CFS PHOENIX

PHOENIX RISING: A CFS/FMS NEWSLETTER by Cort Johnson	SPECIAL EDITION: LAYMEN'S GUIDE TO THE 8th IACFS CONFERENCE
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These overviews do not follow the conference's agenda (fatigue, pain, gender, sleep, etc.). Several of those sessions were undersubscribed and had papers on different subjects shoehorned in to fill them out. In order to obtain a more orderly presentation, some new sections (cardiovascular/vascular, Exercise and CFS) are added in this overview while others are retained (Brain, Immune, etc.). Papers that I found most interesting are highlighted. Some overviews are found under more than one category.

THE BRAIN

The brain imaging studies have brought some real excitement to the CFS research field. Among others they have suggested CFS patients have reduced blood flows to the brain, altered patterns of brain activation, reduced grey matter volume, altered serotonergic neurotransmission, reduced acetyl carnitine uptake and others. Notice how often one area of the brain, the anterior cingulate, is mentioned in this section.

Introduction – Dr. Gudrun Lange

The brain imaging studies have brought some real excitement to the CFS research field. Among others they have suggested CFS patients have reduced blood flows to the brain, altered patterns of brain activation, reduced grey matter volume, altered serotonergic neurotransmission, reduced acetyl carnitine uptake and others.

Dr. Lange is a careful and conservative researcher and her talk brought us down to earth a bit. She noted that the brain is a difficult organ to study and elucidated a large number of possibly confounding variables (amount of resolution, different normalizing protocols, different types of brain slices, etc.) found in them. She noted that all the early brain imaging studies had poor methodology or sampling techniques. Her point was elucidated when a physician asked her about the remarkable similarity he had seen in the brain images of his CFS and MS patients. Dr. Lange replied that the CFS sample set must be very carefully assessed and gathered, that she sees no such similarities in her CFS patients, and that these kinds of findings are a big problem in CFS research.

This said, she gave us her view of what we can say with some assurance about the CNS research in CFS:

- The major cognitive problem seen is in 'information processing'.
- The studies showing reduced cerebral blood flows are starting to show consistency.
- There appears to be a problem with serotonergic neurotransmission in the hippocampus and anterior cingulate regions of the brain.
- The brain volume reductions appear to be relatively minor.
- There appear to be spinal fluid abnormalities
- fMRI studies are showing altered patterns of brain activation in CFS.

Dr. Lange believes CFS studies need to be more rigorous. She believes CFS patients need to be carefully screened and to be accompanied by appropriate control groups and they should be stratified according to sex, type of onset, presence of mood disorder (and probably others). She also, much like Dr. Hanna of the NIH, wants more hypothesis driven studies and fewer fishing expeditions. She sounds like she is quite intrigued but not yet convinced about the central nervous system findings to date.

CONFERENCE HIGHLIGHT

EXPLAINING THE BRAIN DYSFUNCTION IN CFS?

James Baraniuk. Proteomic biosignature of Chronic Fatigue Syndrome in cerebrospinal fluid.

Dr. Baraniuk didn't really give us any new information – he simply repeated the findings of his stunning cerebrospinal fluid (CSF) study (**See Paper of the Year**) but he did so in the context of other research efforts in CFS and in this light it was such a compelling presentation that it was, for me, a conference highlight. Look at how closely the protein signature he found appears to agree with other research findings. SHA

- Two proteins suggest a protease – antiprotease imbalance is present. This implicates increased elastase production
- Several proteins suggest amyloid deposition in the blood vessels of the brain is causing microhemmorhaging
- One protein suggests altered rates of apoptosis are present
- Another suggests increased free radical production is present
- Another suggests problems with the vasoconstriction of the blood vessels and endothelial cell damage
- Another is associated with inflammation.

One protein found, keratin, is particularly interesting, as he said this is the first time in 25 years it has been found in CSF samples. It's associated with inflammation of the leptomeningeal cells that make up the membranes covering the brain and spinal cord.

The confluence seems pretty astounding; elastase, vascular problems, apoptosis, free radical production, and inflammation have all been highlighted during this conference.

Not only did Dr. Baraniuk's study enable him to project a coherent theory - a rarity in these gene expression studies – but his findings made sense according the results of past studies, almost all of which looked not at the brain but in the rest of the body. This would seem to suggest, at least to me, a layman, that CFS has a strong systemic component.

A good number of central nervous system studies have characterized different brain abnormalities in CFS but they have been unable to take the next big step and tell us why they are there. This study is potentially so important because it may help researchers answer that question.

We're getting some real movement in the proteome field. Courtesy of the NH's Neuroimmune Grant (RFA) Dr. Baraniuk is continuing his research in this area. Dr. Sullivan also has an NIH grant to study CSF protein signatures. Dr. Natelson has been trying to get a similar cerebrospinal fluid proteome study for some time. I asked him if he had got it going and he said that he had. This, like the gene expression arena, is one of the few areas of CFS research getting some good funding.

A NEURO-IMMUNE CONNECTION?

A Garcia Quintana. I. Roca, A. Garcia-Burillo, J. Alegre-Martin, I. Mena, K. De Meirleir. Brain Spet quantification in CFS

Just about everybody believes that neuro-immune interface is disturbed in CFS but this is the first study I know of that has tried to unite immune findings with brain scans. This international collaboration between researchers from Spain, Belgium and Australia used a SPET scan to look at patterns of brain activity. Not surprisingly they found that areas of the frontal lobe including the anterior cingulate had reduced activity levels.

They then checked to see if these abnormalities were correlated with abnormal immune readings and they found that they were; they found that CFS patients with more abnormal RNase L measures, in particular, but also elastase levels tended to display the most altered brain activity patterns. The brain abnormalities were not, however, correlated with symptom expression, i.e. they were not accentuated in the most severely ill patients. Unfortunately there was no control group.

THE CFS BRAIN ON EXERCISE - NOT A HAPPY PLACE CFS

A. Garcia Quintana, A. Garcia-Burillo, J. Alegre-Martin, I Mena, J. Garcia-Quintana. Brain SPET quantification in Chronic Fatigue Syndrome: comparison of basal and post-stress studies.

This group from Spain used a SPET scan to examine brain activity before and after an exercise session. This, again, is the first time, to my knowledge, that this has been done. It found that one area in particular, the Wernicke area, showed evidence of reduced activity after exercise. This area, which is found in the cerebral cortex, is thought to be 'essential for understanding and formulating coherent speech. *This certainly rings true for me.* Other areas in the temporal lobe were affected. Interestingly it was difficult to tell if the anterior cingulate region was affected because the activity in this region was too low to begin with.

CONFERENCE HIGHLIGHT

THE EXHAUSTED BRAIN

Paul Nestad, Sanjay Mathew, Xiangling Mao, Kathryn Keegan, Susan Levine, Dikoma Shungu. A comparison of neurometabolites in chronic fatigue syndrome, generalized anxiety and healthy volunteers.

This study used proton resonance spectroscopy to compare brain metabolite levels in CFS patients with and without depression, anxiety patients and healthy volunteers. It found several things; first it found greatly increased lactate levels (about 300% higher!) in the CFS patients relative to the control groups. Many people know of lactate in connection with muscle fatigue but lactate is actually a general index of anaerobic energy production. Our cells switch from aerobic to anaerobic energy production when the aerobic system has become exhausted or is damaged. These high lactate levels appear to reflect the existence of a lot of really exhausted cells in the brains of CFS patients and suggest, Paul Nestadt said, problems with mitochondrial activity are present. Importantly these researchers found that people with high lactate levels were the most fatigued and they suggest that the increased lactate levels could be a biomarker for CFS.

Next, a reduced NAA to creatine ratio suggested an impaired metabolic process was present. That this ratio was significantly more reduced in CFS patients without depression than in those with depression buttressed Natelson's findings of greater brain abnormalities in CFS patients without mood disorders.

This looks like a really important study. It had highly significant findings, it contained several control groups, it implicated the mitochondria and the metabolism and it replicated Dr. Natelson's findings of increased brain abnormalities in CFS patients who do not have mood disorders. This group is now looking at much larger patient groups, this time using depressed patients and first degree relatives as control groups.

The CFIDS Assoc. of America is trying to leverage its limited research dollars by funding small studies ('seed grants') that it hopes major funders will expand on. It looks like they picked a real winner here. This study was also supported by the NIH. This group is in the fund-raising stage right now.

A KEY TO THE SLEEP PROBLEMS IN CFS?

Estimation of the fatigue state in patients with chronic fatigue syndrome using actigraphy and R-R interval power spectrum analysis – Saiki Tajima, M.D.

The actigraphy (activity) study found that there were four different types of fatigue; long sleepers (hypersomnia-like), severe insomnia, short sleep ('wired but tired' – hyposomnia), and delayed sleepers. When this researcher looked at heart beat variability he found that parasympathetic nervous system activation was significantly decreased during sleep in CFS patients.

This is an interesting finding given the number of sleep studies that have not found sleep problems in many CFS patients. Reduced HRV in CFS has now been found by Israeli, U.S. and Japanese researchers and is one of the few consistently found findings in CFS. It suggests that autonomic nervous system problems are present in CFS. For more on this interesting subject click here.

CONFERENCE HIGHLIGHT

Hirohiko Kuratsune - Brain Session Summary

BRAIN DYSFUNCTION IS A KEY ABNORMALITY FOR UNDERSTANDING THE STATE OF CHRONIC FATIGUE SYNDROME

First Dr. Kuratsune pointed out several abnormal central nervous system findings that he thinks play a central role in CFS. Chief among these are reduced blood flows and reduced acetyl-carnitine uptake in areas of the brain (prefrontal cortices, anterior cingulate, cerebellum) involved in autonomic nervous system functioning, sleep and concentration, pain and motivation. Since acetyl-carnitine plays an important role in the synthesis of several neurotransmitters, reduced acetyl-carnitine uptake could be associated with reduced activity seen in thosel parts of the brain where it is found. He noted that

low serotonergic activity in a specific area of the anterior cingulate produces pain. He believes this suggests that a similar problem in another part of the anterior cingulate could produce the fatigue in CFS. After this summary he presented his hypothesis regarding CFS.

A Hypothesis: The Neuro-molecular Mechanisms Leading to Chronic Fatigue

Dr. Kuratsune believes CFS starts with physical/chemical/biological stressors that perhaps in combination with inherited vulnerabilities cause an injury to the central nervous system (CNS). This CNS dysfunction causes the immune system to pump out cytokines (IFN/TGF-B) that disrupt serotonin activity in the brain and alter HPA axis functioning. Altered HPA axis functioning causes reduced acetyl-carnitine uptake in the brain and this further impairs neurotransmission, particularly in the anterior cingulate, basal ganglia and brainstem. This leads to profound fatigue, memory problems, autonomic nervous system problems (orthostatic intolerance, gastrointestinal discomfort) and the consequent circulation, breathing, muscle and temperature regulation problems in CFS. Immune dysfunction results in pathogen reactivation which further exacerbates the immune problems and – via cytokine production – further disrupts the central nervous system.

This intriguing theory is not unlike some others at least in its general aspects. Several researchers believe a stressor causes an injury to the CNS but most have difficulty explaining the first part; how a physical, chemical, biological or psychological stressor causes enough CNS damage to cause someone with CFS to essentially fall apart. (The exception to this are researchers that believe a CNS infection is present in CFS.

GENES AND GENETICS

Heredity Subsection

T00 CLOSE FOR COMFORT - MOTHERS WITH CFS AND THEIR CHILDREN

Rosemary Underhill and Ruth O'Gorman. Chronic Fatigue Syndrome in the offspring of mothers with CFS.

This study examined how often CFS shows up in the children of mothers with CFS. It found a rather shockingly high rate of either CFS (5.5%) or chronic fatigue (11.5%) in these children. Remarkably 24% of the mothers with CFS had at least one child with CFS or CF. Dr. Underhill noted that these numbers were low as some children will develop CFS as they age. Interestingly, most of the children with CFS were born before their mothers came down with it. This perhaps suggests an infectious component is present (?) That none of the adopted or step children became ill suggested that genetics plays an important role. Recovery rates seemed pretty high with half the children with CFS recovering over time.

Unfortunately I missed this most interesting paper but I was able to listen in on a discussion about it between Dr. Underhill and Dr. Spence. It was clear to Dr. Spence that there was an infectious component to this disease but what he said about the genetic component was fascinating. He said that the offspring of men with CFS don't get this disease but that the offspring of women with CFS often do. He said this suggests, if I remember correctly, that the genetic predisposition to this disease may be carried in the mitochondrial DNA. The mitochondrial genes are not found in the nucleus of the cell but in the mitochondria and they are passed down through the mother. What an interesting idea given the increasing evidence that the mitochondria are affected in this disease.

Next up we have a study that appears to confirm Dr. Underhill's findings.

A CHIP OFF THE OLD BLOCK? HEREDITY AND CFS

Frederick Albright. Genetic contribution to Chronic Fatigue Syndrome (CFS) and associated pain-and fatigue-related diagnoses described in a population-based genealogical resource in Utah.

Utah is our Sweden, in that the Mormons' fascination with genealogy has left us with a data base that can be used to tease out the role heredity plays in disease. These researchers did statistical analyses on over 600 people with CFS to determine if they tended to be more related than would be expected. They found that they were. This suggests that some people have a genetic predisposition to getting CFS.

Then they looked at the CFS patients closest relatives to determine if they had higher rates than normal of pain and fatigue related diseases and again they did; these people had much higher than normal rates of migraine, irritable bowel syndrome, Raynaud's disease, temporal mandibular disorder, osteoarthritis and myalgia. What about fibromyalgia? Rates of myalgia (muscle pain) were increased even in these patients' distant relatives. This suggests that a genetic abnormality may underlie all these diseases and that they are at least distantly related to CFS.

They concluded that genetics plays a significant role in CFS.

CFS and FIBROMYALGIA - OVERLAPPING DISORDERS OR SEPARATE DISEASES?

F. Garcia-Fructuoso. Genetic profiles in severe forms of fibromyalgia and Chronic Fatigue Syndrome.

Some researchers believe that CFS and fibromyalgia and other disorders such as TMD/TMJ, IBS and MCS are part of a broad spectrum of overlapping disorders that have a similar central nervous system abnormality that remains to be uncovered. We have seen, for instance, Dr. Kuratsune posit that dysfunctions in two closely related parts of the brain result in diseases either of pain or fatigue. People with problems in both experience both pain and fatigue.

This large study (217 CFS/184 FM) of well defined female patients examined the distribution of 90 single nucleotide polymorphisms (small gene mutations) to determine if the two groups had a similar genetic makeup or a different one.

It found that each group had a set of mutations that were unique to it, suggesting that these two diseases are quite different. Interestingly if they collapsed the CFS and FM patient data together, they couldn't differentiate them from the controls. This suggests that not only did each disease present with unique gene mutations but that they didn't even share many gene mutations. This indicates that, at least with regard to the mutations tested, these two groups are genetically quite different – a surprising finding.

Importantly this study highlighted many of the same genes as did the CDC studies on gene mutations; they included corticotropin releasing factor receptors, several serotonin transporters, glucocorticoid and dopamine receptors, trytophan metabolism and intriguingly a gene involved in inducible nitric oxide synthase, IL-6, and and to round it off, even a calcium channel transporter. This illustrates that the CDC and this group are very much on the right track here.

Gene and Protein Expression Subsection

B. Evengard, H. Grans, M. Nilsson, K. Dalman-Wright. Reduced levels of oestrogen receptor (beta) mRNA in Swedish patients with Chronic Fatigue Syndrome. *Click here for a review of this paper in an earlier Phoenix Rising newsletter.*

CHASING DOWN THE FATIGUE GENES

K. Rokutan, Application of DNA chip for fatigue assessment.

The Japanese effort on chronic fatigue has extended to identifying unique gene expression profiles not just in CFS but in all sorts of fatiguing conditions including acute mental stress (e.g., a PhD defense), chronic psychological distress (e.g., a medical license examination), aerobic exercise, exhaustive exercise, mood disorder and CFS. These studies will help researchers determine if the stress response in CFS differs from that occurring in healthy people when they are exhausted or under stress. They could help to tease out what has gone wrong in the stress response of CFS patients.

In these studies they examined the expression of 1467 genes that code for factors known to be involved in the stress response. These include hormones, neurotransmitters, cytokines, chemokines, growth factors, transcription factors, heat shock proteins, cell cycle and apoptosis related molecules, etc.

The study results were quite interesting. One school of thought has posited that stress is stress; that the stress response is essentially the same no matter what kind of stress is present. These studies indicate that this is not true; the gene signatures provoked by psychological stress and exhaustive stress and aerobic exercise all had differences. The gene expression profiles of people undergoing exhaustive exercise were, however, more similar to those of people undergoing psychological stress than they were to people undergoing aerobic exercise (!).

The exhaustive study results indicated that a unique set of genes spiked 24 hours afterwards. Being physically exhausted then is not simply an extension of being tired or having exercised; it calls forth a unique response from the body – and this response shows up about 24 hours later. It is intriguing that this is about the time CFS patients are really getting nailed when they over-exercise. This raises an intriguing question - are these post-exertional exhaustion genes up regulated in CFS patients all the time?

This group found 9 genes with altered activity levels in the CFS patients – none of which were found to be altered in the healthy group 24 hours after exercise. The stress system in CFS is not functioning as though CFS patients were simply suffering from exercise-induced exhaustion – it is functioning in a different manner. The 9 genes were G2MA, ATP5J2, COX5B, DBI, HINT, ARHC, PSMA3, PSMA4, STAT5.

These genes are involved in mitochondrial functioning (3), neurotransmission (1), immune system (3), metabolism (1), endocrine system (1) – a very common cast of characters for CFS gene expression studies.

More specifically ATP5J2 and COX5B genes are mitochondrial genes, DBI, a GABA receptor modulator, is widely expressed in the central nervous system and is particularly abundant in the adrenal cortex, testis, and ovary where it appears to effect the mitochondria. GZMA - is a T cell- and natural killer cell-specific enzyme involved in T and NK cell lysis of infected cells. What an intriguing gene given the poor NK cell functioning we have seen. The ARHC gene is involved in signal transduction, proliferation, vesicle trafficking, and regulation of the actin cytoskeleton (= MHC signaling/immune system?). HINT – purine metabolism, PSMA3 - a proteasome involved in the processing of class I MHC peptides (immune system). STAT5 has roles in prolactin receptor and growth hormone receptor mediated signaling.

This study has a number of limitations - only a small number of genes were examined, the sample group was quite small (11 patients) and they only tested for known genes. Dr. Kerr strongly urges the use of Taqman to verify results and they did use it. Taqman knocked out – as Dr. Kerr posited – about 30% of the genes this team initially identified. Several CFS studies are finding large numbers of unknown or not yet characterized genes in their r. Have we seen these genes in past gene studies?

CONFERENCE HIGHLIGHT

Jonathan Kerr: Gene Session Summary

GENETICS/PROTEOMICS WITH A CFS PERSPECTIVE

All eyes were on Dr. Kerr as he began his summary. Dr. Kerr is engaged in the largest and most important gene expression study yet done on CFS. Thus far CFS gene expression studies have, for the most part, failed the test of replication; while they have had the same general results (immune, nervous system, mitochondrial genes, etc.) none have highlighted the same genes to a convincing degree.

Dr. Kerr believes that the failure of most gene expression studies to rigorously double-check their results has been one cause of this disturbing heterogeneity. There are surely other reasons as well; different methodologies used, different sets of genes examined, possibly inaccurate gene data bases, different kinds of CFS patients taking part, etc. By examining the entire genome and rigorously double-checking his results, Dr. Kerr is accounting for many of these. If any gene expression study will 'work', i.e. can be replicated one would think it would be his.

I was, therefore, kind of holding my breath during Dr. Kerr's presentation. He stated that his analysis of 100 CFS patients is almost complete. His gene expression studies are finding three main abnormalities in CFS patients that involve the immune system, mitochondrial function and G-protein signaling and, yes, he is validating his original gene expression results. (What a relief!) He mentioned three genes, in particular; gelsolin – which is involved in apoptosis and amyloidosis, another that is upregulated by organophosphate pesticides, and EIF – a mitochondrial gene involved in the demyelination of nerves, and may be implicated in viral activity.

He next indicated that while hereditary factors are at work in CFS that he doesn't believe they play a really major role. He then singled out the powerful pro-inflammatory cytokine TNF-a, which has not only been found elevated in CFS patients but has a mutation that is associated with fatigue. Dr. Kerr is currently engaged in a trial of the TNF-a inhibitor, Etanercept, in a select number of CFS patients.

Dr. Kerr then noted several intersections between his gene expression results and other findings. Both that his gene expression and Dr. Baraniuk's cerebral spinal fluid proteome results have highlighted gelsolin - a possible marker of amyloidosis. Likewise the Nestad study suggested that mitochondrial problems caused the increased lactate brain levels found.

THE FUTURE

A. Jacks, K. Dellenvall, N. Pedersen, P. Sullivan, K. Dahlman-Wright, G. Hedlund, B. Evengard. Preliminary observations from a case-control study on Chronic Fatigue Syndrome in monozygotic Swedish Twins.

The Swedish Twin registry is the largest in the world and we are lucky to have Dr. Evengard mining its depths. This is a report of an exciting study in progress. These researchers are identifying twins, one of which has and one which does not have CFS and assessing their gene expression profiles in the blood and protein profiles from the cerebrospinal fluid. They are also doing brain imaging – most of which has been done. They should be getting the gene expression results in spring of 2007. Nobody has tried to integrate this kind of data before. This study

was funded by the NIH and is the kind of study – big, complicated and expensive – that we rely on governmental institutions such as the NIH and CDC for.