

AACFS 6th INTERNATIONAL CONFERENCE

Reported by R.Vallings

From 31st January to 2nd February 2003, I was privileged to attend the AACFS 6th International Conference on CFS, FM and related syndromes, held at Chantilly, Virginia. The first day was a clinical conference for physicians working in the field of CFS, followed by a day and a half of research presentations.

DAY 1.

The conference opened with an introduction and overview by Charles Lapp (Charlotte,NC) and Leonard Jason (Chicago,IL). Lapp ran through the history of CFS, which was described by Hammurabi as early as 2000 BC. Jason reviewed the problem of CFS and its definition, citing that 50 million Americans suffer from fatigue, of which 14 million have prolonged fatigue and 8 million have a diagnosis of Chronic Fatigue. CFS fitting the research case definition probably affects 800,000 in the USA. He outlined the difficulties in diagnosis and overlap with major depression. Chronic Fatigue is a diagnostic feature of major depressive disorder (MDD) with 4 of the minor CFS symptoms occurring concurrently (unrefreshing sleep, joint pain, muscle pain and impaired concentration). He then outlined the major distinguishing features between CFS and MDD and other disorders such as generalised anxiety disorder and somatization disorder.

Epidemiologically, a major study showed that there is a predominance of females with CFS, and almost double the number of Latinos compared to American whites or Afro-Americans. There was no history of abuse in the majority of cases and in 50% of the cases there was a family history of auto-immune disease. Those with CFS were found to be more functionally impaired than those with Type 2 diabetes, congestive heart failure, MS or end-stage renal disease. Many do however show improvement over 2 years, though the majority do remain significantly impaired. Various physical and psychological scales were discussed to measure outcomes and co-morbidity, including wearing a device to produce actigraphs showing daily activity. Those with CFS particularly showed reduced activity and non-restorative sleep.

Lapp then discussed the Fukuda case definition, which is a research definition with likely future revision. Those with a history of alcohol or substance abuse should only be excluded for 2 years, and for those with morbid obesity, the BMI will be raised to >45 for exclusion. (This represents a 5'8" person weighing more than 300 lb) He then made note of the Provider Education Project. This is a web based course in CFS for physicians with a competency certificate at the end.

He then reviewed physical examination in CFS pointing out particularly that lymph glands and skin maybe very tender. Laboratory findings in CFS were usually essentially normal, though there maybe abnormal immune complexes, atypical lymphocytes, lowered IgG, small increase 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 do

occur in other diseases and are non-diagnostic. SPECT scans to demonstrate function show decreases in cerebral blood flow with exercise, often worse 24 hours later.

There was acute onset in 85% cases, and in 72% the main precipitating factor was infection, with a small number of cases following trauma, surgery, childbirth, allergic reaction and emotional trauma. He reviewed possible causes of CFS, including various infectious agents, immunological defects leading to T cell activation, increases in cytokines and decreased NK cell function, HPA axis dysfunction with lowered cortisol levels and orthostatic intolerance. 92% of patients with CFS can become syncopal with orthostatic intolerance, and as well as having a drop in BP, symptoms may come on after a delay of 15 minutes.

A diagnostic decision making model was then presented with a useful flow chart for physicians.

The differential diagnosis covered a very wide range of diseases, and the audience participated in discussion of the characteristic diagnostic features of other conditions such as:

- Evidence of a tick bite and presence of arthritis in Lyme disease
- Optic neuritis and ocular nerve disorders in MS
- Butterfly rash and arthritis in SLE
- Genital infection followed by arthritis (particularly in heel and lower spine) in Reiter's disease
- Skin discoloration and immediate light headedness on tilt in Addison's disease
- SSA antibodies in Sjorgren's syndrome
- Hypercalcaemia with polyuria in parathyroidism
- High ferritin levels in haemochromatosis
- Gluten sensitivity and low ferritin in coeliac disease
- Raised SGOT in hepatitis etc etc.

Lab tests for all of the above should be performed according to the symptoms and history. Further investigation should be pursued if the ESR is elevated as that is not characteristic of CFS, when it tends to be low.

A diagnosis of fibromyalgia (FM) is made if there is widespread pain of at least 3 months' duration coupled with tenderness in 11 of the 18 classical tender point. Gulf War Illness (GWI) tends to overlap with CFS but there are important differences, such as gastrointestinal, respiratory and skin symptoms, which are uncommon in CFS. The 1999 case definition for Multiple Chemical Sensitivity (MCS) was presented. The main symptoms are cognitive impairment, mood disorder, disequilibrium, respiratory problems, headaches, nausea and fatigue. Symptoms are reproducible with repeated exposure and tend to improve when incitants are removed. There is considerable overlap between MCS and CFS with 30% of those with MCS fulfilling the criteria for CFS.

Lapp then presented his stepwise approach to the management of CFS:

1. Education

2. Activity - balancing light activity with rest and increasing the level of activity slowly over time.

3. Nutrition - avoiding malnutrition, minimising sugar, caffeine, alcohol and tobacco, keeping fats low if suffering from diarrhoea and avoiding dairy products and or/gluten for 5 days to see if there is any improvement.

4. Specific symptom therapy:

a) Sleep management - Initially try melatonin, phototherapy or OTC medication, then clonazepam 0.5mg and/or doxepin 10mg - (clonazepam is habituating but not addictive). Trazadone 50mg can give improvement in levels 3 - 4 sleep. Hypnotics may be needed by some patients, and Flexeril can be considered in combination with any of the above.

b) Central activation - reduced levels of dopamine and serotonin can lead to sleep disturbance, low pain threshold, loss of motivation and depressed mood. SSRIs and SNIs (venlafaxine) can be useful as can dopamine agonists such as wellbutrin.

c) Autonomic Nervous System dysfunction - treatment aimed at volume expansion with 2 quarts (2.5L) fluid per day with 1-2 teaspoons of salt daily. Some will benefit from fludrocortisone 0.1 - 0.3 mg daily. Vasoconstrictors such as ephedrine and midodrine can be useful.

d) Pain control - a review of a personalised algorithmic approach was then presented by B Natelson (New Jersey):

Stage 1: NSAIDS - celebrex 200mg bd - often not much help.

Plaquenil - raises pain threshold, but has side effects

Tricyclics - amitriptyline 20-50mg, particularly if there is a sleep problem

Flexeril

Effexor - venlafaxineXR 75 -225 mg daily if depressed

Stage 2 Anti-epileptics: Neurontin 100mg daily, increasing to 300mg qds, can possibly go up to 3 gm daily

Lamotrigine 25mg daily

initially rising to 100mg tds.

Trileptal 150mg bd rising to 600mg bd

Topamax - good if there is a weight problem

Stage 3 Plaquenil - 6 month trial
Tizanidine - 2 - 4mg bd (very expensive)
Mexelitine - 150 - 300mg daily (a local anaesthetic)
Lidocaine patches maybe useful for focal pain.
Tramadol - 50mg qds.

Stage 4 Opiates - Morphine sulph contin up to 30mg bd
Methadone (cheap but has long half
life)
Prednisone - does not work in FM, but Hydrocortisone
25mg daily is often helpful. A four week trial is worthwhile

Several other drugs were then discussed re their relevance in CFS:
dexamphetamine, eldepryl, cylert, methylphenindate, modafinil and a new drug
used for ADD called amoxetine.

Disability evaluation of those with CFS was then discussed by C Lapp. He pointed out that 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 FM. Up to 50% of these people are unable to work. Evaluation needs to be done by a primary carer familiar with CFS. Standardised psychometric and functional testing instruments need to be used. For presentation to Social Security in the US, CFS patients must fit the 1994 Fukuda definition, with one or more specific medical signs clinically evaluated over at least 6 consecutive months (eg swollen or tender nodes, tender points etc) - and certain specific lab findings are acceptable. (eg NMH by tilt table testing, abnormal cranial MRI). Documentation of cognitive and emotional difficulties is also important. Physicians world wide should be aware of the requirements to keep good notes on relevant issues for these patients.

S.Schwartz (Tulsa OK), an infectious diseases physician, then outlined his ideas as to what to do when "you reach the end of the prescription pad". He uses a "5 points of a star" approach looking at:

1. Pain control
2. Improved cognitive function
3. Acceptance, understanding and modification of lifestyle
4. Improved sleep
5. Energy improvement

He emphasised particularly that other measures will not work until sleep is fixed. The aim should be to prevent permanent disability. It is important to collect as much data as possible before seeing the patient, using appropriate history forms, looking at impact rather than symptoms, and measuring instruments designed for the job should be used. Adequate time then needs to be allowed for the consultation. One should measure what is there rather than what is not. Such scales should measure fatigue, depression, memory/recall etc. The patient needs reassurance that he does not have dementia. The patient needs an island of care including the physician, the nurse and other medical assistants (physiotherapist and/or occupational therapist, rehab consultant), psychosocial

support persons (psychologist, social worker, neuropsychologist) and possibly an attorney.

Sleep management, graded exercise, goal setting, counselling, CBT and family involvement all need to be addressed coupled with relearning and restructuring environment. Vocational rehabilitation should include workplace adaptations, disability issues and rights. Professionally led support groups are helpful but patient led support groups can reinforce negative cognition. Schwartz runs an annual seminar for patients, family and friends.

D.Uslan (Seattle WA) a rehabilitation consultant, then outlined his approach to CFS management. He often uses workbooks and aims to see patients very regularly. Self management, pacing and education are important, and cultural, religious and ethnic orientations should be considered. The workplace maybe "pathological" and leave of absence maybe required. Attention to troubled relationships, sleep management (avoidance of obsessive thinking), cognitive rehabilitation (as opposed to CBT) is needed.

P.Fennell (Albany NY) then discussed a systematic approach to management of CFS, using her 4-phase theory for psycho-social intervention.

1. Crisis
2. Stabilization
3. Resolution
4. Integration

Physical/behavioural, psychological and social/interactive features for each phase were illustrated. Work is aimed at stabilization in each phase. 44 subjects had been studied using the Fennell phase inventory, and the study supported the distinction between the phases. Assessment and review throughout the process was discussed.

C Lapp (Charlotte NC) then rounded off the formal part of this day with 2 case presentations which provided interactive discussion, and were examples of how the Provider Education Project is presented to participants.

Opportunity to view the posters (covered later) was then provided, followed by a dinner symposium at which Trudie Chalder discussed CBT.

Dinner Symposium - T Chalder (London UK) acknowledged the physical as opposed to psychological nature of this illness. CBT focuses on educating the patient about the illness and diminishing the focus on symptoms. There should be concentration on overcoming symptoms rather than looking for a cause of symptoms. At her clinic patients are seen regularly for 12 sessions or more, but there is never any pressure brought to bear. The emphasis is on achieving normality. For example, in sleep management, a sleep diary is kept, with encouragement to get up early, to keep regular hours and avoid cat naps. An exercise plan needs to progress very slowly, particularly if the illness is severe, as there is usually a fear of bringing on symptoms with activity. A crash and burn approach needs to be avoided. Several short exercise spells each

day are recommended and the length of the spell may only increase in length by 1 minute per week.. Patients may experience worsening symptoms each time the exercise is stepped up. The patient needs to understand this and realise no harm is likely. The eventual aim is to return to normal life in a carefully graded fashion.

DAY 2

The 2nd day of the conference focussed on research and the first session covered:

EPIDEMIOLOGY - the opening address was given by L Jason (Chicago IL) when he again emphasised the prevalence of fatigue. Many studies have been done looking at prevalence of CFS with wide variation ranging from 7.4 to 2600 per 100,000, but for those meeting the current research definition criteria 1-4 per thousand seems the most likely incidence. Latinos represent the highest racial group with CFS in the USA, probably due to poorer health status. Of those with CFS, 41% meet the criteria for MCS, 16% for FM and 5% of those with GWI match the criteria for CFS. Most studies show a female predominance and paediatric prevalence ranges from 60 per thousand to 2%.

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

W.Reeves (Atlanta GA) said that the research definition is now under review, including ambiguities associated with exclusionary and comorbid conditions, using standardised applicable international measuring instruments to measure intensity and disability associated with fatigue. Exclusions may be permanent or temporary. Temporary exclusions (until treated) may include sleep disorders, hypothyroidism, diabetes and morbid obesity with a BMI>40. Major depressive disorder with psychotic features and PH of anorexia/bulimia are not exclusionary if there has been resolution for 5 years.

Suitable measuring instruments:

Psychological - SCID or DIS

Fatigue - intensity - CIS or Chalder or Krupp severity scale

Somatic and psych health report - SPHERE - measures anxiety, depression and fatigue

Functional disability - SF36 or SIF

Sleep - Pittsburg sleep questionnaire, SAQ - to exclude apnoea and narcolepsy.

Memory and cognition - Cambridge neuro-psych test, RTB , CFI

Pain - SPHERE or McGill pain questionnaire.

Where there is a psychological condition in the differential diagnosis, the patient must have a structured interview with an experienced physician and SCID or DIS should be used.

The symptom list has been re-ordered:

Post-exertional malaise
Unrefreshing sleep
Cognitive difficulties
Headache
Myalgia
Joint pain
Sore throat
Tender nodes

The most prevalent symptom is non-refreshing sleep.

In summary, it is mandatory to use a standard definition and standard methods must be used for assessment. Publications must show how the definition was used and adequately describe the study subjects.

E Unger (Atlanta GA) confirmed that unrefreshing sleep is a defining symptom and the most frequent. This is a chicken and egg situation whereby the poor sleep aggravates the CFS, which in turn worsens the sleep. Formal studies such as all night poly-somnography including sleep latency measurement can be used.

T Chalder (London UK) presented her paper looking at the rate of CFS in childhood in a large (4240) London sample. She concluded that CFS was rare in this age group. 0.19% met the criteria for CFS. 0.4% parents thought their child had CFS, but there was no overlap between the child's symptoms and parental labelling. It seems that parents and children have different perceptions of symptom experience. There was considerable overlap between fatigue and psychological disorders, and there was frequent maternal neuroticism.

K Busichio (Newark NJ) looked at physical impairment in CFS. Her group found that fatigue was only modestly associated with physical functioning in 102 women with CFS (average age 40). Pain was a better predictor of work impairment in CFS-only and FM/CFS patients.

BIOCHEMISTRY

R Suhadolnik (Temple Univ) gave an overview of the biochemistry and genetics of CFS, which he explained encompassed a huge overlap of all disciplines. He acknowledged the many people who had contributed to the many advances in the understanding of CFS. 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.

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

2. 2-5A/RNaseL abnormalities have been shown in CFS, particularly in the severely ill. 37kDa RNaseL is found in PBMCs in CFS in Suhadolnik's and de Meirleir's studies and not in healthy controls, depressed or FM patients. He stressed that there was no time lapse in the examination of the US samples, which W Behan has cited as a risk for false positives .

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

4. Apoptosis - (programmed cell death) is evident in CFS

5. Skeletal muscle function and mitochondrial function - reduced intracellular concentration of ATP suggests a defect in oxidative metabolism with a resultant 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 patients.

There is evidence for changes in brain metabolism.

In addition to altered biochemical processes, there is evidence for some genetic predisposition to CFS, which coupled with a triggering event can lead to immune dysregulation. Ongoing twin studies are providing useful information. Vernon and Behan have both been using micro-arraying techniques for gene expression profiling.

4 papers then followed relevant to Suhadolnik's presentation.

S Vernon (Atlanta GA) discussed the utility of the blood for gene expression profiling and biomarkers in CFS, using micro-array. In her study, she had found that the results were successful in distinguishing CFS subjects from healthy controls. Gene activity differences were identified implicating some of the pathways involved in CFS. She noted that there could be age differences in this study and that in future there is need to control for all variables. She stressed that the more genes one can measure the better.

W Behan (Glasgow, Scotland) compared the muscle of patients with fatigue due to different chronic diseases using micro-array technology to establish whether or not there is a common profile of gene expression. She said age matching and gender was very important. Comparison between the groups identified a range of genes that were differentially expressed more than 3-fold. Symptoms of fatigue and myalgia in CFS are similar to that in other common conditions (COPD, CHF). Studies show profound deconditioning in all groups, but additional mechanisms must be going on. A large number of transcripts were identified in those deconditioned but absent in controls.

G Kennedy (Dundee, Scotland) provided further evidence for dysfunction in oxidative pathways in CFS. High levels of isoprostanes were found. 8-iso-PGF₂? is a sensitive and reliable measure for oxidative stress in vitro. Viral infections increase isoprostanes, but the changes shown in the sample of CFS

patients studied were not present in those with organo-phosphate poisoning or GWI, in which conditions the effects are due to anti-cholinergic effects. Isoprostanes are potent vasoconstrictors, and this may help to explain some of the symptoms in CFS.

D Racciati (Chieti, Italy) explained how oxidative stress may play a fundamental role in CFS pathology. The oxidative stress may be a result of elevated peroxynitrite, 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 NY) introduced this session with a presentation showing the evidence for infection and immunological changes in CFS.

INFECTIONS correlate with disease and fatigue and many CFS patients report an infectious episode at onset. More than 30 infectious agents have been investigated in the quest for a cause of this illness including picornaviruses, EBV and retroviruses. Some of the likely organisms leading to CFS-like illness include:

HHV6 and 7 - minimally found in CFS patients and probably not significant
Bornaviruses - ? involved in humans - but found in a small number of CFS patients.

Borrelia burg (Lyme disease) - those who are sero-positive are likely to have symptoms of CFS

Mycoplasma - Komaroff found no antibodies for these organisms, but Vojdani found 34% positives in CFS patients compared to 8% of controls.

Parvovirus B19 - a large percentage of people carrying this virus do have fatigue, but it cannot be diagnosed after the acute phase.

He concluded that there was no consistent pattern of infection and a number of organisms can lead to the CFS state.

IMMUNE DYSFUNCTION may be involved, as administration of cytokines gives rise to symptoms similar to CFS. eg parvovirus may cause dysregulation of cytokines (TNF α and IFN γ). Other cytokines such as IL-1 α and IL-6 were studied. IL-6 was found to be increased following exercise in CFS.

NK cells showed low activity in 25% CFS patients compared with 7% in controls (Whiteside, 1998) but no differences were found in monozygotic twin studies (Sabath, 2002).

Suhadolnik and de Meirleir found up regulation of the RNaseL pathway in CFS while Gow et al had no significant evidence for this.

ALLERGY - many with CFS report atopy. IgE and CFS were found to correlate in 2 recent studies.

AUTO-IMMUNITY is an appealing potential link. Konstantinov (1996) found significantly increased ANA positives in CFS, but Skower (2002) had less promising results.

In conclusion Hay said that as yet there is no consensus for immune dysfunction 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.

3 further papers were presented at this session.

K Maher (Miami,FL) 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 therefore be NK specific but may encompass the cytotoxic T cell subset as well.

P McGaffney (Minneapolis,MN) found a significant difference in gene expression, detecting 166 genes. 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. This may give insight into the pathophysiology of CFS but there is still a long way to go.

R.Suhadolnok (Temple Univ) enlarged further on the biochemistry and clinical differences. His team studied 3 groups: CFS patients, healthy controls and those with depression. He had again found a close association between the upregulated 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 and to identify homogenous subsets within the population. This would thus prove useful in studying treatment methodologies for various subsets.

TREATMENT

B Natelson (New Jersey) introducing this session explained the trials and tribulations of drug research in CFS. One could compare an assortment of biological functions between patients and healthy controls, or one could use a trial of a specific pharmacological agent. Such a trial may give a clue as to cause.

3 trials using phenelzine, selegiline and ambrotose only showed minor statistical improvement. He reported on a larger trial using Modafinil, a drug used to combat fatigue and sleepiness in conditions such as narcolepsy and MS. It was thought it could have a role in CFS. A double blind, placebo-controlled trial in moderately ill patients was performed. The trial lasted 4 weeks and the dose was increased from 100mg daily to 200mg over the first few days. Drop out rate was 20% mainly due to adverse effects such as headache and nausea. The trial was conducted in 6 sites and many measures were studied. No significant improvements were seen. There was a tendency for slight improvement on the drug and in 2

sites there was an amazing placebo effect! The subtle therapeutic effects were not backed up by research.

A number of factors deemed to be important for future research emerged from this study:

1. Choose only those reporting sudden onset consistent with viral illness
2. Psychiatric diagnoses should be excluded.
3. Those with MCS or FM should be excluded as they have higher levels of comorbid psychopathology.

This will ensure a more homogenous sample. It may also be preferable to use only one site.

O Zachrisson (Goteborg, Sweden) presented a randomised controlled study on the use of staphylococcus toxoid in FM/CFS. His group found that over 6 months there was significant improvement. There was good tolerability with only 10% dropout. 65% of the CFS group improved significantly, but there was worsening of symptoms on withdrawal. The symptoms that improved were: fatigue, sleep, cognition, sadness and irritability. The antibody response was related to the clinical response. Maintenance treatment is needed to prevent relapse and this agent is no longer on the market as it contains a preservative which breaks down to mercury and salicylate.

D Clauw (Washington DC) had studied the effectiveness of aerobic exercise and CBT in 1000+ Gulf War veterans with chronic multisystem illnesses. Patients were excluded if they already had an exercise plan. 4 groups were studied: usual care, exercise alone, CBT alone and a CBT+exercise group. Physical functioning was not significantly improved in any of the 4 treatment groups. However both exercise alone and CBT+exercise improved fatigue, cognition, distress and mental health functioning. Affective pain was improved with CBT alone and CBT+exercise, but 3 other pain measures were not improved.

C Lennartson (Stockholm, Sweden) studied the effects of low intensity interval training in 30 women with CFS. 20 were in the training group, which involved walking (15-30 min), stretching and relaxation. 10 were controls. Rest periods were included. 5 dropped out of the training group. This type of light intensity training was found significantly to be useful for those with CFS, and this exercise did not appear to exacerbate symptoms, so that patients could continue the programme without fear of relapse.

PSYCHO-SOCIAL ISSUES

T Chalder (London, UK) introduced this session and gave an overview of her thoughts on Chronic Fatigue. She described labelling difficulties with medically unexplained illnesses. eg psychosomatic, somatization, hysteria, conversion disorder etc. She preferred to divide these illnesses in terms of:

Functional - absence of pathology but with physiological processes not clearly understood.

Medically unexplained
Miscellaneous eg FM,IBS,CFS.

She suggested we should try to study the physiological mechanisms alongside cognitive and behavioural factors. Precipitating factors such as life events, social support, lack of fitness and coping ability are determinants in the level of fatigue. She has used several different questionnaires to determine the level of fatigue, and found that the perceived lack of practical rather than emotional support was predictive of fatigue level. She noted that CBT could target the cognitive and emotional effects.

T Giesecke (Washington DC) had looked at the roles played by biological, psychological and cognitive factors in subsets of patients with FM. 3 groups were identified: a) Those with FM with extreme tenderness and no identifiable psych/cognitive contribution. b) Those who are moderately tender with normal mood and c) those where mood and cognitive factors contribute considerably to tenderness.

R Taylor (Chicago IL) evaluated the effects of an empowerment orientated rehabilitation programme on QOL and outcomes related to symptoms and disability.

These programmes which were consumer driven were found to be effective. Patients set their own goals and determined steps. They also took primary control over evaluation.

D Williams (Michigan MI) had worked with Gulf War vets with chronic multi-system illness. The aim was to improve symptoms and physical functioning using 12 weeks of aerobic exercise and CBT alone or in combination. Results had been less than expected despite some improvement. Results were more specifically analysed looking at functional status, mental health, pain, fatigue and memory. Sex, mood disorders, personality disorders, disability issues and dolorimeter threshold were all associated with negative changes in outcome. Tender point count was predictive of positive outcome in both exercise and CBT.

A Peckerman (New Jersey NJ) found that PTSD contributes to dysregulation of cardiovascular responses to mental and orthostatic stress, leading to more physical symptoms in Gulf War vets with CSF/ICF.

DAY 3

CENTRAL NERVOUS SYSTEM

D Peterson (Incline Village NV) introduced this session and discussed the role of the brain in medically unexplained illnesses. He described structural and functional abnormalities. A number of structural abnormalities have been reported such as "MS-like" changes on MRI and Chiari syndrome, which he described as rare.

Functional abnormalities include:

Altered HPA axis
Cognitive impairment
Abnormal sleep patterns
Regional hypoperfusion in the brain (SPECT studies)
Hypo brain metabolism (PET studies)
Autonomic dysfunction (NMH shown using tilt table)
Perturbation of brain hormones in neurotransmitters.
Primary or reactivated CNS infection

Abnormal spinal taps often have shown that something abnormal is going on in the brain - one study in children showed that a large cohort of children had evidence of HHV6A (using culture and PCR) in the spinal fluid, which is unusual as the childhood illness is usually HHV6B. If there are prominent CNS symptoms, a spinal tap maybe helpful, and studies have shown increased opening pressure, increased total protein and lymphocytosis. He stressed that blood tests for HHV6 are unreliable. Treatment with antiviral agents has proved often dramatic in these cases, who had often been severely ill for a long time.

He warned however that these tests are invasive and therapy expensive, and he presented a useful algorithm for assessment of those in whom these procedures are worthwhile.

B Natelson (New Jersey NJ) described earlier hypotheses suggesting that some patients may have covert encephalopathy as had been demonstrated by MRI and larger ventricular volumes. The more severe the CFS, the larger the volume tended to be. CFS patients without comorbid Axis 1 psychological disorders also had more neuropsychological dysfunction than those with psychological disorder or controls. 44% of those with CFS were found to have spinal tap results in the abnormal range for protein or WBCs thus supporting the hypotheses that some CFS patients do have underlying pathologic brain processes responsible for their symptoms. For those with normal cerebro-spinal fluid (CSF), 29% showed signs of depression within a few weeks, while those with abnormal CSF did not. Further studies will investigate correlation between those with CSF abnormality and psychological and cognitive status.

R Gracely (Michigan MI) found that patients with FM/CFS showed higher subjective ratings and significantly increased cerebral responses to a constant pressure stimulus. This was assessed using functional MRI comparing constant pressure with fluctuating stimulation. In CFS patients there was also unique activation in the thalamus and putamen consistent with the hypothesis of augmented pain processing in these patients.

A Tomoda (Kumamoto, Japan) discussed his team's work with children, analysing event related potentials (ERPs) using a visual oddball paradigm. The large group of 319 children with CFS studied, plus 264 controls, showed 3 types of abnormalities in this measue.

Prolonged response
Significantly shorter response
Normal results

These responses appeared to correlate with level of illness.

TECHNOLOGY

Advances in technology for measuring abnormalities in CFS patients were discussed by Y. Yamamoto (Tokyo, Japan). He reviewed many different measuring devices now in use leading up to the development of a new behaviour monitor known as an ECOLOG. This is a watch type computer for ecological momentary assessment of mood, physical symptoms and cognitive function. There is a built in actigraph for locomotor activity data. It can operate continuously for more than 30 days. A vast amount of material can thus be analysed and this device seems infinitely superior to those used in the past.

K Yoshinuchi (Tokyo, Japan) then explained a study using this device to track symptoms in CFS patients before and after an exercise test. This provides further evidence that CFS patients do develop symptoms following exercise and the onset of symptoms may be delayed.

P. Lyden (Michigan MI) reported on a study in patients with FM/CFS using an actigraph measuring activity over 5 days. Participants rated symptoms 5 times daily. They tended to have a day of activity followed by 1-2 days of very limited activity, but there was a lack of correlation between activity and reported pain or fatigue. She described the actigraph as being useful but not really adequate. The cost of each watch is about \$1200US, and data analysis is very costly.

PHYSIOLOGY

The session was introduced and overviewed by P. Gold (Nat Inst of Mental Health), who showed how HPA function is different between those with CFS and those with depression. In major depression there is elevation of 24 hour plasma cortisol and 24 hour CSF norepinephrine. This is evident usually even in mild depression. BP is generally also higher in depression. In CFS patients, cortisol tends to be lower, but it may also be slightly down in those with depression with severe fatigue, who also often have pain and some immune activation. IN CFS patients cortisol and ACTH levels are reduced in response to exercise Catecholamine levels also tend to be lower in CFS.

J. Stewart (Valhalla, NY) discussed some of the physiology underlying POTS. He described 2 groups in relation to metabolic mediated vasodilatation and the skeletal muscle pump:

- a) Those with increased flow and lowered resistance
- b) Those with low flow and high resistance.

Arterial remodelling does not occur in CFS. It maybe that there is a subset of patients with CFS who would not therefore benefit from support stockings.

V. Spence (Dundee, Scotland) reported that cholinergic abnormalities exist in the peripheral micro-circulation of CFS patients, as evidenced by enhanced skin vascular responses to graded doses of transdermally-applied acetylcholine. This

has not been shown in other diseases. Acetylcholine 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 acetylcholine, indicating that what is happening is a specific sensitivity to acetylcholine.

The abnormal peripheral cholinergic activity in CFS may perhaps be related to altered cholinesterase activity. These effects can be worsened using the drug Mestinon and Spence had some concerns regarding the use of galanthamine also.

K Yoshiuchi (Tokyo, Japan) presented a study which suggested that patients with CFS without POTS have a change in sympatho-vagal balance in favour of a sympathetic predominance during head up tilt.

D Clauw (Michigan MI) reported on his group's study of catecholamine levels in response to standardised stressors in FM and CFS patients. Data suggests that those with CFS/FM have higher catecholamine levels than controls while performing the same activities. The responses were consistently different for CFS and FM with individuals with CFS displaying attenuated responses while those with FM showing normal response.

POSTER PRESENTATIONS

EPIDEMIOLOGY

D Keye (Salt Lake City, UT) found that CFS patients frequently do have an infective episode in the month preceding onset of illness, while those with FM will have often had metabolic or mechanical injury. A. Logan (Mahwah NJ) showed that of those with CFS of sudden onset, the majority of cases occurred during the influenza season.

E Van Hoof (Belgium) had looked at the activity differences between CFS and FM and the data indicated a lack of differences, sustaining the growing awareness of the great similarity between the 2 syndromes. Her group had also developed a new questionnaire - the CFS activities and participation questionnaire (CFS-APQ). It was found to have good internal consistency and validity. C Snell (Stockton CA) confirmed that those with CFS exhibit non normal responses to exercise with post-exertional malaise being a major debilitating symptom.

P. Levine (Washington DC) had looked at the cluster of neurologic symptoms in Gulf deployed and non-deployed sufferers of CFS. The study showed an even distribution of these symptoms in deployed and non-deployed, and no specific aetiology for this cluster of symptoms was identified. Multiple vaccines, exposure to the Khamisiyah plume and deployment to Kuwait/Iraq maybe potentiating factors.

A Chester (Washington DC) found that those with unexplained chronic fatigue had more rhinosinusitis symptoms than those with fatigue explained by mental or physical illness.

IMMUNOLGY

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. Further studies using controls need to be done however, as this has been challenged by Gow et al. K De Meirleir (Belgium) suggested that RNaseL truncation could lead to dysregulation leading to degradation of cellular mRNAs which are not normal targets of native RNaseL. W Behan et al (Glasgow, Scotland) concludes in her studies that if activation of the antiviral pathway is observed in patients then the data suggests that the patient is suffering from a current or recent infection, not that the patient has CFS. It would therefore be inappropriate to use the RNaseL/PKR antiviral pathway as a basis for a diagnostic test for CFS.

M Antoni (Miami FL) describes the picture in CFS as dual immunologic with low NK cell activity and high activation of other aspects of the immune system. K de Meirleir (Brussels, Belgium) also had data confirming immune activation in CFS patients. However immune activation was less controlled in those infected with Mycoplasma than those without. A further poster showed no association between the RNaseL ratio and antibody titres of C.pneumoniae.

A small study by T Jhodoi et al (Kumamoto, Japan) showed some clinical improvement following treatment with low dose γ -globulin therapy in their CFS patients who had lower levels of TGF- β 1. However a study by G Kennedy (Dundee) showed that their CFS patients had higher levels of TGF- β 1 with increased neutrophil apoptosis.

Patients who had been tested with C.albicans antigen were shown by G Cozon (Lyon, France) to have delayed reactivity, suggesting that this antibody may be implicated in the development of CFS in a subgroup of patients, who may therefore benefit from probiotics and low sugar diet. J Allegre (Barcelona, Spain) had looked at atopy prevalence in CFS and found no difference between CFS patients and controls.

A sleep study presented by E Van Hoof (Brussels, Belgium) showed that immune alterations may increase the percentage of alpha intrusion due to ant-infectious activity.

PHYSIOLOGY

D Cook (New Jersey) found that there were some differences in autonomic function between healthy controls and CFS patients. Exercise exaggerated differences in the reactivity to postural change between the 2 groups, including both periodic and fractal components of heart rate variability.

A Peckerman (Newark NJ) found that patients with CFS demonstrated abnormal breathing adjustments to postural stress. There was inefficient utilization of respiratory muscles while standing associated with increased light headedness. Further studies are needed to determine whether the abnormal adjustments were due to posture itself or to greater energy expenditure required when standing.

T Friedman (Los Angeles CA) 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. Further studies may offer unique treatment options.

J M Van Ness (Stockton CA) noted the importance of considering gender as a variable when designing and conducting CFS research as there were noted male/female differences in his studies on exercise capacity. Exercise testing was also investigated by K Ambrose (Michigan MI) and she found physical performance and physiological responses similar for most patients and healthy controls. She noted that particular subgroups of patients may perform differently than others and broad generalizations should be avoided. She also found in a further study that there were differences between the genders on various tests, in that females had altered heart rate variability in FM, CFS and GWI but males and healthy controls did not. Again the importance of gender effects must be considered when analysing results.

TREATMENT

Treatment of CFS patients with Ampligen (200-400mg twice weekly) was reviewed by D Strayer (Philadelphia PA) Significant improvements were seen in physical performance, cognitive function, vitality and physical activity in 81 severely ill patients after 24 weeks' treatment. The treatment was well tolerated and most patients were continuing beyond 24 weeks.

A Logan (Mahwah NJ) showed that CFS patients report consumption of a wide variety of herbal/dietary supplements. The potential for drug interaction is high and patients need to be aware of telling their doctors what they are taking. He suggests that further research is needed into which, if any supplements have benefit in CFS.

Mind/Body interventions were also frequently used by CFS patients as shown by A Basted (Toronto, Canada). Again this seems to be an under-researched area warranting further study of psycho-physiological mechanisms. Eye movement desensitization as a means of achieving relaxation was demonstrated in a poster by F Friedberg (New York), and is described as being useful when other relaxation techniques fail.

T Madarame (Tokyo, Japan) had graphic illustrations of the use of moxibustion on "Shitsumin" in 26 CFS patients. It was found to be an effective treatment for these patients.

Administration of Transfer Factor for HHV-6 was illustrated by J Brewer (Kansas City, MO). Patients with CFS and documented HHV6 viraemia improved symptomatically and immunologically after administration, and such treatment may have an important role to play in some with CFS.

A study by A Logan (Mahwah NJ) showed that dietary modification was frequent in CFS patients in an effort to deal with possible food sensitivities. The sensitivities reported appear to be a result of CFS and may exacerbate symptoms,

but research is scant in this area. There appeared to be no significant connection between pre-illness migraine and food sensitivity reporting.

The work presented earlier by O Zachrisson (Goteborg, Sweden) on the use of staphylococcus toxoid was further demonstrated in his poster showing that the greater the serologic response the better the clinical outcome. He also had a preliminary poster discussing a new Fibro-Fatigue scale to measure outcome following treatment.

BIOCHEMISTRY and CNS

G Moorkens (Antwerp, Belgium) looked at serum and RBC magnesium and Vitamin D status in 3 groups: CFS, FM and autonomic dysfunction. A number of patients in each group were found to have deficiencies, and appropriate supplementation may therefore be important for some patients.

The cognitive function scale (CFI) was used by G Lange (Newark NJ) to measure impaired brain function in CFS groups with and without brain abnormalities as assessed by MRI. Those with brain abnormalities were significantly more impaired than those without.

D Cook (New Jersey NJ) found that CFS patients showed subtle baseline cognitive deficits, but cognitive performance was not worsened by light exercise. Light exercise appears to improve short term memory. Clarification on relationship between cognitive performance and exercise in CFS may be useful in determining prognosis and defining those who may benefit from exercise.

M Pall (Pullman WA) outlined the proposed mechanism of elevated nitric oxide/peroxynitrite theory of CFS/FM and related conditions, and his poster reviewed the literature and data thus far.

Gene expression profiling using micro-array technology was illustrated by H Ojaniemi (Stockholm, Sweden)

E Georgiades (Glasgow, Scotland) had looked at peripheral and central mechanisms of fatigue in the aetiology of CFS by examining cardiopulmonary and metabolic responses, and the profiles of selected serotonergic and dopaminergic modulators during symptom-limited exercise and subsequent recovery in CFS compared to controls. The findings supported impaired exercise tolerance.

There was heterogeneity in the cardiovascular and metabolic responses arguing that these peripheral mechanisms have a variable contribution to the underlying pathogenesis in CFS. More uniform differences were seen between CFS and control subjects in the serotonergic and dopaminergic modulators and this may reflect a more global involvement of central mechanisms in the premature fatigue that characterises CFS.

PSYCHOSOCIAL

K de Meirleir (Brussels, Belgium) had evidence for a high rate of kinesiphobia (fear of movement) in CFS patients. A fear/avoidance behaviour may thus develop as a result

of chronic disability. Also from Belgium, E Van Hoof (Brussels) found a strong link between psychological variables and immune parameters. The link could be mediated by cytokines. Sickness behaviour may help the body to recuperate.

The poster by K Busichio (New Jersey NJ) stressed the importance of understanding the neuropsychobiological correlates in finding a cure for CFS. A study using tryptophan was used to illustrate effects on the serotonergic/dopaminergic system. There appears to be a normal relationship to prolactin release in CFS, since the effects of serotonin on prolactin release are mediated via a decreased inhibition of the dopaminergic system, and it maybe that disorders of this system are characteristic of CFS.

R Taylor (Chicago IL) introduced their model of Human Occupation for functional capacity assessment in CFS. This model conceptualises occupational participation as influenced by volition, habituation, performance capacity and the environment. S Song (Chicago IL) had done a study which suggests that chronic fatigue syndrome and psychiatrically explained chronic fatigue are not the same conditions.

Findings in a study by S Torres-Harding (Chicago IL) suggest an underlying family disposition toward the development of both CFS and auto-immune disorders. This is consistent with the hypothesis that CFS represents a dysregulation of the immune system.

I would finally like to thank the Associated NZ ME Societies for supporting my attendance at this excellent conference.

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[Note: Posted here with Dr. Vallings' kind permission.]

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