

# Lyndonville News

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Information and Support for the ME/CFS/FM Community

David S. Bell MD, FAAP, Editor

LynNews@DavidSBell.com

## **Meeting of the American Association for Chronic Fatigue Syndrome, (AACFS) October 8-10, 2004; Madison, Wisconsin**

### ***Introduction:***

This edition is devoted to the 7<sup>th</sup> AACFS conference in Madison Wisconsin, and as such will lack some of the usual features. I am hoping that the next newsletter will come out in January about treatments for pain in ME/CFS/FM.

I think the conference was a great success and stands as a tribute to the huge amount that we have come to know about CFS. Much, even most of the credit goes to the support community whose ongoing work has made it possible. The support community has carried CFS research by activism, funding, and organizing conferences like this.

In recent years there has been, in my opinion, an apathy that has crept in and pervaded some parts of the support community. Perhaps it has been due to ill health, perhaps the patient community is giving up, discouraged by a perceived lack of progress. Maybe it is that the old-timers are just getting older. But whatever the reason, people need to remember that nearly everything good that has come to patients with CFS has come via the support community. This includes the excellent conference in Madison, Wisconsin, sponsored by the Wisconsin support community and the excellent conference summary by Dr. Roz Vallings, who attended the conference thanks to the patient organization in Australia and New Zealand, ANZMES. The guest section of this newsletter is a part of her report, reproduced here with her kind permission. So, support people, don't give up. Don't get discouraged. Follow your hopes/dreams/passions, and if this includes activism, get involved.

### **Definition of Chronic Fatigue Syndrome (CFS)**

It is inappropriate for physicians to say that there is nothing known about chronic fatigue syndrome, and that maybe it isn't even real. While many blanks remain to be filled in, including

nearly all the blanks on treatment, there are many basics about CFS that are now accepted by most physicians interested in the illness. And the medical literature of nearly 1000 good articles can support the basic premises of CFS, which I would state as follows:

**Cause:** CFS, for most persons, is a post infectious dysautonomia. It occurs after roughly 5% of persons with EBV (Epstein-Barr virus) mononucleosis, Ross River virus, Q fever, and Lyme disease. It likely follows mycoplasma and parvovirus infections, several strains of enterovirus, and numerous unusual infections such as psittacosis and histoplasmosis. For the majority of patients with CFS the initiating infection is unknown. This is usually because the initial infection was assumed to be minor and the specific organism was never searched for at the time. The initiating organism is the “cause” because it precipitates the illness, just like a strep throat “causes” rheumatic fever or a Yersinia infection precipitates a post-infectious arthropathy.

It is probable that there are other ‘types’ of chronic fatigue syndrome with different “causes”. For about 10% it is an illness that follows head injury. The mechanism here is likely to be the same mechanism that causes the post-concussive syndrome. Other persons with a gradual onset of CFS symptoms in early adulthood have a history of attention deficit disorder (ADD) in childhood, and their illness is likely a neurotransmitter-specific dysautonomia. Some patients with neurotransmitter abnormalities have a genetic predisposition that may be the crucial factor. And there may be a combination of genetic, neurotransmitter, traumatic, and infectious factors in some patients.

**Symptom Pattern:** The symptoms of CFS result from a common end pathway initiated by the causes listed above. This pathway includes both endocrine and immune factors in the central nervous system. These factors include hormones and cytokines and cause orthostatic intolerance and the other symptoms of the illness.

## **Literature Review**

There were several lectures at the recent AACFS meetings that were so exciting they made my socks roll up and down. The CFS scientific community is maturing and beginning to put together the knowledge that has existed in a fragmentary way over the past twenty years.

The first outstanding lecture was by the Centers for Disease Control and Prevention and delivered by **Dr. J. Jones**, called the Dubbo Infection Outcomes Study. Dubbo is a region of Australia where several illnesses that seem to initiate CFS are seen. It is a prospective study with 101 patients with EBV mononucleosis, 88 patients with Ross River virus, and 65 patients with Q fever followed over time to see who develops the symptom pattern of CFS. At 12 months, 6% of subjects met criteria for CFS. The most important predictor of developing CFS was the severity of initiating infection, and emotions were not a predictive factor.

This outstanding study is formalizing the post-infective aspect of CFS. The study is not yet finished, and we will have to eagerly await full results: is there a difference between the CFS after EBV or the CFS after Ross River virus? What is the reason some people get CFS and others do not? What role does abnormal interferon or genetic markers play? Stay tuned.

The second lecture that was outstanding in my opinion was about hepatitis C. **Dr. Charles Raison** presented a study he and co-workers have been working on concerning the treatment of hepatitis C with interferon (IFN). All patients had active hepatitis C, and prior to treatment, 22% had moderate fatigue with 3% bad enough to qualify for the diagnosis of CFS. During interferon treatment, the fatigue had risen to 70% with 30% having the severity and associated symptoms of CFS. Therefore, IFN clearly causes fatigue, worsening fatigue, and/or CFS-like symptoms in this group of patients with a known active infection with hepatitis C.

Well, we sort of knew that already, so it is not that big a deal. What is a big deal is what Dr. Raison said. The patients were monitored by measuring the viral load, and those patients with difficulty in clearing hepatitis C virus with interferon were the ones more likely to develop CFS type symptoms.

If proven true in subsequent and follow-up studies, this is remarkable. It implies that hepatitis C is a CFS-causing infection like the ones seen in the Dubbo study. Moreover, there seems to be a link between post-infectious fatigue, interferon, and difficulty clearing the virus (immune difficulties) even with interferon treatment. I would hope that this group of researchers is continuing to look into these relationships. This study is also a great reason why we cannot have blinders on – we need to look at experiences from illnesses causing the symptom of fatigue such as cancer and specific infections like hepatitis C.

The third and fourth superb studies followed. The third was presented by **Dr. Julian Stewart** titled “Regional blood volume and peripheral blood flow”. Dr. Stewart has been studying autonomic intolerance in young people with CFS. What he has shown with tilt-table testing is that there are regional changes in blood flow that are not normal. Among these is a marked reduction in thoracic blood volume related to inadequate cardiac venous return.

I love it. Perhaps even those patients who measure a normal circulating blood volume may, in effect, be hypovolemic in the heart and lungs. **Kazuhiro Yoshiuchi** presented a paper shortly after Dr. Stewart showing a reduction in cerebral blood flow in CFS patients.

## **Guest Review: AACFS 7th INTERNATIONAL CONFERENCE, Rosamund Vallings MB BS**

**RESEARCH OVERVIEW, by A. Komaroff (Boston).** In Chronic Fatigue Syndrome, functional status is much reduced in all areas and \$9 billion is lost annually in productivity in the USA. Over time 10% of sufferers can expect complete remission and 23% will receive an alternative diagnosis eventually. The illness follows a relapsing and remitting course, and research has shown abnormalities in many systems: Brain: Abnormalities seen on MRI and SPECT scans. Cognition: IQ within normal range, but marked difficulties in mental processing. Sleep: poly-somnographic abnormalities, with up to 28% increase in non-refreshing sleep. Neuro-endocrine: Autonomic dysfunction with basal and postural hypotension, reduced peak O2 consumption and haemodynamic instability. Immune activation: Activated lymphocytes cross the blood-brain barrier leading to microglial activation and perivascular activation. These effects

can last decades, and lead to the secretion of pro-inflammatory cytokines and nitric oxide, with resulting injury to the peripheral nervous system and chronic low level immune activation in the brain. There is also increased neutrophil apoptosis. Microbiological studies: Many different post-viral fatigue states have been described. Examples include: Enteroviruses (Coxsackie, polio, echo) abnormal lactate response to sub-anaerobic exercise demonstrated. Enteroviral RNA in muscle without p-1 protein suggests defective viral replication. Q Fever (ricketsial) nucleic acid persists for up to 10 years in circulating mononuclear cells. Parvovirus: ongoing elevation of IFN $\alpha$  with associated fatigue. Mycoplasma: found in up to 68% of European CFS patients (5.6% in controls) Energy metabolism: Disturbances seen in urinary metabolites: such as depletion of amino-hydroxy-N-methyl pyrrolidine, slight elevation of  $\alpha$  alanine and depletion of UM2 (serine). Gene expression: The genes involved in immune activation and energy metabolism are turned on more often in CFS. Vitamin D connection: Low levels lead to musculo-skeletal pain. Patients who have fibromyalgia tend to have lower plasma levels of Vit D as do people living in areas with long periods of darkness in the winter, with resultant tendency to osteoporosis. Treatment: Placebo controlled trials of treatment with omega-3 fatty acids have shown benefit in CFS. There is decreased production of inflammatory mediators and direct antiviral activity. Endogenous levels may be reduced by chronic viral infection.

**EPIDEMIOLOGY OVERVIEW, by W. C. Reeves (Atlanta).** Fatigue is a very common symptom in medical practice, involved in up to 50% consultations of which 75% are psychiatric. The prevalence of CFS (existing cases) in the US is 4 - 75 per 100,000. Onset is usually sudden and average duration is 5 years (range 2-7 years). In the US it is more common in rural areas, with a predominance in females and lower socio-economic groups. Minority races are at greatest risk. Annual loss in productivity in the US is \$9 billion and the average annual loss in family income due to CFS is \$20,000. In the UK, \$4 billion is spent on direct costs such as medication. Patients are often as severely or more disabled than those with heart failure or COPD.

**FIBROMYALGIA OVERVIEW, by D. Clauw (Michigan).** There has been a paradigm shift in diagnosis of fibromyalgia (FM) considering tenderness as part of a continuum rather than relying on definite numbers of specific tender points. The tenderness is usually diffuse, and using tender points for diagnostic purposes is affected by anxiety, expectation and distress. Random measures of tenderness are more relevant and accurate. Causes of FM include a strong genetic tendency and abnormality in pain-processing. This correlates with abnormalities in other sensory areas such as light and sound. There is generalised hyperalgesia and allodynia. Pain processing is either psychological (expectancy, hypervigilance) or neurobiological (peripheral or central). Dimensions of pain may be sensory, cognitive or affective. Functional MRI (fMRI) shows brain changes correlating with pain experiences and there is no correlation with depression. Cognitive factors such as catastrophizing and loss of locus of control may cause changes in pain processing and correlate with poor prognosis. Other regional pain syndromes show similar changes in fMRI to that seen in FM. Treatment: SSRIs, tricyclics and norepinephrine reuptake inhibitors all have some benefits in FM. Amitriptyline and imipramine are more analgesic than nortriptyline. Milnacipran is a new drug showing promise.

**MICROBIOLOGY and IMMUNOLOGY:** This part of the conference was introduced by Dharam Ablashi who listed the many viruses and other microbial agents studied in relation to

CFS. HHV6, enteroviruses, Mycoplasma, Chlamydia and parasitic infections are all creating interest.

**R. Suhadolnik (Philadelphia)** discussed the current immunological situation 20 years after the Lake Tahoe epidemic and reported on a recent study of 66 CFS patients, 62 controls and 51 depressed patients. CFS patients showed marked impairment compared to the other two groups. The study supports the cytokine/immune activation model, showing direct correlation between the abnormalities in the RNaseL pathway and NK cell function. The 37/80 kDa ratio strongly correlated with the changes seen in CFS and symptom severity. The RNaseL activity leads to an ion channelopathy with patients experiencing many symptoms.

**C. Raison (Atlanta GA)** had experience with the use of IFN $\alpha$  in the treatment of hepatitis C. IFN (interferon) is a cytokine released early in viral infection and causes a variety of symptoms including fatigue. 109 patients receiving IFN $\alpha$ -26 for treatment of hepatitis C were studied. During treatment 70% of patients reported marked fatigue and 30% developed symptoms sufficient to fit the criteria for CFS. ( $p=.0001$ ) This study supports the role of antiviral immune response in the pathophysiology of fatiguing illnesses.

**J. Jones (Atlanta GA)** reviewed the Dubbo Infections Outcome Study on behalf of Sydney colleagues. Patients who had had infectious mono, Q Fever and Ross River virus were followed up. He concluded that post-infective fatigue states (PIFS) following documented infection represent a valid and informative model for CFS. CFS occurred in 10% after these illnesses. Severity of the primary illness was the strongest predictor of development of PIFS and was not associated with premorbid psychiatric characteristics.

Signal transducers and activators of transcription (STAT) are a family of proteins playing a central role in the responses of cells to cytokines and were discussed by **K. Knox (Milwaukee WI)**. She suggested that a study of a sub group of CFS patients who had an abnormally low STAT1 response to interferons, may explain the increased susceptibility to infections sometimes seen in this illness.

Decreased NK cells cytotoxicity is a frequently reported abnormality in CFS patients, and **K. J. Maher (Miami FL)** reported abnormalities in cytotoxic T cells and NK cells including reduced perforin and reduced concentrations of Granzyme A and B. These changes may provide biomarkers in the future.

**M. Fremont (Brussels, Belgium)** discussed immune dysregulation associated with interferon $\alpha$  synthesis. He explained how RNaseL is cleaved by apoptotic and inflammatory proteases, and said that Mycoplasma infections are strongly associated with RNaseL cleavage. PKR is also shown to be activated in the PMBCs of CFS patients, and this can lead to immune dysregulation and induction of iNOS, with resulting muscle dysfunction and CNS and neuro-endocrine dysfunction such as hypothyroidism with intense fatigue

## **EPIDEMIOLOGY**

**D. Wagner (Atlanta GA)** compared two scales measuring fatigue and health: the MFI and the SF36. These two scales as anticipated were found to be negatively correlated i.e. higher fatigue associated with lower mental functioning, and this supports the construct validity of the MFI.

Artificial neural networks are computer generated networks likened to the human brain and are used, for example, to help with decision making. A system has been devised, and was described by **A. Morris (Chicago)** to help determine the types of symptoms that may be useful in diagnosing CFS. Two different networks were created with 26 relevant questions common to both networks, but this is early stage work and cannot yet be generalised.

**H. Harrison (Phoenix AZ)** produced support for the hypothesis that there are genetic contributions to coagulation protein abnormalities seen in some CFS/FM patients. Distinguishing these factors may help to guide therapy.

**R. Underhill (New Jersey)** in a pilot study showed that secondary cases of CFS occurring in unrelated household members may indicate that a low level infectious agent causing CFS may persist and be shed into the environment. Increased prevalence in genetic relatives indicates that genetic factors may be involved in a subgroup of CFS patients.

## NEUROPHYSIOLOGY

**J. Stewart (New York NY)** overviewed the varieties of orthostatic intolerance in CFS. He described three types of peripheral blood flow in these patients: low flow, normal flow and high flow. During orthostasis it was shown that there is enhanced thoracic hypovolemia related to inadequate cardiac venous return.

**H. Kuratsune (Osaka, Japan)** showed results of PET scans showing cerebral hypoperfusion in CFS suggesting that CNS dysfunction may be related to the neuropsychiatric symptoms found in CFS. Density of 5HTT in the anterior cingulate cortex was significantly reduced in a study of CFS patients and this was negatively correlated with pain scores. This alteration in serotonergic neurons is thought to play a key role in the pathophysiology of CFS. These results may help explain why SSRIs are sometimes helpful in CFS patients.

Elastase activity in relation to impaired exercise capacity in CFS was demonstrated in a study presented by **J. Nijs (Brussels, Belgium)**. The data provides evidence for an association between intracellular immune dysregulation and impairments in cardiorespiratory fitness. Results showed correlation between increased elastase activity and exercise functionability and may be related to impairments of lung diffusion and oxygen delivery to the tissues. NB Antibiotics decrease elastase activity in humans.

Reduced cerebral blood flow (CBF) in CFS was further confirmed in a study presented by **K. Yoshiuchi (Newark NJ)**, who also found that psychiatric status and severity of illness do not play a role. Xenon CT was used which provides absolute measures of CBF.

## PHYSIOLOGY

**S. Levine (Columbia)** analysed the metabolic features of CFS using multislice 1H MRSI. There was elevated lactate production in a significant number suggesting the possibility of a mitochondrial metabolism dysfunction. Elevation of thalamic choline was also demonstrated in some patients, suggesting the presence of neuronal damage.

**U. Hannestad (Stockholm, Sweden)** showed in a small study that the more severe the symptoms of CFS the greater the excretion of  $\alpha$ -alanine. The level in one patient was exceedingly high and was associated with severe symptoms. There are structural similarities between  $\alpha$ -alanine and GABA, and high concentrations in the CNS may account for some of the typical CFS symptoms. Symptoms similar to CFS are often seen as side effects in those with epilepsy being treated with drugs which increase GABA.

**M. Fremont (Brussels, Belgium)** presented a further study showing that cells expressing ankyrin fragments of RNaseL have been demonstrated, and this can contribute to increased sensitivity of patients to chemicals including heavy metals. Involvement in the maintenance of Th1/Th2 balance by interaction of the multidrug-resistance protein (MRP-1) and the ankyrin fragments is also relevant in CFS.

**M. Pall (Washington State)** described a number of mechanisms operational in CFS and related illnesses and produced evidence of increased nitric oxide and peroxynitrite levels in CFS, which lead to oxidative damage and further increase in cytokine levels. He described Vitamin B12 as a nitric oxide scavenger, which may help explain why some people do well on B12 despite having normal blood levels.

## CLINICAL CONFERENCE

**A. Lyden (Michigan MI)** presented evidence that two disparate sensory experiences (somatic pain and exertion during exercise) are processed similarly in patients and controls. There is a left shift in FM patients, who feel more pain at the same time as feeling more "work".

CFS patients were shown by **C. Javierre (Barcelona, Spain)** to have lowered oxygen uptake when exercising. She had compared CFS patients with sedentary and physically active people using both an exercycle and an arm ergometer. Maximum power output was higher for all groups on the cycle as compared to the arm ergometer.

**J. Alegre (Barcelona, Spain)** evaluated 511 outpatients at a fatigue clinic and found that 350 fulfilled the CDC criteria for CFS. These patients had substantial reduction in physical and work activities. 50% experienced gradual onset and there was significant elevation of RNaseL. 10% patients improved over time and 53% worsened. Only 33% were able to work.

**F. Friedberg (Stony Brook)** had done a cross sectional study of support group attendees looking at the benefits and problems encountered. In general, subjects had found the group experiences helpful, but somewhat surprisingly active support group members reported greater symptom severity and less illness improvement than inactive members.

Level of occupational disability comparing a maximal exercise stress test and two self report disability measures was presented by **J. Nijs (Brussels, Belgium)**. The associations were too weak to predict occupational disability, and more work is required to establish valid methods of assessment.

The Phase III clinical trial of Ampligen v placebo in CFS was discussed by **D. Strayer (Philadelphia PA)**. The trial involved 234 severely affected patients. 400mg Ampligen or placebo equivalent in saline infusion was given IV twice weekly for 40 weeks. Exercise treadmill duration was improved two-fold over placebo. There were no significant differences in laboratory parameters. Ampligen has provided the most promising results compared with other drugs tried such as galantamine, antidepressants and corticosteroids.

There were many more presentations summarized by Dr. Vallings. For those interested please send a note to ANZMES. A summary by Dr. Charles Lapp is also available in the AACFS newsletter.

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