sci 2001; 933; 185-200
Moss RB et al. J Clin Immunol 1999; 19:314
Kerr JF, et al. J Gen Virol 2001; 82:3011

**Summary: The immune system in CFS**
(Komaroff preceded with "I think …")

- Something has activated several different parts of the immune system
- What has activated immune system is unclear, but infectious agents (a physical, post-traumatic response is also possible)

- Immune system activation in or near the brain & the nerves that come from it could explain many of the symptoms of CFS

**Energy metabolism/Oxidative and Nitrosative Stress/Inflammation**

**The energy metabolism hypothesis**
If the organism experiences a lack of energy, perhaps there is a defect in energy metabolism at the cellular level

Energy metabolic problem: growing evidence of this (didn't go into in talk)

**Studies of infectious agents**
Infections agents linked to CFS (perhaps latent agents (e.g., certain herpes viruses) are reactivated more often in CFS pts) are a plausible possibility)
Epstein-Barr virus
Post Q fever (Coxiella burnetii)
Ross river virus
Lyme (B burgdorgferi) (yes, but unusual)
Parvovirus (yes, but unusual)
Enteroviruses (probably sometimes)
Humans herpes virus – 6 (HHV-6)
Borna disease virus ?? Probably ruled out by research over last few years
Xenotropic murine leukemia-related virus (XMRV)?? Probably ruled out by research over last few years

Acute clinical syndrome comes & goes, but pt is left with CFS

**HHV-6**
Produces lifelong infection in 90-95% of us
Human herpes virus 6: 90% of humans are infected with it
Remarkably broadly tropic (can infect a remarkably wide range of cell types – it's receptor is the "complement" receptor which is found on surface of many cells)
Tropic for T cells, B cells, monocyte/macrophages, salivary gland cells, fibroblasts, intestinal epithelial cells, glial cells, neuroblastoma cells

Disease associated with benign and malignant lymphoproliferative diseases, drug-induced hypersensitivity, myocarditis, vascular endothelial disease, and neurological disease

Salahuddin SZ et al. Science 1986; 234:596
Ablashi DV et al, J Clin virol 2000; 16, 179.
Komaroff AL, J Clin Virol 2006; 37; S39

**Active HHV-6 infection in CFS: Results of studies**

**9 positive studies; 2 negative;** 1061 pts in positive studies; 122 pts in negative studies

**Viruses & CFS – My current view**

- Now solid evidence that CFS can follow a new infection: i.e., some cases appear to be triggered by infection

  CDC study done in small community of Australia; all medical care in one group of facilities, doctors, & labs
  Every case of EBV, ross river, or cox burr could be identified at the time it occurred & followed prospectivly

  11% rate of development of CFS following each of those acute illnesses

  More difficult to show that ongoing illness with these infections perpetuates the illness

- Infectious agents may perpetuate CFS in some patients, but has not been proven
- Several agents associated with CFS cannot be fully eradicated by the immune system, & infect the CNS: could the symptoms of CFS result from a chronic, very low-grade encephalitis?
  Entirely plausible that a low-grade, ongoing encephalitis, or immune attack on something in the CNS, would produce symptoms like those in CFS

**Diagnostic tests for CFS**

While there are now many different objective biological tests that are able to distinguish pts with ME/CFS as a group from health controls & depressed controls

- There are no diagnostic tests with adequate sensitivity or specificity for ME/CFS
- Diagnostic tests are used to diagnose *other* fatiguing illnesses

One (expensive) test presented at conference showed exceptional separation between cases & controls in a small group (nearly perfect sensitivity & specificity); if this result is maintained with a larger group, that could be a diagnostic test

**Reasonable workup for chronic, debilitating fatigue**

**NIH panel recommendation*** (from Schluederberg A. Ann Intern Med 1992; 117:325)

CBC & (manual) differential WBC
Sedimentation rate
Chemistry panel
Urinalysis
Thyroid function test

_____
Antinuclear antibodies (if prominent arthralgias)
IgG, CH50, Immune complexes (measured by sensitive C1q-radiolabeled assay)

**Txs for CFS**

- There are no pharmacologic treatments for CFS proven in large randomized trials, although small recent randomized trials (two he talked about) have reported promising results
- There are some proven treatments in a very similar illness, fibromyalgia, that anecdotally seem to benefit patients with CFS: low-dose tricyclics, dual reuptake inhibitors, pregabalin, and gabapentin

  Guess: fibromyalgia & CFS don't have same etiologic forces behind them, although they may seem clinically similar

**Treatments**

**Probably useful**

Amitryptyline, 5-30 mg qhs
Doxepin, 0-20 mg qhs

Trazodone, 25-50 mg
Alpha-wave intrusion into Delta-wave sleep; pt is short on delta (slow) wave sleep

Non-steroidals (for headache, myalgias, arthralgias)
Cognitive behavioral therapy (for coping purposes; needs to be done by a competent person)
Mischaracterized as a technique used to treat only psychiatric illnesses
Does not mean CFS is a psychological illness
Exercise, gradual
Can't push too hard; post-exertional malaise becomes a problem & pts unwilling to continue

**Not useful/uncertain**
Gamma globulin
Magnesium
Acyclovir
Vit B12
Hydrocortisone
Fludrocortisone
Stimulants (modafinil)?
Rituximab ?

**Rituximab for CFS: An RCT (from Scandinavia)**
Rituximab initially used to treat b-cell lymphomas
Double-blind, placebo-controlled RCT of ritusimab (500 mg/m2) twice, 2 weeks apart
Clinical improvement in 10/15 (67%) of rituximab group vs 2/15 (13%) of placebo group (p=0.003)
Mean clinical response 25 weeks
No adverse effects of treatment
Subsequent larger, longer Phase II studies underway

Fluge O, et al. PLoS One 2011;6:e26358

Valganciclovir ?
**Valganciclovir for CFS: An RCT** Montoya JG, et al., J Med Virol 2013;85:2101
- Double-blind, placebo-controlled RCT of valganciclovir (antiviral drug) for 6 months
- Small study: 30 pts, restricted to just those with reactivated HHV-6 or EBV infections
- Pts taking the antiviral were more likely to show improvement in most but not all measurements (clinical & lab)
- No serious adverse effects of treatment

**In summary, (my own view …)**
- The pathogenesis of CFS is still obscure, and the causes are probably multiple
- The case definitions of CFS likely encompasses several illnesses with similar symptoms, but different triggers
- No tests yet have adequate sensitivity & specificity for diagnosis
- No proven treatments

But …

- The illness is not simply the expression of somatic symptoms by people with a primary psychological disorder
- Case-control studies comparing patients with CFS to both disease comparison groups & healthy control subjects find robust evidence of an underlying biological process involving:
  - The brain & autonomic nervous system
  - Immune system
  - Energy metabolism
  - Oxidative & nitrosative stress

Questions:
Does coexistent of orthostatic hypotension or autonomic hypotension define a subset of CFS who are more likely to benefit from treatment?
It's never been studied

Anecdotally: only tx which works better in that group is tx directed at the orthostatic hypotension, i.e., salt-retaining treatment like _____

Second question not loud enough; replied it has not been studied & that he has no experience with the therapy that was asked about, but that he thought no one has had much response from it

Third question: long and could not hear; Komaroff said "I agree with all of those comments & will repeat them quickly")
Absolutely right that most of the studies of CBT (cognitive behavioral therapy) employed a case definition that I think is sub-optimal & may include many pts with major depression who wouldn't meet better case definitions of CFS
Some of the studies of CBT from Great Britain that used the Oxford criteria did not find any benefit

I take your point that CBT when used for organic illnesses is never recommended blanket for pts with those illnesses. When I have used it, it has been with people who have been really having problems coping with the symptoms and are thrown by it psychologically, and just dealing with it that way has helped them function better.

Q3:I wanted to ask, since it's a diffuse illness that has been difficult to diagnose clinically, what do we know if there is a chronicity that is a complete straight line, or whether there can be a full remission? (Q1)
Did you mention an animal model of any form? (Q2)

Q1: This is an illness that is clearly cyclic. Virtually every one with it has good days, bad days, good weeks, bad weeks. About 10-15% of pts over long term follow-up have returned to full health, but then some of them have subsequently relapsed. So I definitely have pts who were really hobbled by this illness but who are now fully functional, but it's a small number of pts. And, as you might imagine, if you studied those folks, is there any thing about them that is different, lab results, that would predict that they're going to be the one who do better? We have been unable to find that.

Q4: You've made a very good plea in a way for why we need to do outcome studies. Is there a list of things that maybe don't work? I've been at this 22 years. Those do work, frequently. But you're right, it's the subgroups; I don't know who to use them on. Dr. Montoya, you spent a lot of money to find out that Valcyte works in a subgroup some of the time. If we don't have the money to do that for all the rest of these treatments, and there are myriad ones out there – I probably do 50, and they work sometimes – and we need to do outcome studies, because we're never going to do it by double-blind placebo controlled studies. There's not enough money.

(Part 2 of Q4) If I remember correctly, even if XMRV doesn't exist, there are retroviruses that exist, and some people do respond to retroviral therapy. Again, a small group.

Response to Q4: I think you're making the general point that even though we worship at the altar of the randomized trial, the very best that the randomized trial can do for us is to tell us with some confidence what the average person who was in that trial – how they did in response to a particular intervention. We all know that within those trials, there are probably subgroups that never would have responded, and if you knew that in advance, you never would have enrolled them in the trial, and vice versa. Like the tyrosine kinase inhibitors in certain kinds of cancer: had dramatic effects in avg pts with those cancers, but as the genetics became clearer, there were subsets where the response was truly dramatic, and other pts where you could predict in advance – with the knowledge you now have – that they never would respond to that tyrosine kinase inhibitor. I'm not an oncologist, but that's my understanding of the lit.

Q5: about a 10 year old pt with congenital herpes that was cleared with a homeopathic remedy. (Lots of comments I didn't transcribe)