8th International Conference on Chronic Fatigue Syndrome, Fibromyalgia and other related illnesses. January 10-14, 2007 Fort Lauderdale, Florida.

Summary by Anthony Komaroff

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What I'm about to do is dicey because they've asked me in 15 minutes to try to pull together common themes that we've heard from so many different speakers using different technologies, to say what have we learned in this conference, at least, what's one person's view.

> This illness is defined only by symptoms, and anyone can say they have symptoms. But is there any objective biological evidence that there is something that could plausibly explain the symptoms?
> "Is there any there there?"

So let me begin with this observation that all of us know, that one of the reasons that there has been controversy surrounding this illness is that it is officially defined only by a group of symptoms, and anyone can say they have symptoms, so the obvious question that any doctor or any scientist wants to ask is, is there objective biologic evidence that there's something actually wrong with these people who say they have symptoms and that that something could explain those symptoms. Or, as a colleague of mine ten years ago or so very smugly said to me: "Is there anything there there about this illness?" So, I think, in this conference we've seen some there, and we'll talk about it.

The Main Themes

- The role of the brain
- Mitochondrial dysfunction/oxidative stress
- Molecular markers
- Epidemiologic findings

To me the main themes that came through in multiple presentations was the importance of the role of the brain, the importance of mitochondrial dysfunction and oxidative stress, the recognition of several new molecular markers and several of the epidemiological findings that were presented.

First the brain. It probably wasn't new data, but I couldn't help to be impressed by the functional MRI studies that Dan Clauw had presented in fibromyalgia patients, not CFS, in which they demonstrated not only a

lowered threshold for pain, but for all sensory signals. So, studies had been done ten years ago that suggested a lower pain threshold, if you pressed on the thumb of a fibromyalgia patient with a certain defined amount of pressure, and then you did the same with a healthy patient, the patient with fibromyalgia said outch sooner. But the question still was, well, they say ouch sooner, but are they really experiencing pain sooner, and the functional MRI studies show that when they reach that point, when they say outch, their brains are lighting up in the pain centers and the healthy controls are not. And when they get the full pressure, their pain centers were a lot more lit up than those of healthy controls. So, using newly available neuroimaging technology, that Dr. Vine described so wonderfully yesterday, has allowed us to ask questions about that black box, the human brain, that are literally impossible to study in human beings until the last five or ten years.
Another very important paper several people have alluded to is the paper by Nestadt and colleagues that demonstrated increased lactic acid in the ventricles of the brain - I'll come back to the implications of that - and then this many studies by Drs. Wantabe and Kuratsune showing diminished blood flow, diminished uptake of acetylcarnitine and diminished serotonine transporters in specific regions of the brain that are associated with short term memory, attention, pain recognition, autonomic function.

Mitochondrial Dysfunction/ Oxidative Stress

- Increased lactate and lowered N-acetyl aspartate in the brain (Nestadt)
- Impaired oxygen utilization and lowered anaerobic threshold on exercise testing (Cidolella, Vermeulen)
- "Fatiguability" of the brain function on prolongued mental challenge (Kuratsune)
- Impaired mitochondrial pathways for regulating apoptosis (Whistler)

What about mitochondrial dysfunction and oxidative stress? There was a paper again by Nestadt, that found not only the increased lactate but lowered N-acetyl aspartate in the brain, both of which suggest mitochondrial dysfunction and oxidative stress – not a direct measure of that, but a fairly provocative indirect measure. And the exercise testing studies by Cicolella and Vermeulen, showing impaired oxygen utilisation and lowered anaerobic thresholds on exercise testing, particularly not at the first exercise test but upon a test repeated X hours later. This along with the study by Dr. Kuratsune, showing the fatiguability of brain function not on an exercise challenge but on a mental challenge. The theme that came through in four or five papers was that, at baseline, when you first challenge patients either with exercise or with cognitive tests, they may not perform that much worse than matched controls, but

on repeated challenge, at a time when they've been pushed and exhausted, their function starts to attenuate whereas that is not the case in healthy controls. A very important observation, it seems to me.

Mitochondrial Dysfunction/ Oxidative Stress (cont'd)

- Proteins reflecting oxidative damage in spinal fluid (Baraniuk)
- Mitochondrial gene expression abnormalities (Kerr, Rokutan)
- Increased markers of oxidative stress (Spence and Belch)
- Myocardial dysfunction (Cheney, Lerner)

Impaired mitochondrial pathways for regulating apoptosis, that Dr. Whistler described, proteins in the spinal fluid, reflecting oxidative damage, as Baraniuk described, mitochondrial gene expression abnormalities reported both by Dr. Kerr and Rokutan, increased markers of oxidative stress in the paper by Spence and Belch, and then finally the provocative findings of myocardial dysfunction which it is very plausible to suggest, although not directly proved, could be reflective of mitochondrial dysfunction, by Dr. Cheney and Lerner.

Molecular Markers

- Near infrared analysis reveals near perfect discrimination between CFS and controls (Sakudo)
- 5-10 proteins found in spinal fluid of most patients with CFS(& FM and GWI) and vitually no healthy controls (Baraniuk)
- miRNA expression signatures (Kerr)
- Gene expression signatures from multiple different groups reveal involvement of genes responsible for similar functions (CDC, Kerr)

There are also several molecular markers. The one that the most impressed me was the paper by Sakudo in which using near infrared spectrophone matter photometric analysis he found nearly perfect discrimination between Chronic Fatigue Syndrome patients and controls. Now, there are many, many biological markers that clearly separate populations with CFS and healthy controls and disease controls, but none perfectly. And sometimes the early perfect study becomes a little less than perfect when it gets larger, but this was a really impressive discrimination, in fact. That little image with those blue dots, controls, up here and those red dot cases down here was more beautiful to me than Elisabeth Taylor when she was young on a good day. (Laughter) Five to ten proteins found in the spinal fluid of most patients with Chronic Fatigue Syndrome and Fibromyalgia and Gulf War Illness and in virtually no healthy controls, most patients, no healthy controls, using two different spectrometric techniques for looking for these proteins, identical findings with two

techniques and recalled by Dr. Baraniuk, the chance of that having occurred by chance was ten to minus 15.
Micro RNA expression signatures reported very briefly by Dr. Kerr in a poster, potentially very impressive, I think, most people know, but micro RNAs are a whole new category of molecules discovered in the last ten years, really nailed in the last eight years, that control the expression of genes throughout all of biology, honoured with last year's Nobel prize, to… you would expect a biological phenomenon that is so important and central, that if – in patients with a discrete illness, there would be a characteristic fingerprint, and Dr. Kerr says, that there is. Gene expression signatures that were reported by multiple groups, that involved the genes responsible for similar functions. So you had several groups looking at different genes coalescing on the view that the immune system is activated as reflected in gene expression, that oxidative metabolism is affected and that certain neurotransmitters, particularly those involved in the stress response are affected in this illness. And some correlation between the gene expression studies and Baraniuks proteomics study showing that the same genes that make proteins that are expressed are reflected in the proteins found in the spinal fluid, not disparate findings – findings that coalesce in a biologically meaningful way.

Epidemiology

- Definition of subgroups by statistical methods (Porter, Lin & Reeves)
- Consistent estimates of the point prevalence of CFS-like illness and CFS across different societies
- Association of allostatic load with CFS (Maloney)
- Rising estimates of the cost of CFS to society (Reeves, Jason, Kuratsune)

And then finally the highlight what struck me about some of the important epidemiological papers. Several papers that looked at the job of defining subgroups using statistical methods, in other words, instead of what has happened up till now with most diseases including this, a group of experts getting around the table and saying how do we define this disease, this approach just collects meticulously data on patients without imposing any biases on it and says, let the data speak for itself, let's see where these statistics can find symptoms and laboratory findings that cling together as if they are defining a discrete group, and people are finding that, and that is very important. The other kinds of subgroups that are being suggested in this meeting are the subgroups defined by laboratory studies such as particular viruses or particular fingerprints of gene expression. Consistent estimates across very different societies that we've heard about the point prevalence of CFS-like illness would be around 2,5 to 3 percent and around CFS itself about 0,5 to 1 percent across different societies. Association – a whole new thing – association of allostatic load with

Chronic Fatigue Syndrome reported by Dr. Maloney, very interesting, and since increased allostatic load or, at least, the components that define it, are so important in health, something that if there is this association is probably telling us a lot about the illness. And then finally the rising estimates of the cost of Chronic Fatigue Syndrome to our society. Dr. Reeves and his group had estimated that the annual cost, not including medical care cost, just lost productivity, was 9 billion Dollars. Dr. Jason looked again at that question and came up with an estimate that is nearly double, and then he estimated or calculated the medical care costs on top of the lost productivity of two to seven billion and so got up to a number in the 20 billion, 25 billion a year range, which is, to put it in context, about three times the bottom line of the world's biggest company Walmart. Dr. Kuratsune also reported what on a per capita basis would be a very similar cost per citizen of lost productivity from CFS in Japan, very similar numbers in a different society.

„So is there any there there?"

So, in summary, it seems to me that the answer to the question "So is there any there there?" is "There's lots there." It's been lots there for fifteen years, to use Dr. Evingards phrase, the invisible has been made visible, and what's most important at the end of these three days is not just that we've added more there to the there that's there (Laughter), but that we see converging evidence from different investigators, using different technologies, studying whole different groups of patients that are telling us something about, that are helping us understand where the there is located, where to look to make scientific advances in understanding this illness and, ultimately, in fixing it. Thank you very much.

Script von Regina Clos

Deutsche Übersetzung zu finden unter:
www.cfs-aktuell.de/April07_1.htm