Some salient points arising from the AACFS 6th International Conference which the MRC Research Advisory Group on "CFS/ME" might wish to consider

These short notes have been prepared by Margaret Williams and are taken directly from the Report of the Conference by Dr Rosamund Vallings of New Zealand (available on Co Cure, 27th February 2003 or here), to whom grateful acknowledgement is made.

The Conference was held at Chantilly, Virginia, USA from 31st January to 2nd February 2003 under the auspices of the American Association of Chronic Fatigue Syndrome.

INTRODUCTION AND OVERVIEW

Professor Charles Lapp (Charlotte, North Carolina) and Professor Leonard Jason (Chicago, Illinois)

In 50% of cases there was a family history of auto-immune disease.

People with (ME) CFS were found to be more functionally impaired than those with Type 2 diabetes, congestive heart failure, MS or end-stage renal disease.

The majority remain significantly impaired.

Physical examination particularly reveals that lymph glands and skin may be very tender.

There may be abnormal laboratory findings including immune complexes, atypical lymphocytes, lowered IgG, small increases in alk phos, elevations in cholesterol and small increases in ANA and thyroid antibodies.

MRI studies of the brain have demonstrated high intensity T2 weighted lesions, but these occur in other diseases and are non-diagnostic. SPECT scans to demonstrate function show decreases in cerebral blood flow with exercise.

92% of patients with CFS can become syncopal with orthostatic intolerance.

Gulf War Illness tends to overlap with CFS but there are important differences.

The 1999 case definition for Multiple Chemical Sensitivity was presented; there is considerable overlap between MCS and CFS, with 30% of those with MCS fulfilling the criteria for CFS.

In the US, primary care physicians are faced with the task of advocating for 800,000 patients with CFS and more than 2 million with fibromyalgia.

Up to 50% of these people are unable to work.

EPIDEMIOLOGY

Professor Leonard Jason (Chicago, Illinois)

Of those with CFS, 41% meet the criteria for MCS; 16% for FM and 5% of those with GWL match the criteria for CFS.

With so many studies showing different rates, there needs to be a standardisation of diagnostic criteria.

Dr William Reeves (Centres for Disease Control, Atlanta, Georgia)

The current CDC (Fukuda, Sharpe, Wessely et al) research definition is now under review, including ambiguities associated with comorbid conditions.

[Trudi Chalder, London (a former Registered Mental Nurse who now works with Simon Wessely as a behavioural therapist; a member of the CMO's Key Group)

Believes there is considerable overlap between "fatigue" and psychological disorders.

Stated that in her study of the rate of CFS in childhood, there was frequent maternal neuroticism.

At the Dinner Symposium, Ms Chalder stated that there should be concentration on overcoming symptoms rather than looking for a cause of symptoms.

Ms Chalder introduced the session on Psycho-Social issues, giving an overview of her thoughts on Chronic Fatigue (sic): one of her thoughts was that precipitating factors such as lack of fitness and coping ability are determinants in the level of fatigue]

BIOCHEMISTRY

Professor Robert Suhadolnick (Temple University, Philadelphia)

Gave an overview of the biochemistry and genetics of CFS, which he explained encompassed a huge overlap of all disciplines (of medicine).

He then outlined the various biochemical processes which had been shown to be altered in CFS. Immune activation and NK cell decrease seem to be evident in most patients.

Oxidative stress -- described using the peroxynitrite model, whereby elevated levels of various cytokines cause elevation of nitric oxide – can decrease NK cell function, and also leads to mitochondrial dysfunction and HPA axis (and other organ) dysfunction, causing fatigue and many other symptoms. Suhadolnick showed that there was an increase in markers of oxidative damage. Oxidative stress can thus damage muscles and the ATP generated system.

2-5A RnaseL abnormalities have been shown in CFS, particularly in the severely ill. 37kDa RnaseL is found in CFS in both Suhadolnick's and De Meirleir's studies, but not in healthy controls, depressed patients or in FM.

p68 kinase (PKR) mRNA expression has been shown to be increased in CFS, leading to increased PKR activity.

Apoptosis (programmed cell death) is evident in CFS.

Skeletal muscle function and mitochondrial function suggests a defect in oxidative metabolism with a residual acceleration of glycolysis in the working skeletal muscles in CFS. There is also reduced oxidative muscle metabolism (shown by MRI), and muscle recovery is delayed.

Elevated levels of RNaseL are associated with reduced VO2 max and exercise duration in CFS patients.

There is evidence of changes in brain function.

S Vernon (Atlanta, Georgia)

She found that the results of the utility of the blood for gene expression profiling and biomarkers in CFS (using micro-array) were successful in distinguishing CFS subjects from healthy controls. Gene activity differences were identified, implicating some of the pathways involved in CFS.

Dr Gwen Kennedy (Dundee, Scotland)

She provided further evidence for the dysfunction in oxidative pathways in CFS.

High levels of isoprostanes were found. Isoprostanes are potent vasoconstrictors, and this may explain some of the symptoms in CFS. Viral infections increase isoprostanes.

The changes found in CFS were not present in those with Gulf War Illness or organo-phosphate poisoning.

Dr D Racciatti (Chieti, Italy)

Explained how oxidative stress may play a fundamental role in CFS pathology; it may be a result of elevated peroxinitrites, leading to a self-perpetuating vicious cycle mechanism, producing a chronic pathological condition in response to a trigger such as a viral infection.

INFECTION AND IMMUNOLOGY

John Hay (Buffalo, New York)

Gave a presentation showing the evidence for infection and immunological changes in CFS.

He concluded that a number of organisms can lead to the CFS state.

Immune dysfunction may be involved, as administration of cytokines give rise to symptoms similar to CFS. Cytokines such as IL-1 beta and IL-6 were studied: IL-6 was found to be increased following exercise in CFS patients. NK cells showed low activity compared with controls.

Many people with CFS report allergy / atopy.

Auto-immunity is an appealing potential link and Konstantinov (1996) found significantly increased ANA positives in CFS.

Patients need to be divided prior to any data analysis, as there are many routes to this disease, making research data potentially difficult to assess.

K Maher (Miami, Florida)

Discussed molecular defects associated with CFS, in particular determining the molecular mechanisms underlying decreased cytotoxicity. The cytotoxic armamentarium involves perforin, granzyme A and granzyme B, and all are down in CFS.

NK cells were also found to contain fewer molecules of CD11a and CD26, and the cytotoxic protein content of T6 cells was reduced.

Cytotoxic effects may not be NK specific but may encompass the cytotoxic T cell subset as well.

P McGaffney (Minneapolis, Minnesota)

Found a significant difference in gene expression. In particular, the analysis revealed elevated expression of mRNA for IL-1 and the IL-1 receptor, type 2. IL-1 is a very potent inflammatory cytokine and these genes were dysregulated in almost all patients and none of the controls.

Professor Robert Suhadolnick (Temple University, Philadelphia)

His team studied three groups: those with CFS; healthy controls, and those with depression. He again found a close association between the up-regulated 2-5A RNaseL immune defence pathway and the clinical presentation of CFS. These markers can be used together with clinical parameters to identify CFS patients.

CENTRAL NERVOUS SYSTEM

Dr Daniel Peterson (Incline Village, Nevada)

He discussed the role of the brain in medically unexplained illnesses. He described structural and functional abnormalities in CFS: a number of structural abnormalities have been reported such as "MS-like" changes on MRI.

Functional abnormalities included: altered HPA axis; cognitive impairment; abnormal sleep patterns; regional hypoperfusion in the brain; hypo brain metabolism; autonomic dysfunction; peturbation of brain hormones and primary or reactivated CNS infection.

Abnormal lumbar puncture (spinal taps) have often shown that something abnormal is going on in the brain; studies have shown increased opening pressure and increased total protein and lymphocytosis.

Professor Ben Natelson (New Jersey, NJ)

He described earlier hypotheses suggesting that some patients may have covert eneephalopathy as had been demonstrated by MRI and larger ventricular volumes: the more severe the CFS, the larger the volume tended to be.

44% pf those with CFS were found to have spinal tap (lumbar puncture) results in the abnormal range for protein or WBC, thus supporting the view that some CFS patients do have underlying pathologic brain processes responsible for their symptoms.

In patients who had normal cerebro-spinal fluid (CSF) results, 29% showed signs of depression, while those whose CSF results were abnormal showed no signs of depression.

PHYSIOLOGY

P Gold (National institute of Mental Health)

Showed how HPA function is different between those with CFS and those with depression.

Dr Vance Spence (Dundee, Scotland)

He reported that cholinergic abnormalities exist in the peripheral micro-circulation of CFS patients. **This has not been shown in other diseases**.

Acetlycholine leads to release of nitric oxide, which causes blood vessel dilatation. Nitroprusside also leads to release of nitric oxide, but administering nitroprusside does not lead to the same response as acetlycholine, indicating that what is happening is a specific sensitivity to acetlycholine.

Dr Daniel Clauw (Michigan,MI)

He reported on his group's study of catecholamine levels in response to standardised stressors in both CFS and FM patients. The responses were consistently different for CFS and FM, with individuals with CFS displaying attenuated responses while those with FM showed normal response.

POSTER PRESENTATIONS

EPIDEMIOLOGY

Christopher Snell (Stockton, California)

He confirmed that those with CFS exhibit non-normal responses to exercise, with post-exertional malaise being a major debilitating symptom.

IMMUNOLOGY

K Tiev (Montpellier, France)

Confirmed that a ratio of RNaseL isoforms higher than 0.4 seems to be sensitive to screen patients with CFS in the absence of known infection.

Professor Kenny de Meirleir (Brussels, Belgium)

He suggested that RNaseL truncation could lead to dysregulation leading to degeneration of cellular mRNAs which are not normal targets of native RNaseL.

Dr Gwen Kennedy (Dundee, Scotland)

Showed that CFS patients had higher levels of TGF-beta 1 with increased neutrophil apoptosis.

A Peckerman (Newark, New Jersey)

Found that patients with CFS demonstrated abnormal breathing adjustments to postural stress and that there was inefficient utlisation of respiratory muscles while standing, associated with increased light-headedness.

T Friedman (Los Angeles, California)

Concluded that CFS patients in his study had defects in the renin-aldosterone axis, with impaired mineralocorticoid activity, reduced blood volume and impaired cerebral blood flow.

JM Van Ness (Stockton, California)

She noted that particular subgroups of patients may perform differently from others and that broad generalisations should be avoided.

Professor Martin Pall (Pullman, WA)

He outlined the mechanism of elevated nitric oxide / peroxynitrite theory of CFS and his poster reviewed the literature and data on this topic.

E Georgiades (Glasgow, Scotland)

Had examined the cardiopulmonary and metabolic responses to exercise in CFS patients and subsequent recovery in CFS patients compared with controls. The findings supported impaired exercise tolerance.

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