

Abstracts Presented at the Sydney '98 CFS Conference

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CLINICAL FEATURES OF M.E./CFS

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Christine Hunter has asked me to speak on the clinical features of M.E./CFS as reviewed in Nightingale's textbook *The Clinical and Scientific Basis Of Myalgic Encephalomyelitis*. In this publication we discuss the clinical features of individuals who fell ill acutely, either individually or in clusters or in epidemics and who manifested a troubling, sometimes profound and usually chronic alteration of certain of their normal Central Nervous System resiliency and control mechanisms. This phenomenon has been referred to by several names most commonly Myalgic Encephalomyelitis and Chronic Fatigue Syndrome.

The information in these clinical chapters were the result of the investigation, at Nightingale, of in excess of 1000 patients who had fallen ill, primarily during the 1984-88 pandemic in the United States and Canada; the new wave of disease first heralded by Drs. Paul Cheney and Daniel Peterson in Lake Tahoe. This clinical information was supplemented by work of Dr. John Richardson of the Newcastle Research Group in the U.K. Dr. Richardson had for over 40 years followed thousands of M.E. patients, and it was he who has pointed out repeatedly that M.E. was not merely an acquired injury to the CNS but that the end organs, principally the heart, endocrine glands and gastrointestinal system were often and sometimes significantly affected. These chapters on clinical findings were further supplemented by the wealth of clinical information documented in more than 50 epidemics of similar disease since 1934. I strongly advise both patient and physicians to read these chapters for a better understanding of M.E./CFS.

In this meeting in New South Wales I shall depart from the text and look at the findings of a specific cluster epidemic that occurred during the Christmas period of 1993 in Ottawa and Montreal drawing attention first to 3 individuals that were identified as a cluster by the presence of an identical novel enterovirus common to each patient. I will discuss the features and physical findings in 3 individuals who fell ill within the same 10-day period, in the same manner and with the same genetically identical virus but who were separated by geography by 20 and 40 kilometres. Within this cluster, identified by time, manner of onset, and immediate proximity of homes, I will discuss the onset of a spectrum of illnesses that include classical M.E./CFS, Fibromyalgia Syndrome in a mother and identical twin daughter. The identical twin daughters are particularly interesting in that they both fell ill at the age of 16 and at that time were identical in appearance and size and weight. One of the twins recovered within a year and went on to grow and now weighs 124 lbs. The other twin has recovered to some degree but still remains ill and is now shorter in stature and weighs approximately 98 lbs. The daughter who remains to some degree ill demonstrates lower than normal human growth hormone levels and antibodies to her mitochondria. The mother who was the most disabled demonstrates brain atrophy by MRI. Also affected immediately across the street was another 16 year old. The next door neighbour who fell ill with the same or similar infectious illness was within a short period after diagnosed as chronic lymphatic leukemia. Three doors up the street another patient developed Crohns Disease (terminal ileitis).

If time permits I will then discuss the clinical aspects of the most recent 100-CFS patients. These patients had all been seen from 5-20 physicians. Depending upon the physician they had been diagnosed as CFS, FS, or patients with psychiatric disease. Of the 100 patients, no more than 4 had clearly recognizable psychiatric illness and the remaining group consisted of those who were positive for the unique enterovirus noted. However a significant majority of these patients had a wide range of either well-known or little known medical illnesses. Time permitting, some of these findings will be discussed and the implications that these have on the validity of the American CDC, CFS guidelines as a technique to access a uniform or consistent disease pattern.

I will call for the recognition of M.E. as a more distinct clinical entity than CFS. I will also note that CDC as described by the CDC and the UK and Australian groups is actually a more diverse disease spectrum associated by a common group of symptoms but often with vastly different etiology, physical findings and clinical outcome. I will further call for a repudiation of the policy statement limiting the degree of investigation and note the necessity of a more in depth investigation of all CFS patients since these patients usually represent severe underlying disease processes or injuries to the CNS or CNS and end organ sites.

I will conclude by pointing out the lack of rational in attempting to seek a common treatment for patients described as CDC which appears to be a large spectrum of diverse and often serious disease entities.

OVERVIEW OF AMPLIGEN THERAPY

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Double-stranded RNA has been used for the treatment of veterinary viral infections for over 3 decades, but was considered too toxic for human use. The inclusion of a uridine molecule in one of the strands, however, makes the molecule quite safe for human use. Poly(I):Poly(C12U), or Ampligen, has been shown to be both antiviral and immunomodulatory in human beings.

Initial studies have demonstrated considerable efficacy and safety in the treatment of chronic fatigue syndrome (CFS). An open-label study of Ampligen involving 15 subjects who met the 1988 CDC Criteria for CFS was begun in 1988. Over 24 weeks of therapy with Ampligen, general performance scores and cognition improved progressively, and HHV-6 reactivation was significantly reduced.

Based on this pilot study, a randomized, placebo-controlled, double-blind, multicenter study of Ampligen was undertaken in 1989. Again, general performance and cognition improved as did activities of daily living and exercise treadmill performance.

This presentation will review the pharmacology of Ampligen, as well as the pilot study and the randomized trial. We will describe current trials of Ampligen in the US and Europe, particularly our experience with five subjects in Charlotte.

CARDIAC INVOLVEMENT IN PATIENTS WITH CFS

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A sentinel patient, a 58 year-old male in prior excellent health, was seen in 1988. He demonstrated the sudden onset of incapacitating fatigue, inability to exercise, light-headedness and palpitations. His 24-Hr ECG monitor (Holter) showed oscillating ischemic-appearing T-waves, but the coronary angiogram was normal. His left ventricular ejection fraction at radioisotopic gated blood pool (MUGA) method was 44% with global left ventricular (LV) dilatation (normal 3 50%). Right ventricular endomyocardial biopsy showed a lymphocytic myocarditis. MUGA studies remained abnormal through 1997, and his prior vigorous life style did not return.

Thereafter, controlled blinded clinical trials (2 separate studies) showed that all patients (over 100 patients) with CFS have abnormal oscillating T-wave flattenings and/or T-wave inversions appearing with sinus tachycardias, and often disappearing with return of normal sinus rhythms. Significant numbers (epidemiologic studies under way) of CFS patients show abnormal LV dynamics and decreased EFs. Right ventricular endomyocardial biopsy studies in these CFS patients demonstrate cardiomyopathic changes of myofiber disarray, myofiber hypertrophy, and increased fat, lipofuscin granules and mitochondria or occasionally lymphocytic myocarditis. Cardiac symptoms in CFS patients are light-headedness, palpitations, non-exertional dull aching, chest pain coming on at the end of the day with increasing fatigue. We suspect persistent infection in the myofiber of the heart of CFS patients with Epstein-Barr virus, human cytomegalovirus or the 2 herpes viruses together in the same patient as the cause of CFS. This hypothesis is directly open to blinded controlled clinical trials.

THE TGF β , T-CELL IMMUNOPROTEINS AND CFS

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A number of studies have suggested immune abnormalities in CFS. Although there is no consensus on the issue, there is evidence to indicate immune activation but also impaired cell mediated immunity and reduced activity and numbers of natural killer cells. There are also variable reports of abnormalities of cytokine production, including of TNF α and TGF β .

The symptoms of CFS suggest the possibility of functional disturbances in the CNS. It is unclear as to the extent of which these alterations are due to identifiable biological processes. However, it is possible that at least in some cases of CFS, immune activation is occurring with effects on the central nervous system. If immune processes are activated in such cases, possible incitants include not only micro-organisms, but also environmental exposures including ingestants (i.e. foods) and airborne exposures such as chemicals and moulds. In some respects the symptoms of CFS resemble those reported in the disorders where immune processes are activated, for example, infectious diseases.

There are reports of patients developing symptoms typical of CFS following the ingestion of certain foods. In addition, there are similarities between symptoms described in patients with the controversial entity, chemical sensitivity, and CFS. Although well described immune process such as delayed hypersensitivity and IgE antibody production do not appear implicated in reactions to foods and chemicals in patients with CFS, there may be other possibilities.

Patients sensitive to foods/chemicals have been studied who develop symptoms resembling CFS on exposure. In a group of milk-intolerant patients, raised levels of IgG and TABM (T-cell antigen binding molecules) were found against three milk proteins. In a group of patients assessed as sensitive to solvents, there were raised levels of TABM, but not IgG, to benzoic acid conjugated to human serum albumin.

TABM are thought to play an important role in the suppression of cell mediated immunity and may accompany humoral immune response. Preliminary work indicates that these molecules are antigen specific and linked to immuno-suppressive cytokines, particularly TGF β . In sensitive patients, TABM may serve to concentrate cytokines such as TABM to where antigen is localized. These local concentrations of cytokines may affect local tissue function and perhaps central nervous system function.

Preliminary work in animals has shown that TGF β acts on afferent nerve endings to modulate the release of neuro-peptides such as substance P. It is proposed that TABM specific for environmental antigens may be implicated in symptom production in some patients with CFS.

Dr Hilton Lowe

Sydney, Australia

Chronic fatigue syndrome is the end result of multi-system dysfunction. There are probably multiple aetiologies. The nutritional approach to correct physiological function is aimed at the digestive tract, liver function, inflammatory control and adrenal dysfunction. Assessment and optimization of physiological function at these integral areas show a predictable benefit using nutritional supplements combined with minimal use of synthetic pharmaceuticals. The approach is wholistic.

Blood tests are used to exclude recognised diseases and to assess liver status, vitamin status, immune function, allergic inflammatory status and intestinal absorption; three day faecal fats to reflect digestive ability; urinary indican for intestinal dysbiosis; hair mineral analysis to reveal mineral imbalances and reflect on adrenal function. The interpretation of these tests is critical.

Discussion of physiology and biochemical pathways is incorporated in this article to support the use of nutritional supplements. The information is resourced from recognised medical texts, as well as, the latest research articles. For example, adrenal cortex insufficiency leads to sodium, hydrogen, ammonia and magnesium loss via the kidneys. Increased sodium excretion and potassium retention leads to muscular weakness, acidosis, hypotension and decreased cardiac output. These patients react poorly to chemical or physical stress and are less able to tolerate nutritional deficiency, infection, sensitising agents and noxious chemicals.

As the precipitating factors may be multiple, individual cases of Chronic Fatigue Syndrome will have varied therapy around the main therapeutic regimen. Although depression may be an important symptom, the successful nutritional treatment of these patients supports the hypothesis that Chronic Fatigue Syndrome is the result of selective nutritional deficiencies.

Two case presentations of patients who fulfilled the diagnostic criteria of Holmes, Kaplan, Grant et al, are used to demonstrate the principles of assessment and therapy.

Peter B, a thirty-three year old male with a twelve year history of intermittent exhaustion and progressively more severe fatigue, presented in September, 1997. Having found no previous benefit with the medical profession, Peter had placed himself on a restricted diet with partial benefits. He reported obvious benefits within two weeks of full therapy.

Karen A, a forty-six year old female, presented in April, 1997. She received an invalid pension for five years due to chronic fatigue syndrome. Karen had consulted multiple doctors and naturopaths with intermittent benefits.

After using my nutritional regimen, Karen had progressively less fatigue. Her progress was hindered by the presence of hypersensitivity reactions, reflux oesophagitis, emotional stress and depression. On December 12, 1997, Karen was well and energetic.

AN INNOVATIVE MULTIDISCIPLINARY INPATIENT APPROACH TO CHRONIC FATIGUE SYNDROME

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Chronic Fatigue Syndrome is a disabling condition with mixed physical and psychological consequences.

We describe a new inpatient based programme developed at the Austin Hospital, Melbourne utilising a multi-disciplinary approach incorporating paediatric, psychiatric, dietetic, nursing and teacher input on the basis of intensive physical rehabilitation.

We have had 15 adolescent patients complete the programme. Twelve completed the follow up questionnaire, 10 females and 2 males. All have had severe symptoms resulting in 10-24 months of illness, inability to attend school and undertake physical activities and all satisfied the criteria for diagnosis. Their disabilities ranged from being wheelchair bound to having the strength to move around the house for short periods only. Most were on strong analgesics (one on pethidine) for muscle pain and all were surrounded by families in crisis.

All spent 4 weeks on the ward utilising a programme which was designed specifically for each patient after meeting the team.

6 months later

At follow up all were back at school, none was using analgesics and all felt dramatically better. Five regarded themselves as being back to normal, 7 felt they still had mild limitation but were no longer disabled and 1 was finding reintegration into school difficult but had no major C.F.S. Symptoms.

The small numbers make conclusions difficult to draw. However, this approach utilising an inpatient approach with psychological and physical rehabilitation has not been previously described in the literature. We are aware that these results may be short lived and are currently planning a prospective study to examine the long term outcome in these patients.

PERSONAL EXPERIENCE WITH MYALGIC ENCEPHALOMYELITIS / CHRONIC FATIGUE SYNDROME

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M.E. / C.F.S. Sufferer
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multi-system dysfunction

Future research indicated to refine biological markers for convenient titration of treatments via this EFAM model

Host versus Acquired Responses in Defined CFS Patients.

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The current CFS definitions define a heterogeneous group of conditions. The CFS definition can be divided into two sub-components, those symptoms related to the host response (fatigue, pain, cognitive alterations) and those symptoms indicative of an acquired or infectious response (fever, sore throat, lymphadenopathy). Common host responses such as fatigue and pain are of multiple types and initiated by many different mechanisms. The use of these common highly variable host responses, such as fatigue or pain, as diagnostic markers of any disease is philosophically flawed as they give little indication of the potential aetiology(s). Therefore analysis of those features associated with the acquired or infectious responses may allow determination of the potential aetiology of a number of conditions currently defined as CFS, whilst analysis of host response may allow determination of genetic or acquired host susceptibility to the various acquired conditions.

Analysis of the lipid and urinary organic and amino acid excretion along with symptom presentation allow the detection of both acquired and host responses, which could be used to differentiate between the various potential disease entities.

Combinations of auto-immune, persistent viral (e.g. enteroviruses), chronic bacterial infections/toxicity, environmental toxin exposure and secondary viral reactivation along with host genetic and acquired susceptibility can be used to determine the patients disease status in many cases.

These data clearly indicate the heterogeneous nature of the disease entities currently defined by the CFS definition. The use of CFS as a clinical diagnosis is not supported by the available data and should be replaced with the diagnosis of a chronic fatigue disorder.

Alterations in plasma lipid composition in patients with chronic fatigue syndrome.

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A study of 60 CDC-defined CFS patients and 39 age- and sex-matched controls was undertaken to determine whether the plasma lipid composition of CFS patients was different to that measured in control subjects. There were no differences in the total concentrations of plasma lipids between the two groups. Multivariate analyses revealed that the total plasma concentrations were associated with cholesterol synthesis and lipogenesis in both CFS and control subjects. However, alterations in n-6 fatty acids were also a major factor in the CFS patients' regulation of plasma lipid concentration, but not in controls. The alterations in the n-6 fatty acids reflected the dysregulation of D6-desaturase activity and the supply of the prostaglandin precursor fatty acids. The changes observed in the CFS patients were consistent with a low-grade inflammation response. No evidence was found for changes in lipid homeostasis which reflected insulin resistance or changes in activities of D5-desaturase, elongase and stearoyl-CoA desaturase.

The increase in the plasma lipid concentrations in the CFS patients was associated with dysregulation of D6-desaturase activity and the n-6 polyunsaturated fatty acids, which were consistent with an inflammatory mediated event in the CFS patients.

DENTAL AMALGAMS AND CFS

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Abstract: Ninety-eight CFS patients and 81 age- and sex-matched controls were assessed for the changes in symptoms (clinically determined and questionnaire), SCL-90-R psychological responses, blood cell parameters, blood biochemistry and the urinary excretion of organic and amino acids in relationship to their dental amalgam status. There was no difference in the number of dental amalgams per subject, the number of subjects who had their dental amalgams removed and the number of subjects who reported improvement following removal of their amalgams between the CFS patients and the control subjects. No amalgam parameter was associated with CFS. There was no association between increasing numbers of amalgams or amalgam removal and any alterations in the clinical or patient-reported symptoms (prevalence, severity), SCL-90-R psychological responses, blood cell parameters, blood chemistry or urinary excretion of organic and amino acids in either the CFS patients or the control subjects. Those subjects who perceived that they had an improvement in symptom expression following amalgam removal did not have any detectable difference in clinical or patient-reported (prevalence, severity) symptoms, SCL-90-R psychological responses, blood cell parameters, blood chemistry or urinary excretion of organic and amino acids.

Conclusions: No differences in symptom expression or pathology could be detected in either CFS patients or control for any amalgam parameters. No evidence was found that could support the removal of dental amalgam fillings in either CFS patients or control subjects for relieving poly-symptomatic presentation.

Assessment of Lipid Homeostasis in sudden and gradual onset chronic fatigue syndrome patients.

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A study was undertaken in 60 chronic fatigue syndrome (CFS) patients and 39 age and sex-matched non-CFS control subjects. Plasma saponified lipid products were assessed using capillary gas chromatography - mass spectrometry (GC-MS) to measure qualitative changes in plasma lipid profiles. The major lipid anomalies observed in the CFS patients were reductions in trans-9-octadecenoate (CFS 0.99% vs Controls 0.74%) and cholesterol (CFS 4.13 mmole L⁻¹ vs Controls 3.51 mmole L⁻¹).

Twenty of the CFS patients reported an acute viral-like infection at onset and were assessed for Epstein-Barr virus (EBV) and Cytomegalovirus (CMV) whereas the remaining 40 CFS patients reported a gradual onset. None of the sudden onset patients had immunological evidence of a current common viral infection. This observation was further substantiated by an absence of specific fatty acid anomalies which have been previously reported to be associated with single current acute or chronic viral infections such as by the herpes family of viruses (EBV, CMV) or retroviruses (HIV).

The subgroup of CFS patients reporting a sudden onset had a different lipid profile compared with the controls, with the trans-9-octadecenoate:octadecanoate ratio as the primary inter-group difference. Those CFS patients reporting a gradual-onset also had different lipid profiles compared with controls and the trans-9-octadecenoate:octadecanoate ratio was again the primary discriminant factor. Both sudden onset and gradual onset patients therefore had the same fatty acid anomaly differentiating them from controls.

The sudden-onset CFS group lipid profile could be differentiated from the gradual-onset group profile using the cis-9,12-octadecadienoate:cis-9-octadecanoate ratio. This ratio has been previously identified as a key post-viral (EBV) modification to lipid homeostasis.

Although the patient's viral infective history and subsequent post-viral modifications may play some role in determining the onset and progression of CFS, the primary lipid changes in CFS patients were related to other potentially non-virally-induced lipid changes. The differences in lipid homeostasis characterised for the sudden- and gradual-onset groups provides a molecular basis for the heterogeneity observed in the CFS patients which may have arisen from combinations of underlying genetic, dietary, immunological, environmental or pathogen altered responses.

Classification of chronic fatigue syndrome patients by assessing plasma lipid homeostasis

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A study was undertaken in 60 chronic fatigue syndrome (CFS) patients and 39 age and sex-matched non-CFS control subjects. Plasma saponified lipid products were assessed using capillary gas chromatography - mass spectrometry (GC-MS) to measure qualitative changes in plasma lipid profiles. Previous analyses of these data indicated that the CFS patients had significantly different plasma lipid profiles compared with the controls. This study utilised clustering techniques to determine whether patients could be classified into subgroups on the basis of similarities of lipid profile characteristics.

Five separate subgroups were characterised in this CFS study cohort, which had significantly different lipid, age and sex characteristics, but were independent of the type of onset (sudden, gradual). In contrast, 34 of the 39 control subjects (87%) had a

homogeneous set of lipid profiles which was designated the "control profile".

The characteristics assessed in the 5 CFS profiles were suggestive of anomalies in cholesterol, saturated fatty acid and n-6 fatty acid homeostasis, as well as β -oxidation of fatty acids. This study demonstrates a high degree of heterogeneity in the lipid homeostasis of patients who comply with the CFS definition. The differences in lipid homeostasis may have arisen from combinations of underlying genetic, dietary, immunological, environmental or pathogen altered responses. The lipid profiles can therefore be used to classify patients with similar lipid characteristics to give relatively homogeneous sets of patients for investigation. Individual patients could be aligned with the lipid profiles from our CFS research to assign their altered homeostasis to a particular CFS type.

These data suggest that the current CDC clinical definition of CFS falls well short of producing homogenous sets of patients and should be reviewed to include biochemical data which aligns patients with specific anomalies in cholesterol and fatty acid metabolism.

Assessment of plasma lipid homeostasis in relationship to Epstein Barr virus antibody titres in patients reporting sudden onset chronic fatigue.

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Abstract: A study was undertaken in 20 chronic fatigue syndrome (CFS) patients who reported a sudden viral-like onset and 39 age and sex-matched control subjects. Plasma saponified lipid products were assessed using capillary gas chromatography - mass spectrometry (GC-MS) to measure qualitative changes in plasma lipid profiles. Epstein Barr virus (EBV) IgM, IgG, early antigen (EBEA) and nuclear antigen (EBNA) were measured in the CFS patients.

Eighteen of the 20 sudden-CFS patients had evidence of a past EBV infection. No patients had EBV IgM, 14 (70%) had positive EBV IgG titres, 14 (70%) were EBV nuclear antigen (EBNA) positive and 5 (25%) were EBV early antigen (EBEA) positive. EBEA was associated with changes in cis-5,8,11,14-eicosatetraenoate, cholesterol, 5 α -cholest-7-en-3 β -ol and the 5 α -cholest-7-en-3 β -ol:cholesterol ratio supportive of alterations in phospholipid hydrolysis and cholesterol metabolism consistent with a cytokine response.

These cytokine associated lipid changes, as well as changes associated with EBNA and EBV IgG, were not associated with the lipid alterations differentiating CFS patients from control subjects reported previously. The lipid changes differentiating CFS patients from control subjects may be related to combinations of genetic, dietary, immunological, environmental or pathogen altered responses.

Toxic Coagulase Negative Staphylococci are Associated with Changes in Urinary Organic and Amino Acid Excretion in Chronic Facial Muscle Pain Patients.

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Abstract: CFS patients have an increased prevalence of chronic facial muscle pain. This study of 35 chronic facial muscle pain patients (MP) and 34 age and sex matched control subjects assessed carriage of staphylococcal species, symptoms and changes in urinary excretion of amino and organic acids.

The MP patients had an increase in the carriage of toxic coagulase negative species (TCoNS) ($P < 0.0004$) which produced either d-toxin ($P < 0.002$) or both d-toxin and horse-toxin ($P < 0.004$). The carriage of TCoNS was associated with increases in pain severity (VAS), irritable bowel, palpitations, muscle fatigue and recurrent low-grade fever consistent with the symptom profile of fibromyalgia. The carriage of TCoNS was inversely correlated with the reduced excretion of leucine, which is an important modulator of proteolysis. The carriage of TCoNS was positively associated with increased excretions of tyrosine and 3-methylhistidine, which were indicative of increased non-fibrillar and fibrillar proteolysis respectively. Other anomalies were also associated with the carriage of TCoNS including, increased excretions of the urea cycle intermediate, ornithine; the citric acid cycle intermediate, aconitic acid; the connective tissue amino acids, hydroxyproline and proline; and the excitatory amino acid, aspartic acid. There was an increased excretion of total amino acids suggestive of a low-grade aminoaciduria.

These data indicate that toxic coagulase negative Staphylococcus spp were strongly correlated with anomalies in proteolysis and other aspects of metabolism, and implicate that these organisms may have a major role in the aetiology of chronic muscle pain.

CPRU: NR McGregor, RH Dunstan, S Niblet, K King, HL Butt, T Harrison, W Taylor, TK Roberts, IJ Klineberg. RNS Hospital: P Clifton-Bligh, G Fulcher, J Dunsmore, L Hoskins.

Ninety-eight CFS patients and 81 age- and sex-matched controls were assessed for the changes in symptoms (clinically determined and questionnaire), SCL-90-R psychological responses, blood cell parameters, blood biochemistry and the urinary excretion of organic and amino acids in relationship to their anti-nuclear antibody (ANA) status. CFS patients were divided into ANA positive and ANA negative groups for comparison.

The fatigue responses in the ANA +ve group were more severe than those observed in the remaining CFS -ve patients. The fatigue responses were associated with alterations in red blood cell parameters, which were consistent with an increased compensated haemolysis reaction. Increasing ANA titres were associated with alterations in haemoglobin and red cell volume as well as increases in iron levels and reductions in sodium levels. No change in any immune cell parameter was found. These responses were quite different from those noted in the CFS -ve patients. The ANA patients had an increase in depression scores, which were found to be associated with alterations in red blood cell parameters and increased levels of bilirubin and the bilirubin:albumin ratio. This indicates a potential chemical neurotoxicity and not a psychological depressive state.

These data were consistent with an auto-immune-associated alteration in red cell haemolysis, which has been previously associated with the presentation of fatigue in mild hepatobiliary disorders or porphyrin disorders. These types of fatigue/pain illnesses need to be diagnosed and excluded under the current CFS definition.

Aphthous Ulceration and Symptoms In Polysymptomatic Patients.

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ABSTRACT:

The reporting of a sore throat in patients complying with the CFS definition is often associated with oral and throat recurrent aphthous ulceration (RAU). Current evidence suggests that RAU represents reactivation of viruses such as CMV, Varicella zoster, enterovirus or HSV-6, but not HSV-1.

To evaluate the incidence of RAU in chronic fatigue and chronic pain patients, 319 polysymptomatic patients consisting of 115 non-CFS and 204 CFS patients and 102 control subjects were assessed for presence of aphthous ulceration. A total of 86 out of 319 polysymptomatic patients (26.9%) had recurrent oral ulceration consistent with RAU compared with 25 out of 102 of control subjects (24.6%). These data indicate that the incidence of RAU is the same in the control subjects and the polysymptomatic patients.

A more extensive evaluation was made with the polysymptomatic patient cohort in comparison with a smaller control group (n=32) which had a more extensive array of symptom evaluations and pathology investigations. At the time of examination active RAU was noted in 2 of 32 control subjects (5.9%) compared with 17 of 115 (14.7%) non-CFS polysymptomatic patients and 69 of 204 (33.8%) CFS patients (both $P < 0.005$ compared with controls).

RAU was associated with very similar symptoms in both CFS and non-CFS patients. There were increases in the prevalence of history of spinal disk prolapse problems and appendectomy, and increases in the prevalence and/or severity of low back pain, cervical lymphodinia, palpitations, muscle cramps, problems with concentration, loss of libido as well as reduced gastric motility. Reductions in urinary frequency and the symptoms of irritable bowel were noted with alterations in both ulcer prevalence and severity.

Two potential disease models exist: 1) that CFS patients with RAU have a severe form of an RAU associated disease, such as Behcet's Syndrome; or 2) that viral reactivation is a secondary phenomenon. The RAU/symptom associations however suggest that whilst CFS patients had an equal prevalence of history of RAU they had an increased prevalence of active RAU. This suggests that increased reactivation of existing viral infections occurs in CFS patients and that the symptoms associated with these reactivated viruses not only increase the patient's symptom prevalence and severity but may confound the potential diagnosis of the underlying aetiology.

SCL-90-R Psychological Inventory Responses in Patients With Chronic Fatigue Syndrome.

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A study of 20 chronic fatigue syndrome (CFS) patients and 45 age and sex matched control subjects assessed the psychological attributes of by using the Symptom Check List-90-revised (SCL-90-R) psychological inventory.

The CFS patients had increases in the SCL-90-R somatization, obsessive compulsive, depression, anxiety and phobic anxiety dimension scores. Nineteen of 20 CFS patients had somatization T-scores 363 ($p < 0.0001$) suggestive of a somatization disorder. Multiple regression analysis indicated that somatization was the most important SCL-90-R-defined dimension discriminating CFS from control subjects. Depression and anxiety were not found to be important inter-group determinants. The dimension scores were each related to specific changes in the urinary excretion of organic and amino acids, suggesting that each dimension is biochemically distinct and has an organic basis.

Cluster analysis of dimension profiles revealed that several distinct clusters could be discerned on the basis of the SCL-90-R responses. The results of this analysis showed that the profile with increased prevalence ($P < 0.0001$) in CFS patients was associated with increased excretion of CFSUM1 ($P < 0.005$) and had increases in somatization, obsessive compulsion and depression dimension scores. CFSUM1 was the primary correlate for the somatization dimension (model $P < 0.0008$) but was not associated with any other SCL-90-R defined dimension.

Another unidentified urinary metabolite, coded UM15, was the primary correlate for depression (model $P < 0.0004$), was associated with multiple dimension elevations by both cluster and logistic regression analysis, and the excretion of this compound was unrelated to CFSUM1. These results indicated that, in this CFS cohort, the SCL-90-R defined psychological changes were strongly associated with changes in the biochemical homeostasis of patients, suggestive of an organic basis to CFS.

Chronic Facial Muscle Pain and Dysregulated Cellular Proteolysis.

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ABSTRACT: Chronic muscle pain is a common condition for which there is no known aetiology although its onset has been associated with infectious events, trauma and increasing life stresses. CFS patients have increased prevalence of facial muscle pain compared with the normal population. Muscle pain has been associated with reductions in muscle protein and RNA concentrations. Thirty-five chronic facial pain patients (MP group) and 34 age and sex-matched control subjects were assessed by GCMS for variations in urinary organic and amino acid excretion which could provide evidence of increased energy utilisation or proteolysis.

Compared with the controls, the MP patients had reductions in the excretion of leucine which is an important amino acid for the regulation of proteolysis. The MP patients also had increases in tyrosine excretion, which is a marker of proteolysis. The visual analogue pain scale of average pain intensity (VAS) was inversely correlated with the reduction in leucine excretion. The VAS score was positively correlated with the increased excretion of tyrosine, as well as the increased excretion of glutamic and aspartic acids, which are excitatory amino acids. No association was found between the VAS score and the fibrillar proteolysis marker, 3-methyl-histidine. Increasing VAS scores were associated with an increased total amino acid out-put which is consistent with the reductions in the serum amino acid levels observed in other studies and suggestive of a low grade aminoaciduria. The depletion of leucine may represent a significant anomaly in the regulation of proteolysis.

These data provide evidence to support the hypothesis that dysregulated non-fibrillar proteolysis occurs in chronic facial muscle pain patients which was associated with increasing severity of chronic pain as assessed by VAS scores.

PSYCHOLOGICAL FACTORS IN ADOLESCENTS WITH CHRONIC FATIGUE (CF)

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Chronic fatigue syndrome (CFS) continues to provoke controversy in medical and psychiatric circles, as well as in the popular press. Its aetiology remains unknown, though theories abound, and no definitive treatment is currently available. In the present study the emphasis was on investigating psychological factors in CF in adolescents. A group of adolescents with CFS or idiopathic chronic fatigue (n=30) was compared with: a psychiatric control group (adolescents being treated for anxiety, depression or psychosocial problems: n=17); two control groups of adolescents with chronic diseases (rheumatological conditions (n=22) and diabetes (n=24)); and a healthy control group (adolescents attending accident and emergency for minor acute problems: n=24). The subjects, drawn from hospital inpatient and outpatient populations, were compared on a set of self-report psychological measures. Level of fatigue, depression, and anxiety were measured and group differences were investigated. It was found that the CF group was significantly more fatigued than the control groups. Anxiety and depression were also observed to be significantly higher in the CF subjects and psychiatric group than the other controls. There were no significant differences in anxiety and depression between adolescents with CF

and those in the psychiatric control group. These results support findings in the adult literature, are consistent with (but do not establish) a role for psychological factors in the development of symptoms and thus provide some much lacking information about the psychological aspects of CF in adolescents. Although conclusions as to the causal status of psychological factors in CFS cannot be drawn from this study, it does support a cognitive-behavioural approach to the management of CFS in adolescents.

Alterations in Urinary Amino and Organic Acid Excretion in Patients with Chronic Fatigue Syndrome

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ABSTRACT

100 CDC-defined Chronic Fatigue Syndrome (CFS) patients (27 males; 73 females) and 83 healthy control patients (23 males; 60 females) were recruited for a large collaborative study designed to 1) assess alterations in metabolism and homeostasis associated with CFS 2) relate these changes to physical and neuropsychological symptom expression and changes in nose and throat microbiota and 3) evaluate the homogeneity of a CDC-defined CFS group. All subjects were clinically reviewed and asked to complete questionnaires addressing subject demographics, medical history, presentation of signs, symptoms and sensitivities, psychological status and cognitive function. Over-night fasted blood and urine samples and nose and throat swabs were collected from each subject.

Preliminary statistical analyses revealed significant differences in urinary metabolite excretion profiles in CFS patients compared with healthy controls implicating that changes in metabolism and homeostasis were associated with CFS. The urinary profiles of CFS subjects (percentage composition and excretion rate) had increases in tyrosine, 3-methylhistidine, reductions in succinic acid, asparagine, phenylalanine, and hippuric acid and changes in several compounds which are yet to be identified. Reductions in the excretion rate of alanine, valine, leucine, proline and S-methylcysteine were also associated with CFS. These data are suggestive of alterations in protein and energy metabolism and imply changes in gut bacteria.

Male and female CFS and control subjects could be separated into four groups on the basis of their urinary metabolite profiles suggesting that the profiles were distinctive. The data suggest that gender specific anomalies occur in CFS patients compared with controls. Age was also significantly correlated with changes in the multivariate urinary metabolite excretion profiles in this study. When the groups were further stratified into under 25 and over 25 year old age groups the CFS-control group differences were again distinct. These findings suggest that the pathophysiology of CFS is different in females compared with males and that these differences are themselves influenced by subject age.

It was concluded that alterations in urine metabolite excretion by CFS patients were indicative of changes in metabolism and homeostasis in CFS patients. Preliminary evaluation of the CDC-defined CFS group homogeneity found that sex and age contributed to heterogeneity in the CFS group and suggested that these factors should be considered in future studies of CFS patients. Subsequent analysis of the data from the present study will examine the relationship of CFS-related changes in urinary excretion to clinical and psychological symptom expression and to changes in the other parameters measured. CFS group heterogeneity will be further assessed using cluster analysis and multivariate techniques which will involve sub-grouping patients on the basis of changes to objectively measured parameters such as urine excretion.

HOW CFS ALTERS THE SELF AND EVERYDAY LIFE

Kent Norton and Julie Dunsmore

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Description

In this poster, self reported changes in the self and everyday life of those suffering from CFS are compared with a control group. Those with CFS were more likely than controls to report negative changes for a number of dimensions of their self and everyday life following the onset of CFS, although for some dimensions it appears that the onset of CFS may have had a positive effect. We will describe how and why changes in the self and everyday life occur following the onset of CFS and the potential impact of these changes.

Diagnosis and Treatment of Chronic Fatigue Syndrome

Dr. W. DeB O'Hare BSc.MBBS and Mrs. Chi Chi Murray1

PO Box 898 Shepparton
1. Stevenson Road, Yeppoon

In 1956 I first heard of outbreak of CFS at Royal Free Hospital, London and later in Punta Gorda, Florida. While working at Coast Hospital, Sydney in 1958 several glandular fever patients were admitted with hepatitis - all recovered quickly. In general practice at Nathalia 1960-1990, a few cases of CFS were seen - one after influenza (1968) and another after EBV infection.

From 1970 on, cases began occurring more often and were slow to recover. In 1971 first case of CFS after Ross River virus was seen. While in Central Queensland 1990-1996, more severe prolonged cases were seen.

I met Mrs Chi Chi Murray about 1991 and suggested using her method:

- 1) Gerson Therapy and vegetarian diet; and
- 2) Reliv Now compound.

Initial results were spectacular and I sent some 17 patients to her < word of mouth led to another 11 patients.

Causative Factors (Some Cases Are Combinations)

| | | | | | |
|----|--------------------------|---|-----|----------------------------|---|
| 1) | Ross River Virus | 9 | 6) | Fall Off Horse & Influenza | 1 |
| 2) | EBV Virus | 9 | 7) | Malaria | 1 |
| 3) | Influenza | 1 | 8) | Lupus & RRV | 1 |
| 4) | Hospital Staph Infection | 1 | 9) | Influenza/Lupus | 1 |
| 5) | EBV & RRV | 2 | 10) | Cancer Of Cervix | 1 |
| | | | 11) | Uncertain (Q Fever) | 1 |

Results

| | |
|--------------------------------------|----|
| A Cure - Full Recovery | 19 |
| B Partial - Normal/Lesser Activities | 8 |
| C Failure | 1 |

**"MODELS FOR CHRONIC FATIGUE SYNDROME -
CHANNELOPATHIES AND CIGUATERA"**

John Pearn

Professor of Paediatrics & Child Health and Consultant, Queensland Poisons Information Centre; and Consultant, Poisindex (International); c/- Department of Paediatrics & Child Health, Royal Children's Hospital, Brisbane Old 4029.

Chronic fatigue syndrome comprises a most significant contemporary issue in public health. Clinically, the syndrome is due to anyone of a number of known causes, and a significant proportion of unknown causes. Because of the highly subjective nature of the incapacitating symptoms, and/or models do not exist. In this context, the search for and delineation of human intoxications, with syndromes identical to those of the chronic fatigue syndrome, are important in and understanding of both the aetiology and the natural history of this group of diseases.

Chronic ciguatera is produced by one of the most potent mammalian toxins known, ciguatoxin, which affects sodium channel function at the cellular level. The dramatic nature of acute ciguatera, its devastating longterm effects in perhaps five percent of sufferers and the peculiar syndrome of lowdosage re-challenge, all suggest that the toxin permanently destroys the molecular receptors on the sodium channels to which the toxin becomes affixed. This phenomenon, in turn, has raised questions about the role of channelopathies in other diseases which cause syndromes identical to those of the chronic fatigue syndrome.

Chronic ciguatera is thus a model not only for the chronic fatigue syndrome itself but opens the way to further study of the aetiology of other (in many cases, unknown) causes of the syndrome; and ultimately may lead the way to trials of drug therapy.

**"Ciguatera - Chronic Debility
One cause of the Chronic Fatigue Syndrome"**

Professor John Pearn

Professor of Paediatrics & Child Health and Consultant, Queensland Poisons Information Centre; and Consultant, Poisindex (International); c/- Department of Paediatrics & Child Health, Royal Children's Hospital, Brisbane Old 4029.

Acute ciguatera is a foodchain poisoning which is of particular public health and clinical significance in all parts of the tropical and sub-tropical world. The acute syndrome results from eating ciguatoxic fish. Most fish species are highly prized gourmet foods. Toxic fish cannot be detected by colour, taste or smell; and at this stage all attempts to produce a rapid, sensitive, specific and practical market-place test have been to no avail. After an individual is poisoned, or a mini outbreak occurs, surviving fish samples can be tested (using mice, or cats) in biological test systems. From Queensland, the symptoms include: gastrointestinal tract symptoms (diarrhoea, vomiting, abdominal pain, etc) - 65%; loss of energy - 90%; myalgia - 83%; skin dysesthesia (reversal of thermal sensation) - 76%; arthralgia - 79%; headache - 62%; neck stiffness - 27%; skin rashes - 25%; and abnormalities of perspiration, salivation and dysuria. Some 5% of sufferers progress to chronic symptoms which may be incapacitating. A small proportion of such cases manifest symptoms which last for years, rather than months. Management consists of graded exercise set against the confidence that the symptoms will ultimately disappear completely. Depression, particularly in the face of chronic symptoms, is almost universal. The toxin effects cells at the molecular level, affixing sodium channels in an "open" configuration, thus destabilising cell metabolism in many body cells. Prevention of ciguatera consists of being aware of the risk, eating relatively small quantities of gourmet, at-risk species, and being aware of particular geographic locations where high-risk species occur. Treatment in the acute phase (within 48 hours or so of intoxication) using intravenous mannitol, produces significant reversal or, in some cases, complete relief of symptoms, in approximately 60% of cases. There is no known treatment for the subacute or chronic symptoms other than watchful expectancy. The importance of chronic ciguatera is its role as a model as a probable channelopathy for the more protean symptoms of chronic fatigue, and the identical nature of the chronic ciguatera syndrome with those of some other causes of the chronic fatigue syndrome.

FUNCTIONAL IMPAIRMENT IN A CFS GROUP MEMBERSHIP

N Posner R Madl, V. Siskind

Department of Social and Preventative Medicine, University of Queensland, Australia

The impact that the condition of Chronic Fatigue Syndrome (CFS) has on individual lives, and its implications in terms of public health and services, depends on the degree of functional impairment experienced. The SF36 health status survey was included in a questionnaire sent to the entire membership of the Queensland ME/GFS Society in 1997. Among the 530 responders, 91% had received a diagnosis of ME/CFS. This presentation reports on the SF36 scores for this sample. The means for each of the eight dimensions were found to be markedly lower than the population norms, with the differences being least for the role limitation (emotional) and the mental health dimensions. The greatest difference was in the role limitation (physical) mean scores of 12.9 (our sample) and 79.6 (1995 National Health Survey Queensland). The pattern of impairment found was in line with recently published studies among people with CFS in the USA. The results indicate a very significant degree of functional impairment in this population.

OUTCOME OF A MULTI-DISCIPLINARY REHABILITATION PROGRAMME FOR CFS USING VOCATIONAL MEASURES

Agnes Rappaport, B.A. (Hons), M. Psychology, Liam Wallington, B. Physiotherapy,
Dr. Anne-Marie Fulop, M.B. B. S., F.A.C.R. M. F. A. F. R. M. (R.A.C.P.)

Commonwealth Rehabilitation Service, Darlinghurst, Sydney

There have been numerous studies reported in the literature on the possible causes of Chronic Fatigue Syndrome, psychological/psychiatric aspects of the disorder as well as pharmacological treatments, but very few on vocational outcome following intervention. This paper presents vocational outcome on 52 CFS sufferers who completed a 10 week multi-disciplinary rehabilitation programme at CRS, Darlinghurst, Sydney. Mean duration of the illness was 7 years. The programme involved Physiotherapy, Occupational Therapy, clinical Psychology and Rehabilitation Counselling. Vocational outcome was measured in terms of employment status. The percentage unemployed/not work-ready decreased from 78.8% at the start of the programme to 44.2% and the percentage employed increased from 19.2% to 40.4%. The programme and outcome measures are discussed in more detail. It is suggested that even individuals who have had CFS for a long period can benefit from rehabilitation involving vocational goals.

PROFILE OF CHRONIC FATIGUE IN AN IMMUNOLOGY CLINIC

Glenn Reevesl, Robert Clancy2

1. Hunter Immunology Unit, Hunter Area Pathology Service, Royal Newcastle Hospital
2. Faculty of Medicine and Health Science, University of Newcastle. Introduction

In recent years, a significant proportion of referrals to clinical immunology clinics have presented with the diagnosis of "chronic fatigue syndrome", despite the fact that neither the aetiology nor the pathogenesis of this heterogeneous syndrome has an identified immunological basis. In this retrospective study of 184 consecutive subjects referred with unexplained fatigue of six or more months duration, we set out to provide a more structured framework for the assessment and management of patients with chronic fatigue.

Results

The 184 patients fell into 5 categories: CFS (59%), Organic Disease (18%), Primary Psychiatric Disorder (14%) Fibromyalgia (5%), and Primary Sleep Disorder (2%). 2% of patients were unclassified. The mean duration of symptoms for all patients and CFS patients were 57.1 and 54.4 months respectively. A history of cognitive impairment was found significantly more often in CFS and Psychiatric Disorder patients than in other groups. A history of acute symptom onset was found significantly more often in CFS and Organic Illness than in other groups. Immunoglobulins, T cell subsets and EBV serology did not differentiate between diagnostic groups.

In distinguishing between the two major groups, CFS and Organic Illness, the combination of haemoglobin SR, ANA and TSH was a powerful discriminator.

Conclusions

While there is little doubt that CFS is a real syndrome, it was clear from our study that CFS has become diagnosis often accepted uncritically by both doctor and patient, with 39% of patients referred to this Unit having an alternative diagnosis. The consequence of misdiagnosing CFS in these cases was frustration, multiple referrals, absence of a management plan and delayed diagnosis of often treatable conditions.

Immunological investigations (other than antinuclear antibody) were of no diagnostic benefit.

In conclusion, a significant proportion of patients referred to our Unit with a provisional diagnosis of CFS were found to have other underlying treatable conditions. A thorough clinical history and examination, as well as the judicious use of a limited number of investigations (FBC, ESR, ANA and TSH) is vital in approaching the patients with unexplained chronic fatigue.

ONE-CARBON METABOLISM AND CFS

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One-carbon metabolism is a chain of biochemical reactions that include the synthesis and successive transfer of methyl groups for the remethylation of homocysteine, and which is dependent on the availability of the vitamins cobalamin (B12) and folate.

Twelve outpatients, all women, who fulfilled the criteria for both chronic fatigue syndrome and fibromyalgia were rated on 15 items of the Comprehensive Psychopathological Rating Scale (CPRS-15). These items were selected to constitute a proper neurasthenic subscale. Blood laboratory levels were generally normal. The most obvious finding was that, in all the patients, the homocysteine levels were increased in the cerebrospinal fluid. There was a significant positive correlation between homocysteine levels and fatiguability, and the levels of B12 in the cerebrospinal fluid correlated significantly with the item of fatiguability and with CPRS-15. The correlations between vitamin B12 and clinical variables of the CPRS-scale in this study indicate that low B12 values in the cerebrospinal fluid are of clinical importance. As a follow up open trial, 10 of the patients accepted injective therapy with 1 mg hydroxocobalamin each week for at least three months. The treatment effect was significantly more beneficial if the patient did not carry the thermolabile allele of the polymorphic gene methylenetetrahydrofolate reductase (MTHFR).

In the investigated group of patients, we conclude that vitamin B12 deficiency is probably contributing to the increased homocysteine levels and that the effect of vitamin B12 supplementation is dependent on whether or not the available methyl groups are further deprived by the existence of thermolabile MTHFR.

ME/CFS -- the Evolution of Clinical Diagnosis, Aetiology and Treatment

John Richardson MB,BS

Newcastle Research Group, Newcastle, England

An overview of one doctor's 40 year experience of Myalgic Encephalomyelitis. In the poster are set down the epidemiological and clinical observations of this rural practitioner.

Dr Richardson has followed three generations of patients with ME and carried out four decades of research into the effects of viruses and subsequent organ pathology.

Immunological and Haematological Parameters in Patients with Chronic Fatigue Syndrome

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Abstract: Red and white cell profiles and pokeweed mitogen responses were investigated in 57 CDC-defined CFS patients and 34 age- and sex-matched control subjects. Multivariate analyses revealed that CFS patients had significantly different red and white blood cell

profiles compared with control subjects. Haematological parameters and not immunological parameters were more important in differentiating CFS patients from healthy control subjects. The red cell distribution width (RDW) was the primary differentiating regression factor. RDW was positively associated with mean platelet volume (MPV) in control subjects, but negatively correlated with MPV in CFS patients, indicating a reversal of the functional relationship between these parameters in the CFS patients.

The study subjects were then divided into males and females to perform sex based comparisons of controls and CFS patients. Female CFS patients had increases in RDW and MPV, and decreases in the numbers of T-helper cells, T-cells and lymphocytes compared with control females. These alterations were not observed in corresponding male comparisons.

Conflicting results have been reported in CFS patients for anomalies in the lymphocyte mitogen response to phytohaemagglutinin, concanavalin A, pokeweed mitogen, staphylococcal enterotoxin B and soluble antigens. In this study, there were no differences in the pokeweed mitogen (PWM) responses between the CFS and the control groups. However, in control subjects, an association was observed between pokeweed mitogen responses and Rh(D) antigen status, whereas no similar association was measured in CFS patients. Rh(D)-negative control subjects had a increased mitogen response compared with Rh(D)-positive subjects, whereas in CFS patients, no difference was found.

These data suggest that CFS is manifested in a different manner in females compared with males and provides further evidence of heterogeneity amongst the CDC-defined CFS patients. It was concluded that future blood parameter and lymphocyte mitogen response studies in CFS patients should be controlled for sex and Rh status respectively.

FOLLOW-UP OF YOUNG PEOPLE WITH CHRONIC FATIGUE SYNDROME

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Introduction

Chronic Fatigue Syndrome is a illness of more than 6 months duration of unknown aetiology characterised by excessive fatigue following minimal exercise, headaches, muscle aches and pains and difficulty concentrating. There is no known available treatment and the natural history of the illness in adolescents is also unknown. It has a significant impact on the physical, social and emotional well-being and the education of the young person.

Method

Fifty-six adolescents were involved in a program that included symptom management, graduated exercise, a weekly plan incorporating social contact, appropriate education intervention and access to a support group. Assessment of functioning and their perception of the most useful strategies was made at 6-36 months after original contact at a mean age 16.5 years (10.7-21.3) and an average 3.2 years (sd 1.5, range 1.2-6.8 years) after onset of Chronic Fatigue Syndrome.

Results

14 of the 45 replies (32%) considered that they were 'cured'. Half were attending school or work full time, and a further 14% were attending more than half time. There was a significant association between 'duration of illness' and time taken until appropriate help was received, with 25% enduring 15-48 months before diagnosis and assistance. For those whose illness had lasted more than 3 years, it was an average of 14 months before diagnosis and 18 months before they received help. This contrasted with 6 and 4 months respectively for duration less than 3 years. Seventy percent thought that their management could have been improved, with half stating that ignorance and 'arrogance' by the medical profession in not believing them contributed to their distress. There was no difference in current level of severity of illness or improvement from baseline between those whose illness had lasted greater than compared with less than 3 years, ie., there was marked variation in severity, improvement rate and duration. Alternative therapies were tried by 70% but only found to be useful for temporary symptom relief by 10%. 80% found management that provided information, strategies, support and school liaison was the 'turning point' in their illness.

Conclusion

Early recognition of the illness and implementation of a management plan is associated with patient satisfaction and shorter duration of illness irrespective of severity.

5 YEAR FOLLOW-UP OF YOUNG PEOPLE WITH CHRONIC FATIGUE SYNDROME FOLLOWING THE DOUBLE BLIND RANDOMISED CONTROLLED INTRAVENOUS GAMMAGLOBULIN TRIAL.

Rowe KS.*

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METHODS:

A five year follow of young people involved in the double blind randomised controlled trial of intravenous gammaglobulin has been conducted to determine whether the improvement following the intravenous gammaglobulin was sustained. An 78% contact and follow up was achieved on an intention to treat basis and 84% (74) of those who completed the study were traced. A questionnaire that assessed functional outcomes was used and delayed type skin hypersensitivity reaction was measured (using CMI Multitest) in those who were anergic in the initial study.

RESULTS:

The initial study demonstrated a significant difference between the baseline functional score and 6 month follow up for both groups, and between the mean functional outcomes ($t = -2.12, p < 0.04, df 68$) at 6 months. For the young people who were categorised as anergic (no response) using the CMI Multitest, or hypoergic (response less than 2-9 mm in total) there was a highly significant

difference between treatment with gammaglobulin or placebo on functional outcome, whereas there was no difference between placebo and gammaglobulin in improvement rate for those with normal cell mediated immunity as measured by the CMI Multitest. At follow up there was no deterioration in function in any young person i.e. they all remained improved or continued to improve. Sixteen per cent of those who responded were still moderately unwell with another 16% 'not back to normal yet'. The remainder were well and active. Delayed type hypersensitivity had returned to normal over the five years in those who were 'well'.

CONCLUSION:

There was no deterioration in function over the 5 years following participation in the gammaglobulin trial, and young people continued to improve although a significant number were still disabled. The significance of the abnormal delayed type hypersensitivity reaction for the response to gammaglobulin is uncertain and warrants further investigation.

NEURALLY MEDIATED HYPOTENSION AND CFS

Peter C. Rowe, MD;

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Over the past half century, chronic fatigue has been described as a prominent symptom in a variety of syndromes of orthostatic intolerance. These overlapping syndromes have been variously termed neurally mediated (or vaso-vagal) hypotension, delayed orthostatic hypotension, postural orthostatic tachycardia syndrome, and idiopathic hypovolemia. Perhaps the first suggestion that these abnormalities were responsible for symptoms of what we now call chronic fatigue syndrome (CFS) was made in 1940 by MacLean and Allen. These authors described a syndrome of excessive elevation in heart rate with upright posture seemed identical to "effort syndrome, irritable heart or neurocirculatory asthenia" (JAMA 1940;115:2162-7). They recommended treatment with up to 14 g of sodium per day and sleeping in a head-up position.

Recent work in our center and others has emphasized a high prevalence of neurally mediated hypotension (NMH), and less commonly postural orthostatic tachycardia syndrome, in those with an established diagnosis of CFS. In a 1995 study of 23 adolescents and adults with CFS, we identified hypotension in response to a three stage 70 degree upright tilt table test in 96% of patients, versus 29% of healthy controls. During the first 45 minutes of upright tilt, 16 patients (or 70%) with CFS developed hypotension, while all controls maintained a normal blood pressure. Perhaps more importantly, all 23 with CFS but none of the controls developed orthostatic symptoms during this first stage of tilt testing, suggesting that orthostatic intolerance may be a defining feature of the illness. With open treatment of the NMH, 9 of 19 (47%) reported a substantial improvement in symptoms, defined carefully as a score of 7 or more on a 10 point wellness scale, along with similar degrees of improvement in activity and cognitive function. A further 7 reported being at least somewhat better (JAMA 1995;274:961-7). To determine whether the subjective report of improvement in symptoms was associated with objective improvement in tolerance of upright tilt, 6 of the patients with an almost complete resolution of symptoms on therapy agreed to undergo repeat tilt testing. Five of 6 had normal tilt test responses while on therapy, and the sixth had a marked improvement. Three others with mild improvements in symptoms continued to have abnormal tilt tests (Pediatr Res 1995;37:33A).

These observations are being examined more systematically in a randomized trial of fludrocortisone among those with CFS and NMH. In the first 50 subjects, we identified abnormal hemodynamic responses to an abbreviated, two-stage upright tilt test in 62%; the median time to hypotension for those with NMH was 39 minutes. In response to quiet upright posture, all 50 subjects developed at least four orthostatic symptoms within the first 45 minutes, including fatigue 82%, lightheadedness 78%, non-headache pain 70%, and nausea 62%.

Similar rates of hypotension and provocation of pain in response to upright tilt have been identified in 20 subjects with fibromyalgia. Of interest, those with fibromyalgia had provocation of characteristic pain after a median of 10 minutes after assumption of upright tilt testing. (Clin Exp Rheumatol 1997;15:239-46). Other work has suggested that abnormalities in autonomic tone, as measured by heart rate variability, may be abnormal in those with CFS during upright tilt (JM Stewart, Pediatr Res 1997;41:26A) but our studies have demonstrated no differences between those with CFS and controls (Clin Autonomic Res 1997;7:293-7). This talk will discuss selected issues in the clinical overlap of chronic fatigue syndrome and orthostatic intolerance.

NEW CLINICAL INSIGHTS IN THE TREATMENT OF CFS

Peter C. Rowe, MD

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Although neurally mediated hypotension (NMH) is now recognized as the most common cause of orthostatic intolerance in those with CFS, and postural orthostatic tachycardia syndrome (POTS) is also relatively common, we do not yet have definitive data from randomized controlled trials to confirm that therapy of either disorder does more good than harm. Until such data become available, we have developed the following recommendations for those who elect to begin empiric treatment of NMH and POTS in their patients with CFS, recognizing that some of these recommendations change rapidly. Treatment of NMH and POTS is not optimal unless careful attention is directed to general medical problems including inflammatory disorders (such as food allergy, allergic rhinitis, asthma), painful conditions (such as endometriosis), as well as panic disorder and depression, as each of these conditions can exacerbate orthostatic symptoms.

Reduced blood volume, excessive orthostatic pooling of blood, and excessive levels of catecholamines are thought to be the main contributors to symptoms in NMH and other orthostatic intolerance syndromes. Treatment begins with avoidance of the conditions that (1) lead to excessive venous pooling (such as prolonged quiet sitting or standing, excessive histamine release, vasodilating medications), (2) lead to lowered blood volume (such as inadequate sodium and fluid intake, excessive environmental heat, diuretics), or (3) lead to excessive catecholamine levels (adrenergic agonist medications). To reduce venous pooling, non-pharmacologic maneuvers include compression stockings, as well as abdominal binders to reduce pooling in the splanchnic circulation, and postural

maneuvers that increase muscular activity in the legs or raise blood pressure (such as standing in a legs-crossed position, squatting, sitting in the knee-chest position or with the knees higher than the hips, bending forward, or putting a foot on a chair while standing). To increase blood volume, a simple method is to increase intake of dietary sodium chloride, accompanied by at least a 2 liter per day intake of fluids. In those whose orthostatic symptoms can be supported sufficiently to allow it, a progressive exercise program may help by increasing plasma and red blood cell volume. In those with asthma and CFS, inhaled glucocorticoids reduce reliance on the adrenergic agonists that can activate the vaso-vagal reflex.

There is no consensus about which medications are most effective for neurally mediated hypotension, and the efficacy of each remains to be established. Fludrocortisone in doses from 0.05 to 0.2 mg per day, always with supplemental potassium intake, is the most frequently used method of expanding blood volume. Vasoconstrictors such as midodrine, methylphenidate, dextroamphetamine, and pseudoephedrine may be particularly effective for those with excessive venous pooling. Drugs that reduce activation of C-fiber mechanoreceptors in the left ventricle can reduce the frequency with which the vaso-vagal reflex is activated, and among these are atenolol and pindolol (usually avoided in those with asthma), or disopyramide. In open trials, selective serotonin reuptake inhibitors (SSRI) improve both the tolerance of upright tilt and the frequency of clinical symptoms in non-depressed patients with NMH refractory to other measures. Other drugs used in the setting of orthostatic hypotension may have a role for those with NMH, including erythropoietin, but have not been studied in those with NMH and CFS. The use of several medications (a vasoconstrictor, a mineralocorticoid, a beta-blocker) concurrently may be necessary for the improvement of severe NMH.

"Nine year CFS case study-male"

Dr Lorna Scott, a Sydney general practitioner presents a case which illustrates a well-educated professional male who has been disabled by C.F.S for 9 years. Being his marital partner, she has observed the chronic remitting and relapsing course of his illness at first hand. Relapses included episodes of extreme sleep disturbance. Impaired alertness and concentration accompanied by disabling fatigue, muscle weakness and bowel disturbance.

Successful treatment strategies have included: diagnosis and treatment of bowel infections that included, giardia, yersinia in the ileum, and oral and oesophageal candida: maximising absorption of nutrients through supplements: improving digestion through the use of bitter herbs and digestive enzymes; treating chronic constipation; organising good eating and sleep patterns; and coming to terms emotionally with the chronic need to rest as a recuperative necessity. Rest has been very important also learning to resist the urge to work, exercise, achieve to maximal capacity in the "window of opportunity" when energy becomes suddenly and unpredictably available.

As a clinical psychologist, this patient witnessed and treated many depressed patients prior to his illness. He himself suffered a depressive episode. This case history contrasts the enormous difference in flavour between his experience of depression as a psychological entity, with the depressed functioning and despair that results from chronic physical debility.

NORMAL AEROBIC CAPACITY AND LACTATE THRESHOLD DURING INCREMENTAL EXERCISE IN PATIENTS WITH THE CHRONIC FATIGUE SYNDROME.

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The metabolic responses during incremental exercise to exhaustion in 5 patients with Chronic Fatigue Syndrome (CFS) were compared with 5 healthy sedentary controls matched for gender (3 female, 2 male), age (CFS, 34.80 ± 4.73; controls, 35.20 ± 4.59, yr), height (CFS, 170.40 ± 4.39; controls, 171.70 ± 5.00, cm) and mass (CFS, 72.12 ± 9.58; controls, 76.58 ± 9.80, kg). Control subjects exercised for longer (CFS, 18.80 ± 0.58; controls, 23.66 ± 1.01, min, p<0.006), reached a higher peak work load (CFS, 125.00 ± 7.91; controls, 165.00 ± 12.75, watts, p<0.04), and consequently did more work (CFS, 67.20 ± 8.78; controls, 114.45 ± 16.58, kJ, p<0.05). Peak VO₂ (VO_{2peak}) at exhaustion was not significantly different between these 2 subject groups (CFS, 28.01 ± 1.93; controls, 35.23 ± 3.54; ml·kg⁻¹·min⁻¹, NS) or from their predicted VO_{2max} determined during an earlier submaximal cycling test (CFS, 29.87 ± 1.36; controls, 33.34 ± 3.76; ml·kg⁻¹·min⁻¹; NS). VO_{2peak} was achieved at peak heart rates (HR_{peak}) which were not significantly different from each other (CFS, 177 ± 5; controls, 180 ± 6; beats·min⁻¹) or from their age-predicted maximum heart rates (HR_{max}: CFS, 185 ± 5; controls, 185 ± 5; beats·min⁻¹; NS). The lactate threshold (LT, determined from a log-log plot of absolute VO₂ versus blood lactate concentration) occurred at VO₂ levels which were not significantly different between the 2 groups whether expressed in relative (CFS, 14.53 ± 1.26 ml·kg⁻¹·min⁻¹; controls 14.16 ± 2.05 ml·kg⁻¹·min⁻¹) or percentage (CFS, 52.2 ± 3.4; controls, 41.9 ± 7.8; % VO_{2peak}) terms. Despite doing less work the blood lactate concentration (CFS, 4.54 ± 0.84; controls, 6.38 ± 0.36; mmol·l⁻¹) and VO₂ at exhaustion in patients with CFS were not different from controls. It is concluded that while the work capacity of patients with CFS is significantly less than sedentary controls, aerobic capacity and the LT are not, suggesting that factors other than so-called "deconditioning" are responsible for the earlier fatigue during exercise.

CHRONIC FATIGUE SYNDROME: A NEW ZEALAND PERSPECTIVE

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New Zealand's entry into the world wide phenomena of Chronic Fatigue Syndrome was through an epidemic in a small rural district around the town of Tapanui, West Otago during 1984. It was extensively studied and the results published in the NZMJ Poore.M, Snow.P An unexplained Illness in West Otago 1984. 97.351-354 .

In retrospect the most significant contribution of this article was the symptom profile, which now clearly mimics that of Chronic Giardiasis, a disease then not recognised in New Zealand, but considered at the time by the workers. Low laboratory yields and failed response to flagyl therapy distracted us from pursuing that line.

The combined research of the Department of Conservation, CDC, Ministry of Agriculture and Fisheries whose principal workers Tim Brown and G Ionas have indicated the widespread occurrence of Giardia cysts in all New Zealand waterways and in a wide range of domestic and feral animals.

Martin Wolfe's review on Giardiasis Clinical Microbiological Reviews Jan 1992 p 93-100 indicated the importance of the concept of Chronic Giardiasis and the difficulty in achieving a high laboratory yield. It was also indicated that treatment of clinical cases of Giardiasis despite negative results was acceptable therapeutics.

The availability of effective cysticidal agents such as Nitroimidazoles, Tinidazole and Naxogin both 96% effectivity compared to Metronidazole 40% gave us a more effective therapeutic regime.

Paul Levine's 10 yr follow up of the West Otago or Tapanui outbreak showed a near 100% recovery of this group, all who at various times through that period were treated with the Nitroimidazoles. Archives of Internal Medicine 1997;157 : 750-754 Paul Levine Peter Snow Epidemic Neuromyasthenia and Chronic Fatigue Syndrome in West Otago New Zealand. A ten year follow up M.Holmes, P.Snow as yet unpublished Three Year Study of Fatigue in General Practice confirms the high incidence of bowel disorders in those presenting with Chronic Fatigue and the very low incidence of Chronic Fatigue syndrome as per CDC protocol less than 5%.

It is argued that in the New Zealand experience, a significant cause of Chronic Fatigue is from Chronic Giardiasis, a recently recognised pathogen in New Zealand waterways. The newer Nitroimidazoles have demonstrated to be effective therapeutic agents.

CFS Children and Youth: The Human Rights Perspective

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It is time to stimulate the consciences of two professions, education and medicine, in relation to their service provision, specifically in the areas of human rights issues, to CFS children and youth. Within the Australian context a child is defined as age 0 - 18 and a youth as 15 - 25 years.

The two professions share important similarities, including a focus on best practice, an imposed political agenda and a legislative framework incorporating the duty of care.

In Australia, certain factors impede full incorporation of human rights considerations when providing education and health care. To date, both review processes and legislation neglect the human rights of children with chronic illness. It can be anticipated that this temporary barrier will be defeated by effective advocacy. There are already government and legal initiatives which will, in the long term, ensure that all children and youth, irrespective of health status, are afforded the human rights inherent in the UN Convention on the Rights of the Child.

Important Australian developments to date include a draft Australian Children's Charter (1995), initiatives by the Australian Law Reform Commission and the Human Rights and Equal Opportunity Commission and the establishment of a non-government National Children's and Youth Law Centre.

To ensure CFS children and youth their entitlements in regard to human rights, the education and medical professions need to engage in productive dialogue with the CFS community to identify a way forward. The task is to develop realistic strategies to address the disharmony and disempowerment experienced by CFS children and youth and their parents. The challenge is to identify a new value system and a new consultative culture.

THE USE OF SERINE IN THE MANAGEMENT OF CHRONIC FATIGUE SYNDROME

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Urinary serine levels were checked and found to be low in 7 patients whose illness fitted the CDC criteria for a diagnosis of Chronic Fatigue Syndrome.(1) A low serine level has previously been identified as a possible urinary marker (previously known as CFSUM2) for CFS.(2) Serine was prescribed in a dose of 500mg twice daily to these people. A metabolic screening questionnaire was administered before and after one month of use.

The results of the screening questionnaire and the outcome of the treatment will be presented.

References:

Fukuda K, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. *Annals of Int Med*, 1994, 121, 953-959

McGregor N.R, et al: Preliminary determination of a molecular basis to chronic fatigue syndrome. *Biochemical and Molecular Medicine*, 1996, 57, 73-80

GASTRO-OESOPHAGEAL REFLUX AND CHRONIC FATIGUE IN CHILDREN AND ADOLESCENTS

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Chronic fatigue syndrome (CFS) (post-viral or post-infective fatigue syndrome or myalgic encephalomyelitis) is common in adults and occurs in older children and adolescents. Abdominal pain is reported to be a common feature. Despite intensive research the aetiology remains unknown. Over 36 months we saw in total 19 children and adolescents with symptoms of CFS or idiopathic chronic fatigue. Ages at presentation ranged from 7 to 16.75 years. The male to female ratio was 8:11. The duration of the symptoms at diagnosis varied from 3 months to 4 years. 15 of the 19 patients (79%) had upper gastro-intestinal symptoms. Three of these 15 patients declined further investigations and/or were lost to follow-up. Gastro-oesophageal reflux was found in all of the remaining 12; pH probe demonstrated significant reflux over 24 hours in each. Endoscopy of the upper gastro-intestinal tract was performed in 7 and showed evidence of reflux oesophagitis in 6. In addition lactase deficiency was diagnosed in one of these patients. We treated these children with standard reflux treatment and low lactase diet for the lactase deficient child. Among the 11 with an adequate period of follow-up symptoms of chronic fatigue resolved with improvement of the reflux in 7 children (64%) and remained unchanged in four (36%).

Conclusions:

Gastro-oesophageal reflux may cause symptoms of chronic fatigue in children and adolescents and should be considered in the differential diagnosis of chronic fatigue syndrome. Night time reflux may interfere with a normal sleep pattern, causing symptoms of chronic fatigue. Alternatively, the disease process responsible for chronic fatigue may also interfere with the function of the lower oesophageal sphincter. Since abdominal pain is a recognised feature of CFS, the associated gastrointestinal disease in our patients would have been unrecognised in most cases without definitive investigations. Treatment of reflux (and lactase deficiency) was associated with resolution of chronic fatigue symptoms in more than half of the investigated children and adolescents. A controlled, prospective study appears to be warranted.

CFS - Rickettsial Infection - Case Studies

Dr. C.L. Jadin

Randburg, South Africa

Summary: Since January 1991, over 3,000 patients, previously diagnosed as ME, CFS, psychotic dysfunction, fibromyalgia, arthritic diseases, or unknown, have been treated with Antibiotic therapy. The symptoms of these patients were similar to those exhibited in chronic Rickettsial diseases. The treatment followed the finding that their serum reacted positively to the Giroud micro-agglutination test.

* Giroud Test - specific for testing antibodies to the 5 following antigens: *Rickettsia prowazeki*.; *R. mooseri*; *R. conori*; and *Coxiella burnetti*; done by micro agglutination depending on quality of antigens comparative studies with IFA test gave very similar results Positive reaction = presence of antibodies but by itself does not necessarily mean illness. Because the diagnosis of *Rickettsia* stands on 3 corner stones: Symptoms Clinical findings Biological investigations.

Results Of 500 patient records analysed:

385 patients very well or cured
101 patients stopped consultation after 1 to 3 treatments
26 patients never commenced treatment
15 patients showed no improvement

References Neo-R. Q18

Depression, Psychotic Dysfunction, Rickettsial Infection Case Study

Dr C L Jadin

Randburg
South Africa

Summary: 300 patients, diagnosed as suffering from depression, or other neuropsychiatric dysfunction have been treated with antibiotic. The reason for this treatment was as follows:

1. The symptoms of these patients were similar to those exhibited in chronic Rickettsial diseases.

2. The treatment followed the finding that their serum reacted positively to the Giroud * micro-agglutination test. * Giroud Test - specific for testing antibodies to the 5 following antigens (R36):

Rickettsia Prowazeki

R. Mooseri

R. Conori

Coxiella Burnetti

Neo-R. Q18

done by micro agglutination

depending on quality of antigens

comparitive studies with IFA test gave very similar result

Positive reaction : presence of antibodies; does not necessarily mean illness.

Negative reaction: does not suppress Rickettsial etiology (R1, R25)

Patients and Method will be displayed here

I. Main Symptoms Graphic will be shown here

II. Clinical Examination graphic here

III. Biological Investigations results here

IV. Brain Scan

V. Treatment

VI. Success rate

VII. Detailed revue of 10 cases

Draft Clinical Practice Guidelines on the evaluation of prolonged fatigue and the diagnosis and management of chronic fatigue syndrome

Convenors:

Dr Robert Loblay: Royal Australasian College of Physicians

Associate Professor Graeme Stewart: Royal Australasian College of Physicians;

Former member, Ministerial CFS Review Committee

The exposure draft is being widely circulated to medical practitioners, other health care professionals, and health consumers in order to obtain broadly representative feedback and we would welcome your input.

Your feedback can be personal, or may be consolidated via your relevant College, Special Society or Medical Association. Personal opinions can be submitted either in writing, using the enclosed questionnaire, or electronically via the "feedback button" on the Web version. The Working Group will revise the draft document in the light of comments received, and the final version will be published as a colour supplement to the MJA, and on the World Wide Web, in May, 1998.

Comments should be returned to the Project Officer, Ms Victoria Toulkidis, no later than Monday 16th February, 1998 (postal address: RACP, 145 Macquarie St., Sydney, 2000; e-mail: policy@racp.edu.au)

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