

Bibliography

1. Bell DS, Jordan K, Robinson M. Thirteen-year follow-up of children and adolescents with chronic fatigue syndrome. *Pediatrics* 2001;107:994-8.

Abstract: OBJECTIVE: To describe the educational, social, and symptomatic outcome of children and adolescents with chronic fatigue syndrome 13 years after illness onset. METHODS: Between January 1984 and December 1987, 46 children and adolescents developed an illness suggestive of chronic fatigue syndrome. Follow-up questionnaires were obtained from 35 participants an average of 13 years after illness onset. Data were obtained concerning subsequent medical diagnoses, amount of school missed, presence and severity of current symptoms, and subjective assessment of degree of illness resolution. RESULTS: Of the 35 participants, 24 were female (68.6%) and 11 were male (31.4%). Average age at illness onset was 12.1 years. Eight participants (22.9%) had an acute onset of symptoms, 27 (77.1%) had a gradual onset. No participant received an alternative medical diagnosis that could have explained the symptom complex between illness onset and follow-up. Thirteen participants (37.1%) considered themselves resolved of illness at follow-up; 15 participants (42.9%) considered themselves well but not resolved; 4 (11.4%) considered themselves chronically ill; and 3 (8.6%) considered themselves more ill than during the early years of illness. Correlation with the Medical Outcomes Study Short Form Health Survey was good for current level of symptoms and degree of recovery. Eight participants (22.9%) missed >2 years of school, and 5 of these were still ill at follow-up. Amount of school missed correlated with both illness severity at follow-up and perceived social impact of the illness. CONCLUSIONS: These data demonstrate the presence of an illness consistent with the current definition of chronic fatigue syndrome. Eighty percent of children and adolescents affected had a satisfactory outcome from their fatiguing illness, although the majority of these participants had mild to moderate persisting symptoms. Twenty percent of participants remain ill with significant symptoms and activity limitation 13 years after illness onset. Chronic fatigue syndrome in children and adolescents may result in persistent somatic symptoms and disability in a minority of those affected.

2. Bierl C, Nisenbaum R, Hoaglin DC, Randall B, Jones AB, Unger ER, Reeves WC. Regional distribution of fatiguing illnesses in the United States: a pilot study. *Popul Health Met* 2004 Feb 4;2(1):1.

Chronic fatigue syndrome (CFS) is a debilitating illness with no known cause or effective therapy. Population-based epidemiologic data on CFS prevalence are critical to put CFS in a realistic context for public health officials and others responsible for allocating resources. Methods: We conducted a pilot random-digit-dialing survey to estimate the prevalence of fatiguing illnesses in different geographic regions and in urban and rural populations of the United States. This report focuses on 884 of 7,317 respondents 18 to 69 years old. Fatigued (440) and randomly selected non-fatigued (444) respondents completed telephone questionnaires concerning fatigue, other symptoms, and medical history. Results: We estimated 12,186 per 100,000 persons 18 to 69 years of age suffered from fatigue lasting for at least 6 months (chronic fatigue), and 1,197 per 100,000 described an illness that, though lacking clinical evaluation, met criteria for CFS (CFS-like). Chronic fatigue and CFS-like illness were more common in rural than in urban populations, although the differences were not significant. The prevalence of these fatiguing illnesses did not differ meaningfully among the four regions surveyed, and no significant geographic trends were observed. Conclusions: This investigation estimated that nearly 2.2 million American adults suffer from CFS-like illness. The study also suggested the need to focus future investigations of fatigue on populations with lower incomes and less education. There was no evidence for regional differences in the occurrence of fatiguing illnesses.

3. Buchwald D, Herrell R, Ashton S, et al. A twin study of chronic fatigue. *Psychosom Med* 2001;63:936-43.

Abstract: OBJECTIVE: The etiology of chronic fatigue syndrome is unknown, but genetic influences may be important in its expression. Our objective was to assess the role of genetic and environmental factors in unexplained chronic fatigue. METHODS: A classic twin study was conducted using 146 female-female twin pairs, of whom at least one member reported greater than or equal to 6 months of fatigue. After completing questionnaires on symptoms, zygosity, physical health, and a psychiatric interview, twins were classified using three increasingly stringent definitions: 1) chronic fatigue for greater than or equal to 6 months, 2) chronic fatigue not explained by exclusionary medical conditions, and 3) idiopathic chronic fatigue not explained by medical or psychiatric exclusionary criteria of the chronic fatigue syndrome case definition. Concordance rates in monozygotic and dizygotic twins were calculated for each fatigue definition along with estimates of the relative magnitude of genetic and environmental influences on chronic fatigue. RESULTS: The concordance rate was higher in monozygotic than dizygotic twins for each definition of chronic fatigue. For idiopathic chronic fatigue, the concordance rates were 55% in monozygotic and 19% in dizygotic twins ($p = .042$). The estimated heritability in liability was 19% (95% confidence interval = 0-56) for chronic fatigue greater than or equal to 6 months, 30% (95% confidence interval = 0-81) for chronic fatigue not explained by medical conditions, and 51% (95% confidence interval = 7-96) for idiopathic chronic fatigue. CONCLUSIONS: These results provide evidence supporting the familial aggregation of fatigue and suggest that genes may play a role in the etiology of chronic fatigue syndrome.

4. Busichio K, Tiersky LA, Deluca J, Natelson BH. Neuropsychological deficits in patients with chronic fatigue syndrome. *J Int Neuropsychol Soc* 2004 Mar;10(2):278-85.

[Chronic Fatigue Syndrome Center, Newark, New Jersey 07666, USA.]

The degree of neuropsychological dysfunction across multiple domains was examined in individuals suffering from chronic fatigue syndrome (CFS). In this descriptive study, a similar series of neuropsychological tests was administered to a group of CFS patients and healthy participants. More specifically, CFS patients ($n = 141$) who met the 1994 Case Definition criteria were compared to 76 healthy control participants on tests of memory, attention (concentration), speed of information processing, motor speed, and executive functioning. On the 18 measures administered, CFS patients scored 1 standard deviation below the healthy mean on nine measures and scored 2 standard deviations below the healthy mean on four of the measures. Moreover, results indicated that CFS patients were more likely than healthy controls to fail (1.6 SD below the healthy mean) at least one test in each of the following domains: attention, speed of information processing, and motor speed, but not on measures of memory and executive functioning. Finally, CFS patients demonstrated a greater total number of tests failed across domains.

5. Chaudhuri A, Condon BR, Gow JW, Brennan D, Hadley DM. Proton magnetic resonance spectroscopy of basal ganglia in chronic fatigue syndrome. *Neuroreport* 2003 Feb 10;14(2):225-8.

[Department of Neurology, University of Glasgow, South Glasgow University Hospitals NHS Trust, UK. ac54p@udcf.gla.ac.uk]

Fatigue is a common symptom of neurological diseases that affect basal ganglia function. We used proton magnetic resonance spectroscopy ($(^1\text{H})\text{MRS}$) to study the metabolic functions of the basal ganglia in chronic fatigue syndrome (CFS) to test the hypothesis that fatigue in CFS may have a neurogenic component. $(^1\text{H})\text{MRS}$ of left basal ganglia was carried out in eight non-psychiatric patients with CFS and their results were compared to age- and sex-matched healthy asymptomatic healthy controls. A highly significant increase in the spectra from choline-containing compounds was seen in the CFS patient group ($p < 0.001$). In the absence of regional

structural or inflammatory pathology, increased choline resonance in CFS may be an indicator of higher cell membrane turnover due to gliosis or altered intramembrane signalling.

6. Cleare AJ. The neuroendocrinology of chronic fatigue syndrome. *Endocr Rev* 2003 Apr;24(2):236-52.

[Section of Neurobiology of Mood Disorders, Division of Psychological Medicine, The Institute of Psychiatry, London SE5 8AZ, UK. a.cleare@iop.kcl.ac.uk]

Chronic fatigue syndrome (CFS) is a common and disabling problem; although most likely of biopsychosocial origin, the nature of the pathophysiological components remains unclear. There has been a wealth of interest in the endocrinology of this condition, which will be reviewed in this article. Most studied has been the hypothalamic-pituitary-adrenal (HPA) axis; although the quality of many studies is poor, the overall balance of evidence points to reduced cortisol output in at least some patients, with some evidence that this is linked to symptom production or persistence. There is evidence for heightened negative feedback and glucocorticoid receptor function and for impaired ACTH and cortisol responses to a variety of challenges. However, there is no evidence for a specific or uniform dysfunction of the HPA axis. Given the many factors that may impinge on the HPA axis in CFS, such as inactivity, sleep disturbance, psychiatric comorbidity, medication, and ongoing stress, it seems likely that HPA axis disturbance is heterogeneous and of multifactorial etiology in CFS. Studies assessing GH, dehydroepiandrosterone and its sulfate, melatonin, leptin, and neuroendocrine-monoamine interactions are also reviewed. There is some evidence from these studies to suggest alterations of dehydroepiandrosterone sulfate function and abnormal serotonin function in CFS, but whether these changes are of functional importance remains unclear. To obtain a clearer assessment of the etiological and pathophysiological relevance of endocrine changes in CFS, it is suggested that more prospective cohort studies be undertaken in groups at high risk for CFS, that patients with CFS are followed up into recovery, and that multidimensional assessments are undertaken to unravel the influence of the various confounding factors on the observed endocrine changes in CFS.

7. Daly E, Komaroff AL, Bloomingdale K, Wilson S, Albert MS. Neuropsychological function in patients with chronic fatigue syndrome, multiple sclerosis, and depression. *Appl Neuropsychol* 2001;8:12-22.

Abstract: Patients with chronic fatigue syndrome (CFS), multiple sclerosis (MS), and major depression were compared with controls and with each other on a neuropsychological battery that included standard neuropsychological tests and a computerized set of tasks that spanned the same areas of ability. A total of 101 participants were examined, including 29 participants with CFS, 24 with MS, 23 with major depressive disorder, and 25 healthy controls. There were significant differences among the groups in 3 out of 5 cognitive domains: memory, language, and spatial ability. Assessment of psychiatric symptoms indicated that all 3 patient groups had a higher prevalence of depression than the controls. A total measure of psychiatric symptomatology also differentiated the patients from the controls. After covarying the cognitive test scores by a measure of depression, the patient groups continued to differ from controls primarily in the area of memory. The findings support the view that the cognitive deficits found in CFS cannot be attributed solely to the presence of depressive symptomatology in the patients.

8. Deale A, Husain K, Chalder T, Wessely S. Long-term outcome of cognitive behavior therapy versus relaxation therapy for chronic fatigue syndrome: a 5-year follow-up study. *Am J Psychiatry* 2001 Dec;158(12):2038-42.

[Academic Department of Psychological Medicine, Guy's, King's, and St. Thomas's School of Medicine, London, UK. a.deale@iop.kcl.ac.uk]

OBJECTIVE: This study evaluated the long-term outcome of cognitive behavior therapy versus relaxation therapy for patients with chronic fatigue syndrome. METHOD: Sixty patients who

participated in a randomized controlled trial of cognitive behavior therapy versus relaxation therapy for chronic fatigue syndrome were invited to complete self-rated measures and participate in a 5-year follow-up interview with an assessor who was blind to treatment type. RESULTS: Fifty-three patients (88%) participated in the follow-up study: 25 received cognitive behavior therapy and 28 received relaxation therapy. A total of 68% of the patients who received cognitive behavior therapy and 36% who received relaxation therapy rated themselves as "much improved" or "very much improved" at the 5-year follow-up. Significantly more patients receiving cognitive behavior therapy, in relation to those in relaxation therapy, met criteria for complete recovery, were free of relapse, and experienced symptoms that had steadily improved or were consistently mild or absent since treatment ended. Similar proportions were employed, but patients in the cognitive behavior therapy group worked significantly more mean hours per week. Few patients crossed the threshold for "normal" fatigue, despite achieving a good outcome on other measures. Cognitive behavior therapy was positively evaluated and was still used by over 80% of the patients. CONCLUSIONS: Cognitive behavior therapy for chronic fatigue syndrome can produce some lasting benefits but is not a cure. Once therapy ends, some patients have difficulty making further improvements. In the future, attention should be directed toward ensuring that gains are maintained and extended after regular treatment ends.

9. DeLange FP, Kalkman JS, Bleijenberg G, Hagoort P, van der Werf SP, van der Meer JW, Toni I. Neural correlates of the chronic fatigue syndrome--an fMRI study. *Brain* 2004 Sep;127(Pt 9):1948-57. [Epub 2004 Jul 07]

[F.C. Donders Centre for Cognitive Neuroimaging, University of Nijmegen, NL-6500 HB Nijmegen, The Netherlands E-mail: floris.delange@fcdonders.kun.nl]

Chronic fatigue syndrome (CFS) is characterized by a debilitating fatigue of unknown aetiology. Patients who suffer from CFS report a variety of physical complaints as well as neuropsychological complaints. Therefore, it is conceivable that the CNS plays a role in the pathophysiology of CFS. The purpose of this study was to investigate neural correlates of CFS, and specifically whether there exists a linkage between disturbances in the motor system and CFS. We measured behavioural performance and cerebral activity using rapid event-related functional MRI in 16 CFS patients and 16 matched healthy controls while they were engaged in a motor imagery task and a control visual imagery task. CFS patients were considerably slower on performance of both tasks, but the increase in reaction time with increasing task load was similar between the groups. Both groups used largely overlapping neural resources. However, during the motor imagery task, CFS patients evoked stronger responses in visually related structures. Furthermore, there was a marked between-groups difference during erroneous performance. In both groups, dorsal anterior cingulate cortex was specifically activated during error trials. Conversely, ventral anterior cingulate cortex was active when healthy controls made an error, but remained inactive when CFS patients made an error. Our results support the notion that CFS may be associated with dysfunctional motor planning. Furthermore, the between-groups differences observed during erroneous performance point to motivational disturbances as a crucial component of CFS.

10. DeMeirleir K, Bisbal C, Campine I, et al. A 37 kDa 2-5A binding protein as a potential biochemical marker for chronic fatigue syndrome. *Am J Med* 2000;108:99-105.

Abstract: PURPOSE: Recent studies have revealed abnormalities in the ribonuclease L pathway in peripheral blood mononuclear cells of patients with the chronic fatigue syndrome. We conducted a blinded study to detect possible differences in the distribution of 2-5A binding proteins in the cells of patients with chronic fatigue syndrome and controls. PATIENTS AND METHODS: We studied 57 patients with chronic fatigue syndrome and 53 control subjects (28 healthy subjects and 25 patients with depression or fibromyalgia). A radioactive probe was used to label 2-5A binding proteins in unfractionated peripheral blood mononuclear cell extracts and to compare their distribution in the three groups. RESULTS: A 37 kDa 2-5A binding polypeptide was found in 50 (88%) of the 57 patients with chronic fatigue syndrome compared with 15 (28%) of

the 53 controls ($P < 0.01$). When present, the amount of 37 kDa protein was very low in the control groups. When expressed as the ratio of the 37 kDa protein to the 80 kDa protein, 41 (72%) of the 57 patients with chronic fatigue syndrome had a ratio > 0.05 , compared with 3 (11%) of the 28 healthy subjects and none of the patients with fibromyalgia or depression. CONCLUSION: The presence of a 37 kDa 2-5A binding protein in extracts of peripheral blood mononuclear cells may distinguish patients with chronic fatigue syndrome from healthy subjects and those suffering from other diseases.

11. DiVasta AD, Alexander ME. Fainting freshmen and sinking sophomores: cardiovascular issues of the adolescent. *Curr Opin Pediatr* 2004 Aug;16(4):350-6.

[Division of Adolescent and Young Adult Medicine, Department of Cardiology, Children's Hospital Boston, Harvard Medical School, Boston, Massachusetts 02115, USA.
amy.divasta@childrens.harvard.edu]

PURPOSE OF REVIEW: Syncope is a common symptom in adolescents. The vast majority of cases are the result of benign neurocardiogenic syncope, without associated risk of sudden death. This paper reviews the mainstays of diagnosis and treatment for syncopal episodes, differentiation of syncope from life-threatening arrhythmia and aborted sudden cardiac death, and the patient populations at highest risk for cardiac symptoms and cardiac disease. RECENT FINDINGS: A detailed history (including past medical history and family history that focus on cardiac disease) combined with dynamic physical examination and electrocardiogram identifies the vast majority of adolescents with significant heart disease. Further diagnostic modalities have limited utility. Reassurance and supportive measures remain the treatment of choice, although drug therapy can sometimes be helpful, even if data are limited. Divergent approaches to the screening of the young competitive athlete exist. Particular attention is required in adolescents and young adults with exercise-associated syncope, eating disorders, chronic fatigue syndrome, or history of congenital heart disease. Their symptoms may be either more serious or challenging to manage. SUMMARY: Syncope in the adolescent patient is very common; true cardiac disease is not. The traditional diagnostic screen of history and physical combined with an electrocardiogram will identify the overwhelming majority of patients with significant disease. Patients with abnormalities on this initial office evaluation, history of cardiac disease, or complicating medical illness may benefit from referral to a cardiologist. Even within this patient subset, many will prove to have benign disease.

12. Fulle S, Belia S, Vecchiet J, Morabito C, Vecchiet L, Fano G. Modification of the functional capacity of sarcoplasmic reticulum membranes in patients suffering from chronic fatigue syndrome. *Neuromuscul Disord* 2003 Aug;13(6):79-84.

[Laboratorio Interuniversitario di Miologia, Universita 'G. d'Annunzio', Nuovo Polo Didattico, Via dei Vestini, 31, 66013 Scalo, Chieti, Italy]

In chronic fatigue syndrome, several reported alterations may be related to specific oxidative modifications in muscle. Since sarcoplasmic reticulum membranes are the basic structures involved in excitation-contraction coupling and the thiol groups of $\text{Ca}(2+)$ channels of SR terminal cisternae are specific targets for reactive oxygen species, it is possible that excitation-contraction coupling is involved in this pathology. We investigated the possibility that abnormalities in this compartment are involved in the pathogenesis of chronic fatigue syndrome and consequently responsible for characteristic fatigue. The data presented here support this hypothesis and indicate that the sarcolemmal conduction system and some aspects of $\text{Ca}(2+)$ transport are negatively influenced in chronic fatigue syndrome. In fact, both deregulation of pump activities ($\text{Na}(+)/\text{K}(+)$ and $\text{Ca}(2+)$ -ATPase) and alteration in the opening status of ryanodine channels may result from increased membrane fluidity involving sarcoplasmic reticulum membranes.

13. Georgiades E, Behan WM, Kilduff LP, Hadjicharalambous M, Mackie EE, Wilson J, Ward SA, Pitsiladis YP. Chronic fatigue syndrome: new evidence for a central fatigue disorder. *Clin Sci (Lond)* 2003 Aug;105(2):213-8.

[Centre for Exercise Science and Medicine, Institute of Biomedical & Life Sciences, University of Glasgow, Glasgow G12 8QQ, Scotland, UK.]

Considerable evidence points towards a prominent role for central nervous system (CNS) mechanisms in the pathogenesis of chronic fatigue syndrome (CFS), a disorder characterized chiefly by persistent, often debilitating, fatigue. We wished to characterize circulating profiles of putative amino acid modulators of CNS 5-hydroxytryptamine (5-HT; serotonergic) and dopaminergic function in CFS patients at rest, as well as during symptom-limited exercise and subsequent recovery. Groups of 12 CFS patients and 11 age- and sex-matched sedentary controls, with similar physical activity histories, underwent ramp-incremental exercise to the limit of tolerance. Plasma amino acid concentrations, oxygen uptake and ratings of perceived exertion were measured at rest, and during exercise and recovery. Peak oxygen uptake was significantly lower in the CFS patients compared with controls. Rating of perceived exertion in the patients was higher at all time points measured, including at rest, relative to controls. Levels of free tryptophan (free Trp), the rate-limiting 5-HT precursor, were significantly higher in CFS patients at exhaustion and during recovery, whereas concentrations of branched-chain amino acids (BCAA) and large neutral amino acids (LNAA) were lower in CFS patients at exhaustion, and for LNAA also during recovery. Consequently, the [free Trp]/[BCAA] and [free Trp]/[LNAA] ratios were significantly higher in CFS patients, except at rest. On the other hand, levels of tyrosine, the rate-limiting dopaminergic precursor, were significantly lower at all time points in the CFS patients. The significant differences observed in a number of key putative CNS 5-HT and dopaminergic modulators, coupled with the exacerbated perception of effort, provide further evidence for a potentially significant role for CNS mechanisms in the pathogenesis of CFS.

14. Hanson SJ, Gause W, Natelson B. Detection of immunologically significant factors for chronic fatigue syndrome using neural-network classifiers. *Clin Diagn Lab Immunol* 2001;8:658-62.

Abstract: Neural-network classifiers were used to detect immunological differences in groups of chronic fatigue syndrome (CFS) patients that heretofore had not shown significant differences from controls. In the past linear methods were unable to detect differences between CFS groups and non-CFS control groups in the nonveteran population. An examination of the cluster structure for 29 immunological factors revealed a complex, nonlinear decision surface. Multilayer neural networks showed an over 16% improvement in an n-fold resampling generalization test on unseen data. A sensitivity analysis of the network found differences between groups that are consistent with the hypothesis that CFS symptoms are a consequence of immune system dysregulation. Corresponding decreases in the CD19(+) B-cell compartment and the CD34(+) hematopoietic progenitor subpopulation were also detected by the neural network, consistent with the T-cell expansion. Of significant interest was the fact that, of all the cytokines evaluated, the only one to be in the final model was interleukin-4 (IL-4). Seeing an increase in IL-4 suggests a shift to a type 2 cytokine pattern. Such a shift has been hypothesized, but until now convincing evidence to support that hypothesis has been lacking.

15. Jason LA, Richman JA, Rademaker AW, Jordan KM, Plioplys AV, Taylor RR, McCready W, Huang CF, Plioplys S. A community-based study of chronic fatigue syndrome. *Arch Intern Med* 1999 Oct 11;159(18):2129-37.

[Department of Psychology, DePaul University, Chicago, IL 60614, USA.
ljason@wppost.depaul.edu]

BACKGROUND: Most previous estimates of the prevalence of chronic fatigue syndrome (CFS) have derived largely from treated populations, and have been biased by differential access to health care treatment linked with sex, ethnic identification, and socioeconomic status.

OBJECTIVE: To assess the point prevalence of CFS in an ethnically diverse random community sample. **DESIGN AND PARTICIPANTS:** A sample of 28,673 adults in Chicago, Ill, was screened by telephone, and those with CFS-like symptoms were medically evaluated. **MAIN OUTCOME MEASURES AND ANALYSES:** Self-report questionnaires, psychiatric evaluations, and complete medical examinations with laboratory testing were used to diagnose patients with CFS. Univariate and multivariate statistical techniques were used to delineate the overall rate of CFS in this population, and its relative prevalence was subcategorized by sex, ethnic identification, age, and socioeconomic status. **RESULTS:** There was a 65.1% completion rate for the telephone interviews during the first phase of the study. Findings indicated that CFS occurs in about 0.42% (95% confidence interval, 0.29%-0.56%) of this random community-based sample. The highest levels of CFS were consistently found among women, minority groups, and persons with lower levels of education and occupational status. **CONCLUSIONS:** Chronic fatigue syndrome is a common chronic health condition, especially for women, occurring across ethnic groups. Earlier findings suggesting that CFS is a syndrome primarily affecting white, middle-class patients were not supported by our findings.

16. Jones JF, Nisenbaum R, Solomon L, Reyes M, Reeves WC. Chronic fatigue syndrome and other fatiguing illnesses in adolescents: a population-based study. *J Adolesc Health* 2004 Jul;35(1):34-40.

[National Jewish Medical and Research Center, Denver, Colorado, USA.]

PURPOSE: To estimate the prevalence of chronic fatigue syndrome (CFS) and describe characteristics of other fatiguing illnesses in adolescents (aged 12 through 17 years). **METHODS:** We conducted a random digit dialing survey of the residents of Wichita, Kansas. Adults identified fatigued adolescents in the household and answered questions relating to the child's health. Selected adolescents were invited to attend a clinic with a parent/guardian. After clinical evaluation they were classified as CFS or another fatigue state as defined in the 1994 CFS definition. Annual telephone interviews and clinical evaluations monitored subjects' fatigue status. Data were analyzed using the Kruskal-Wallis test, the Mantel-Haenszel test, and the exact McNemar test. **RESULTS:** The survey contacted 34,018 households with 90,316 residents. Of 8586 adolescents, 138 had fatigue for > or =1 month and most (107 or 78%) had chronic fatigue (> or =6 months) at some point during the 3-year follow-up. Twenty-eight had exclusionary diagnoses. Thirty-one were considered to have a CFS-like illness and were invited for clinical evaluation. Eleven agreed to participate and none met the CFS case definition. The baseline weighted prevalence of CFS-like illness was 338 per 100,000. Significant differences existed between parental and adolescents' descriptions of illness. **CONCLUSIONS:** The prevalence of CFS among adolescents was considerably lower than among adults. Evaluation of CFS in adolescents must consider both parent and patient perception of fatigue and other illnesses that might explain the symptom complex.

17. Kennedy G, Spence V, Underwood C, Belch JJ. Increased neutrophil apoptosis in chronic fatigue syndrome. *J Clin Pathol* 2004 Aug;57(8):891-3.

[Vascular Diseases Research Unit, University Department of Medicine, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK. g.kirk@dundee.ac.uk]

BACKGROUND/AIMS: Many patients with chronic fatigue syndrome (CFS) have symptoms that are consistent with an underlying viral or toxic illness. Because increased neutrophil apoptosis occurs in patients with infection, this study examined whether this phenomenon also occurs in patients with CFS. **METHODS:** Apoptosis was assessed in patients with CFS in conjunction with concentrations of the anti-inflammatory cytokine, transforming growth factor beta1 (TGFbeta1). **RESULTS:** The 47 patients with CFS had higher numbers of apoptotic neutrophils, lower numbers of viable neutrophils, increased annexin V binding, and increased expression of the death receptor, tumour necrosis factor receptor-I, on their neutrophils than did the 34 healthy controls. Patients with CFS also had raised concentrations of active TGFbeta1 ($p < 0.005$).

CONCLUSIONS: These findings provide new evidence that patients with CFS have an underlying detectable abnormality in their immune cells.

18. Naschitz JE, Rosner I, Rozenbaum M, Naschitz S, Musafia-Priselac R, Shaviv N, Fields M, Isseroff H, Zuckerman E, Yeshurun D, Sabo E. The head-up tilt test with haemodynamic instability score in diagnosing chronic fatigue syndrome. *QJM* 2003 Feb;96(2):133-42.

[Department of Internal Medicine A, Bnai Zion Medical Center, Haifa, Israel.
Naschitz@tx.technion.ac.il]

BACKGROUND: Studying patients with chronic fatigue syndrome (CFS), we have developed a method that uses a head-up tilt test (HUTT) to estimate BP and HR instability during tilt, expressed as a 'haemodynamic instability score' (HIS). Aim: To assess HIS sensitivity and specificity in the diagnosis of CFS. DESIGN: Prospective controlled study. METHODS: Patients with CFS (n=40), non-CFS chronic fatigue (n=73), fibromyalgia (n=41), neurally mediated syncope (n=58), generalized anxiety disorder (n=28), familial Mediterranean fever (n=50), arterial hypertension (n=28), and healthy subjects (n=59) were evaluated with a standardized head-up tilt test (HUTT). The HIS was calculated from blood pressure (BP) and heart rate (HR) changes during the HUTT. RESULTS: The tilt was prematurely terminated in 22% of CFS patients when postural symptoms occurred and the HIS could not be calculated. In the remainder, the median(IQR) HIS values were: CFS +2.14(4.67), non-CFS fatigue -3.98(5.35), fibromyalgia -2.81(2.62), syncope -3.7(4.36), generalized anxiety disorder -0.21(6.05), healthy controls -2.66(3.14), FMF -5.09(6.41), hypertensives -5.35(2.74) ($p < 0.0001$ vs. CFS in all groups, except for anxiety disorder, $p = NS$). The sensitivity for CFS at HIS > -0.98 cut-off was 90.3% and the overall specificity was 84.5%. DISCUSSION: There is a particular dysautonomia in CFS that differs from dysautonomia in other disorders, characterized by HIS > -0.98 . The HIS can reinforce the clinician's diagnosis by providing objective criteria for the assessment of CFS, which until now, could only be subjectively inferred.

19. Natelson BH. Chronic fatigue syndrome. *JAMA* 2001;285:2557-9.

Abstract: Chronic fatigue syndrome (CFS), like fibromyalgia and multiple chemical sensitivity, comprises a number of poorly understood signs and symptoms, and whether a patient receives the diagnosis for one or another of these symptom clusters may depend on the specialty of the physician making the diagnosis. Patients with CFS also often fulfill case definitions for these other illnesses. This overlap suggests that these "functional somatic illnesses" may be variants of one another. However, this does not necessarily mean that these syndromes share the same pathobiological processes or causes. For example, patients with fibromyalgia have been found to have elevated levels of substance P in spinal fluid and reduced pain thresholds, while patients with CFS have not. Similarly, the fatigue reported by patients with fibromyalgia may be secondary to chronic sleep disruption because of pain, while fatigue may be primary in CFS.

The case definitions for CFS reflect the observation that the severe fatigue and influenza-like symptoms, which often begin suddenly, were initially thought to represent an underlying viral infection. Thus, the diagnosis requires at least 6 months of new-onset symptoms of fatigue accompanied by infectious, rheumatological, and neuropsychiatric symptoms, and which cannot be explained by other medical diagnoses. In the United States, CFS has a prevalence of 0.52% in women and 0.29% in men. Patients with CFS may experience severe disability; one study reported that patients with CFS have lower self-reported functional status than a group of similar patients with congestive heart failure. In this article, I review the evidence for several proposed hypotheses about the etiology of CFS.

20. Papanicolaou DA, Amsterdam JD, Levine S, McCann SM, Moore RC, Newbrand CH, Allen G, Nisenbaum R, Pfaff DW, Tsokos GC, Vgontzas AN, Kales A. Neuroendocrine aspects of Chronic Fatigue Syndrome. *Neuroimmunomodulation* 2004 Feb;11(2):65-74.

[Department of Medicine/Endocrinology, Emory University, Atlanta, GA, USA.]

Chronic fatigue syndrome (CFS) is a serious health concern affecting over 800,000 Americans of all ages, races, socioeconomic groups and genders. The etiology and pathophysiology of CFS are unknown, yet studies have suggested an involvement of the neuroendocrine system. A symposium was organized in March 2001 to explore the possibility of an association between neuroendocrine dysfunction and CFS, with special emphasis on the interactions between neuroendocrine dysfunction and other abnormalities noted in the immune and autonomic nervous systems of individuals with CFS. This paper represents the consensus of the panel of experts who participated in this meeting.

21. Patarca-Montero R, Antoni M, Fletcher MA, Klimas NG. Cytokine and other immunologic markers in chronic fatigue syndrome and their relation to neuropsychological factors. *Appl Neuropsychol* 2001;8:51-64.

Abstract: The literature is reviewed and data are presented that relate to a model we have developed to account for the perpetuation of the perplexing disorder currently termed chronic fatigue syndrome (CFS). In patients with CFS there is chronic lymphocyte overactivation with cytokine abnormalities that include perturbations in plasma levels of proinflammatory cytokines and decrease in the ratio of Type 1 to Type 2 cytokines produced by lymphocytes in vitro following mitogen stimulation. The initiation of the syndrome is frequently sudden and often follows an acute viral illness. Our model for the subsequent chronicity of this disorder holds that the interaction of psychological factors (distress associated with either CFS-related symptoms or other stressful life events) and the immunologic dysfunction contribute to (a) CFS-related physical symptoms (e.g., perception of fatigue and cognitive difficulties, fever, muscle and joint pain) and increases in illness burden and (b) impaired immune surveillance associated with cytotoxic lymphocytes with resulting activation of latent herpes viruses.

22. Peckerman A, LaManca JJ, Dahl KA, Chemitiganti R, Qureishi B, Natelson BH. Abnormal impedance cardiography predicts symptom severity in chronic fatigue syndrome. *Am J Med Sci* 2003 Aug;326(2):55-60.

[Department of Neurosciences, CFS Cooperative Research Center, University of Medicine and Dentistry of New Jersey, Newark, NJ, USA. apeckerm@njneuromed.org]

BACKGROUND: Findings indicative of a problem with circulation have been reported in patients with chronic fatigue syndrome (CFS). We examined this possibility by measuring the patient's cardiac output and assessing its relation to presenting symptoms. METHODS: Impedance cardiography and symptom data were collected from 38 patients with CFS grouped into cases with severe (n = 18) and less severe (n = 20) illness and compared with those from 27 matched, sedentary control subjects. RESULTS: The patients with severe CFS had significantly lower stroke volume and cardiac output than the controls and less ill patients. Postexertional fatigue and flu-like symptoms of infection differentiated the patients with severe CFS from those with less severe CFS (88.5% concordance) and were predictive ($R^2 = 0.46$, $P < 0.0002$) of lower cardiac output. In contrast, neuropsychiatric symptoms showed no specific association with cardiac output. CONCLUSIONS: These results provide a preliminary indication of reduced circulation in patients with severe CFS. Further research is needed to confirm this finding and to define its clinical implications and pathogenetic mechanisms.

23. Razumovsky AY, DeBusk K, Calkins H, Snader S, Lucas KE, Vyas P, Hanley DF, Rowe PC. Cerebral and systemic hemodynamics changes during upright tilt in chronic fatigue syndrome. *J Neuroimaging* 2003 Jan;13(1):57-67.

[Departments of Anesthesiology/Critical Care Medicine, Neurology, Johns Hopkins Medical Institutions, Baltimore, Maryland, USA. arazumov@surgicalmonitoring.net]

BACKGROUND AND PURPOSE: During head-up tilt (HUT), patients with chronic fatigue syndrome (CFS) have higher rates of neurally mediated hypotension (NMH) and postural tachycardia syndrome (POTS) than healthy controls. The authors studied whether patients with CFS were also more likely to have abnormal cerebral blood flow velocity (CBFV) compared with controls in response to orthostatic stress. **METHODS:** Transcranial Doppler monitoring of middle cerebral artery (MCA) CBFV was performed during 3-stage HUT prospectively in 26 patients with CFS and 23 healthy controls. At the same time, continuous monitoring of arterial blood pressure (BP), heart rate (HR), endtidal CO₂ (ET-CO₂) were performed. Results are reported as mean +/- SD. **RESULTS:** NMH developed in 21 patients with CFS and in 14 controls (P = .22). POTS was present in 9 CFS patients and 7 controls (P = .76). Supine HR was higher in CFS patients, but all other hemodynamics and CBFV measures were similar at baseline. The median time to hypotension did not differ, but the median time to onset of orthostatic symptoms was shorter in those with CFS (P < .001). The CBFV did not differ between groups in the supine posture, at 1 or 5 minutes after upright tilt, at 5 or 1 minute before the end of the test, or at termination of the test. Mean CBFV fell at termination of tilt testing in those with CFS and controls. ET-CO₂ was lower at termination of the test in those with CFS versus controls (P = .002). **CONCLUSIONS:** The results of this study are not consistent with the hypothesis that patients with CFS have a distinctive pattern of MCA CBFV changes in response to orthostatic stress.

24. Reyes M, Nisenbaum R, Hoaglin DC, Unger ER, Emmons C, Randall B, Stewart JA, Abbey S, Jones JF, Gantz N, Minden S, Reeves WC. Prevalence and incidence of chronic fatigue syndrome in Wichita, Kansas. *Arch Intern Med* 2003 Jul 14;163:1530-36.

[Division of Viral and Rickettsial Diseases, National Center for Infectious Diseases, Centers for Disease Control and Prevention, Public Health Service, US Department of Health and Human Services, Atlanta, GA 30333, USA.]

BACKGROUND: Chronic fatigue syndrome (CFS) is a debilitating illness with no known cause or effective therapy. Population-based epidemiologic data on CFS prevalence and incidence are critical to put CFS in a realistic context for public health officials and others responsible for allocating resources and for practicing physicians when examining and caring for patients. **METHODS:** We conducted a random digit-dialing survey and clinical examination to estimate the prevalence of CFS in the general population of Wichita, Kan, and a 1-year follow-up telephone interview and clinical examination to estimate the incidence of CFS. The survey included 33,997 households representing 90,316 residents. This report focuses on 7162 respondents aged 18 to 69 years. Fatigued (n = 3528) and randomly selected nonfatigued (n = 3634) respondents completed telephone questionnaires concerning fatigue, other symptoms, and medical history. The clinical examination included the Diagnostic Interview Schedule for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, laboratory testing, and a physical examination. **RESULTS:** The overall weighted point prevalence of CFS, adjusted for nonresponse, was 235 per 100,000 persons (95% confidence interval, 142-327 per 100,000 persons). The prevalence of CFS was higher among women, 373 per 100,000 persons (95% confidence interval, 210-536 per 100,000 persons), than among men, 83 per 100,000 persons (95% confidence interval, 15-150 per 100,000 persons). Among subjects nonfatigued and fatigued for less than 6 months, the 1-year incidence of CFS was 180 per 100,000 persons (95% confidence interval, 0-466 per 100,000 persons). **CONCLUSIONS:** Chronic fatigue syndrome constitutes a major public health problem. Longitudinal follow-up of this cohort will be used to further evaluate the natural history of this illness.

25. Reynolds KJ, Vernon SD, Bouchery E, Reeves WC. The economic impact of chronic fatigue syndrome. *Cost Eff Resour Alloc* 2004 Jun 21;2(1):4.

[Division of Viral and Rickettsial Diseases, Centers for Disease Control and Prevention, Atlanta, USA. wcr1@cdc.gov]

BACKGROUND: Chronic fatigue syndrome (CFS) is a chronic incapacitating illness that affects between 400,000 and 800,000 Americans. Despite the disabling nature of this illness, scant research has addressed the economic impact of CFS either on those affected or on the national economy. **METHODS:** We used microsimulation methods to analyze data from a surveillance study of CFS in Wichita, Kansas, and derive estimates of productivity losses due to CFS. **RESULTS:** We estimated a 37% decline in household productivity and a 54% reduction in labor force productivity among people with CFS. The annual total value of lost productivity in the United States was \$9.1 billion, which represents about \$20,000 per person with CFS or approximately one-half of the household and labor force productivity of the average person with this syndrome. **CONCLUSION:** Lost productivity due to CFS was substantial both on an individual basis and relative to national estimates for other major illnesses. CFS resulted in a national productivity loss comparable to such losses from diseases of the digestive, immune and nervous systems, and from skin disorders. The extent of the burden indicates that continued research to determine the cause and potential therapies for CFS could provide substantial benefit both for individual patients and for the nation.

26. Siemionow V, Fang Y, Calabrese L, Sahgal V, Yue GH. Altered central nervous system signal during motor performance in chronic fatigue syndrome. *Clin Neurophysiol* 2004 Oct;115(10):2372-81.

[Department of Biomedical Engineering, The Lerner Research Institute, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA.]

Objective: The purpose of this study was to determine whether brain activity of chronic fatigue syndrome (CFS) patients during voluntary motor actions differs from that of healthy individuals. **Methods:** Eight CFS patients and 8 age- and gender-matched healthy volunteers performed isometric handgrip contractions at 50% maximal voluntary contraction level. They first performed 50 contractions with a 10 s rest between adjacent trials--'Non-Fatigue' (NFT) task. Subsequently, the same number of contractions was performed with only a 5 s rest between trials-- 'Fatigue' (FT) task. Fifty-eight channels of surface EEG were recorded simultaneously from the scalp. Spectrum analysis was performed to estimate power of EEG frequency in different tasks. Motor activity-related cortical potential (MRCP) was derived by triggered averaging of EEG signals associated with the muscle contractions. **Results:** Major findings include: (i) Motor performance of the CFS patients was poorer than the controls. (ii) Relative power of EEG theta frequency band (4-8 Hz) during performing the NFT and FT tasks was significantly greater in the CFS than control group [Formula: see text] (iii) The amplitude of MRCP negative potential (NP) for the combined NFT and FT tasks was higher in the CFS than control group [Formula: see text] (iv) Within the CFS group, the NP was greater for the FT than NFT task [Formula: see text] whereas no such difference between the two tasks was found in the control group. **Conclusions:** These results clearly show that CFS involves altered central nervous system signals in controlling voluntary muscle activities, especially when the activities induce fatigue. **Significance:** Physical activity-induced EEG signal changes may serve as physiological markers for more objective diagnosis of CFS.

27. Sorensen B, Streib JE, Strand M, Make B, Giclas PC, Fleshner M, Jones JF. Complement activation in a model of chronic fatigue syndrome. *J Allergy Clin Immunol* 2003 Aug;112(2):397-403.

[Department of Pediatrics, National Jewish Medical and Research Center, Denver, CO, USA.]

BACKGROUND: A need exists to identify biological markers in chronic fatigue syndrome (CFS). **OBJECTIVE:** To use an exercise and/or allergen challenge to induce the symptoms of CFS and to identify a biological marker that correlates with these symptoms. **METHODS:** Patients with CFS (n = 32) and age-matched, normal control patients (n = 29) exercised for 20 minutes on a stationary bike at 70% of their predicted max work load (Watts). Patients from each group with positive skin test results were also challenged with intranasally administered relevant allergens. Symptoms were recorded for 2 weeks before and 1 week after each challenge, using 3 different

instruments. Blood samples were taken before, and 0, 1, 6, and 24 hours after challenges. Levels of complement split products, cell-associated cytokines, and eosinophilic cationic protein were measured. Mean preexercise and postexercise symptom scores were evaluated for each group. RESULTS: Exercise challenge induced significant increases of the complement split product C4a, but not C3a or C5a, at 6 hours after exercise only in the CFS group ($P < .01$), regardless of allergy status. Mean symptom scores were significantly increased after exercise through the use of a daily diary ($P < .03$) and a weekly diary ($P < .01$) for the CFS group only. Mean scores for the Multidimensional Fatigue Inventory categories "reduced activity" and "mental fatigue" were significantly increased in the CFS group only ($P < .04$ and $P < .02$, respectively). CONCLUSIONS: Exercise challenge may be a valuable tool in the development of diagnostic criteria and tests for CFS. Establishment of a role for complement activation products as markers or participants in production of illness requires further study.

28. Spence VA, Khan F, Kennedy G, Abbot NC, Belch JJ. Acetylcholine mediated vasodilatation in the microcirculation of patients with chronic fatigue syndrome. *Prostaglandins Leukot Essent Fatty Acids* 2004 Apr;70(4):403-7.

[Vascular Diseases Research Unit, University Department of Medicine, Ninewells Hospital & Medical School, Dundee DD1 9SY, UK.]

The aetiology of chronic fatigue syndrome (CFS) remains controversial and a number of hypotheses have been put forward to explain it. Research into the condition is hindered by the considerable heterogeneity seen across patients but several reports have highlighted disturbances to cholinergic mechanisms in terms of central nervous system activity, neuromuscular function and autoantibodies to muscarinic cholinergic receptors. This paper examines an altogether separate function for acetylcholine and that is its role as an important and generalized vasodilator. Most diseases are accompanied by a blunted response to acetylcholine but the opposite is true for CFS. Such sensitivity is normally associated with physical training so the finding in CFS is anomalous and may well be relevant to vascular symptoms that characterise many patients. There are several mechanisms that might lead to ACh endothelial sensitivity in CFS patients and various experiments have been designed to unravel the enigma. These are reported here.

29. Stewart CC, Cookfair DL, Hovey KM, Wende KE, Bell DS, Warner CL. Predictive immunophenotypes: Disease-related profile in chronic fatigue syndrome. *Cytometry* 2003 May;53(1):2633.

[Laboratory of Flow Cytometry, Roswell Park Cancer Institute, Buffalo, New York]

BACKGROUND: There is a growing body of evidence supporting the theory that problems with immune function play an important role in chronic fatigue syndrome (CFS). METHODS: We studied 90 CFS cases and 50 healthy controls from two different areas of upstate New York to determine whether there were differences in the absolute number and pattern of natural killer (NK) and cytotoxic T-cell phenotypes between CFS cases and healthy controls in the two regions. One group was from a small town where a cluster of cases existed; the other was from a large metropolitan area where there was not a known cluster. RESULTS: The number of CD56+CD3+CD8+ and CD56+CD3+CD8- cells in cases from the two areas were both significantly elevated over that of controls from the metropolitan area ($P < 0.03$). The number of CD56+CD3-CD8+ and CD56+CD3-CD8- cells was significantly reduced in the two case groups compared to that of controls from the metropolitan area ($P = 0.04$). However, controls who were from the same town as the cluster cases had numbers of CD56+CD3+CD8+, CD56+CD3+CD8-, and CD56+CD3-CD8- cells that were more like that of cases than controls. Only the number of CD56+CD3-CD8+ cells (an NK cell subset) was significantly different in cases versus controls from the cluster area ($P = 0.022$). CONCLUSIONS: These data suggest that differences in controls from cluster and noncluster areas may be responsible for some of the inconsistencies in results from other studies. Furthermore, they suggest the possibility that NK cell function may

play an important role in preventing the development of CFS in individuals who live in a community where a cluster of cases have been identified.

30. Stewart JM. Autonomic nervous system dysfunction in adolescents with postural orthostatic tachycardia syndrome and chronic fatigue syndrome is characterized by attenuated vagal baroreflex and potentiated sympathetic vasomotion. *Pediatr Res* 2000;48:218-26.

Abstract: The objective was to determine the nature of autonomic and vasomotor changes in adolescent patients with orthostatic tachycardia associated with the chronic fatigue syndrome (CFS) and the postural orthostatic tachycardia syndrome (POTS). Continuous electrocardiography and arterial tonometry was used to investigate the heart rate and blood pressure responses before and 3-5 min after head-up tilt in 22 adolescents with POTS and 14 adolescents with CFS, compared with control subjects comprising 10 healthy adolescents and 20 patients with simple faint. Heart rate and blood pressure variability, determined baroreceptor function using transfer function analysis, and measured cardiac vagal and adrenergic autonomic responses were calculated using timed breathing and the quantitative Valsalva maneuver. Two of 10 healthy controls and 14 of 20 simple faint patients experienced vasovagal syncope during head-up tilt. By design, all CFS and POTS patients experienced orthostatic tachycardia, often associated with hypotension. R-R interval and heart rate variability were decreased in CFS and POTS patients compared with control subjects and remained decreased with head-up tilt. Low-frequency (0.05-0.15 Hz) blood pressure variability reflecting vasomotion was increased in CFS and POTS patients compared with control subjects and increased further with head-up tilt. This was associated with depressed baroreflex transfer indicating baroreceptor attenuation through defective vagal efferent response. Only the sympathetic response remained. Heart rate variability declined progressively from normal healthy control subjects through syncope to POTS to CFS patients. Timed breathing and Valsalva maneuver were most often normal in CFS and POTS patients, although abnormalities in select individuals were found. Heart rate and blood pressure regulation in POTS and CFS patients are similar and indicate attenuated efferent vagal baroreflex associated with increased vasomotor tone. Loss of beat-to-beat heart rate control may contribute to a destabilized blood pressure resulting in orthostatic intolerance. The dysautonomia of orthostatic intolerance in POTS and in chronic fatigue are similar.

31. VanNess JM, Snell CR, Strayer DR, Dempsey L 4th, Stevens SR. Subclassifying chronic fatigue syndrome through exercise testing. *Med Sci Sports Exerc* 2003 Jun;35(6):908-13.

[University of the Pacific, Department of Sport Sciences, Stockton, CA 95211, USA.
mvanness@uop.edu]

PURPOSE: The purpose of this study was to examine physiological responses of persons with chronic fatigue syndrome (CFS) to a graded exercise test. **METHODS:** Cardiopulmonary exercise tests were performed on 189 patients diagnosed with CFS. Based on values for peak oxygen consumption, patients were assigned to one of four impairment categories (none, mild, moderate, and severe), using American Medical Association (AMA) guidelines. A one-way MANOVA was used to determine differences between impairment categories for the dependent variables of age, body mass index, percentage of predicted [OV0312]O(2), resting and peak heart rates, resting and peak systolic blood pressure, respiratory quotient (RQ), and rating of perceived exertion. **RESULTS:** Significant differences were found between each impairment level for percentage of predicted [OV0312]O(2) and peak heart rate. Peak systolic blood pressure values for the "moderate," and "severe" groups differed significantly from each other and both other groups. The more impaired groups had lower values. The no impairment group had a significantly higher peak RQ than each of the other impairment levels (all $P < 0.001$). Peak [OV0312]O(2) values were less than predicted for all groups. Compared with the males, the women achieved actual values for peak [OV0312]O(2) that were closer to their predicted values. **CONCLUSION:** Despite a common diagnosis, the functional capacity of CFS patients varies greatly. Stratifying patients by function allows for a more meaningful interpretation of the responses to exercise and may enable differential diagnosis between subsets of CFS patients.

32. Taillefer SS, Kirmayer LJ, Robbins JM, Lasry JC. Psychological correlates of functional status in chronic fatigue syndrome. *J Psychosom Res* 2002 Dec;53(6):1097-106.

[Department of Psychology, Universite de Montreal, Canada.]

BACKGROUND: The present study was designed to test a cognitive model of impairment in chronic fatigue syndrome (CFS) in which disability is a function of severity of fatigue and depressive symptoms, generalized somatic symptom attributions and generalized illness worry. **METHODS:** We compared 45 CFS and 40 multiple sclerosis (MS) outpatients on measures of functional ability, fatigue severity, depressive symptoms, somatic symptom attribution and illness worry. **RESULTS:** The results confirmed previous findings of lower levels of functional status and greater fatigue among CFS patients compared to a group of patients with MS. Fatigue severity was found to be a significant predictor of physical functioning but not of psychosocial functioning in both groups. In CFS, when level of fatigue was controlled, making more somatic attributions was associated with worse physical functioning, and both illness worry and depressive symptoms were associated with worse psychosocial functioning. **CONCLUSIONS:** Our findings support the role of depression and illness cognitions in disability in CFS sufferers. Different cognitive factors account for physical and psychosocial disability in CFS and MS. The SF-36 may be sensitive to symptom attributions, suggesting caution in its interpretation when used with patients with ill-defined medical conditions.

33. Viner R, Gregorowski A, Wine C, Bladen M, Fisher D, Miller M, El Neil S. Outpatient rehabilitative treatment of chronic fatigue syndrome (CFS/ME). *Arch Dis Child* 2004 Jul;89(7):615-9.

[Department of Adolescent Medicine, Great Ormond Street Hospital for Children and University College London Hospitals, London, UK. R.Viner@ich.ucl.ac.uk]

AIMS: To assess the outcome of outpatient multidisciplinary rehabilitative treatment (graded activities/exercise programme, family sessions, and supportive care) compared with supportive care alone for children and adolescents with chronic fatigue syndrome (CFS/ME). **METHODS:** Fifty six young people (aged 9-17 years) with CFS/ME by standard criteria were followed up for 3-24 months. All subjects received supportive care. Families additionally opted to either enter the rehabilitation programme (supportive care plus graded activities/exercise programme and family sessions) or have no additional treatment. **RESULTS:** Twenty two (39%) subjects had supportive care alone and 26 (46%) entered the programme. Treatment groups were comparable at baseline in terms of age, severity and duration of illness, Wellness score, and school attendance. At end of follow up, those in the programme group had significantly higher Wellness score and school attendance than those having supportive care alone. The programme significantly reduced the overall severity of illness: after the programme, 43% had complete resolution of CFS/ME compared to only 4.5% of those having supportive care alone. The presence of depressed mood and family beliefs about the aetiology of CFS/ME were not significantly associated with outcomes. **CONCLUSIONS:** Outpatient rehabilitative treatment offers significant potential to improve the prognosis of CFS/ME in childhood and adolescence.

Bibliographic References

1. Asbring P, Narvanen AL. Ideal versus reality: physicians perspectives on patients with chronic fatigue syndrome (CFS) and fibromyalgia. *Soc Sci Med* 2003 Aug;57(4):711-20.
2. Assefi NP, Coy TV, Uslan D, Smith WR, Buchwald D. Financial, occupational, and personal consequences of disability in patients with CFS and fibromyalgia compared to other fatiguing conditions. *J Rheumatology* 2003 Apr;30(4):804-8.
3. Blockmans D, Persoons P, Van Houdenhove B, Lejeune M, Bobbaers H. Combination therapy with hydrocortisone and fludrocortisone does not improve symptoms in chronic fatigue syndrome: a randomized, placebo-controlled, double-blind, crossover study. *Am J Med* 2003 Jun 15;114(9):736-41.
4. Chaudhuri A, Behan PO. In vivo magnetic resonance spectroscopy in chronic fatigue syndrome. *Prostaglandins Leukot Essent Fatty Acids* 2004 Sep;71(3):181-3.
5. Chaudhuri, Behan P. Fatigue in neurological disorders. *Lancet* 2004 Mar 20;363(9413):978-988.
6. Davey NJ, Puri BK, Catley M, Main J, Nowicky AV, Zaman R. Deficit in motor performance correlates with changed corticospinal excitability in patients with chronic fatigue syndrome. *Int J Clin Pract* 2003 May;57(4):262-4.
7. Douche-Aourik F, Berlier W, Feasson L, Bourlet T, Harrath R, Omar S, Grattard F, Denis C, Pozzetto B. Detection of enterovirus in human skeletal muscle from patients with chronic inflammatory muscle disease or fibromyalgia and healthy subjects. *J Med Virol* 2003 Dec;71(4):540-7.
8. Fisher L, Chalder T. Childhood experiences of illness and parenting in adults with Chronic Fatigue Syndrome. *Jour Psychosom Res* 2003 May;54(5):439-443.
9. Garralda ME, Rangel L. Impairment and coping in children and adolescents with chronic fatigue syndrome: a comparative study with other paediatric disorders. *J Child Psychol Psychiatry* 2004 Mar;45(3):543-52.
10. Gerrity TR, Papanicolaou DA, Amsterdam JD, Bingham S, Grossman A, Hedrick T, Herberman RB, Krueger G, Levine S, Mohaghehpour N, Moore RC, Oleske J, Snell CR; CFIDS Association of America. Immunologic aspects of chronic fatigue syndrome. Report on a Research Symposium convened by The CFIDS Association of America and co-sponsored by the US Centers for Disease Control and Prevention and the National Institutes of Health. *Neuroimmunomodulation* 2004;11(6):351-7.
11. Kennedy G, Abbot NC, Spence V, Underwood C, Belch JJ. The specificity of the CDC-1994 criteria for chronic fatigue syndrome: comparison of health status in three groups of patients who fulfill the criteria. *Ann Epidemiol* 2004 Feb;14(2):95-100.
12. McCully KK, Smith S, Rajaei S, Leigh JS Jr, Natelson BH. Blood flow and muscle metabolism in chronic fatigue syndrome. *Clini Sci* Feb 2003 Jun;104(6):641-7.
13. Naschitz JE, Rosner I, Rozenbaum M, Fields M, Isseroff H, Babich JP, Zuckerman E, Elias N, Yeshurun D, Naschitz S, Sabo E. Patterns of cardiovascular reactivity in disease diagnosis. *QJM* 2004 Mar;97(3):141-51.

14. Nijs J, Vanherberghen K, Duquet W, De Meirleir K. Chronic fatigue syndrome: lack of association between pain-related fear of movement and exercise capacity and disability. *Phys Ther* 2004 Aug;84(8):696-705.
15. Nijs J, De Meirleir K, Wolfs S, Duquet W. Disability evaluation in chronic fatigue syndrome: associations between exercise capacity and activity limitations/participation restrictions. *Clin Rehabil* 2004 Mar;18(2):139-48.
16. Nijs J, De Meirleir K, Truyen S. Hypermobility in patients with chronic fatigue syndrome: Preliminary Observations. *J of Musculoskeletal Pain* 2004;12(1):9-17.
17. Ohashi K, Bleijenberg G, Van Der Werf S, Prins J, Amaral LA, Natelson BH, Yamamoto Y. Decreased fractal correlation in diurnal physical activity in chronic fatigue syndrome. *Methods Inf Med* 2004;43(1):26-9.
18. Page LA, Wessely S. Medically unexplained symptoms: exacerbating factors in the doctor-patient encounter. *Journ Royal Society of Med* 2003 May;96:223-27.
19. Prins JB, Elving LD, Koning H, Bleijenberg G, van der Meer JW. Diagnosing chronic fatigue syndrome: comparison of a protocol and computerised questionnaires. *Neth J Med* 2003 Apr;61(4):120-6.
20. Prins JB, Bos E, Huibers MJH, Servaes P, van der Werf SP, van der Meer JWM, Bleijenberg G. Social support and the persistence of complaints in chronic fatigue syndrome. *Psychotherapy and Psychosomatics* 2004;73:174-182.
21. Raine R, Carter S, Sensky T, Black N. General practitioners' perceptions of chronic fatigue syndrome and beliefs about its management, compared with irritable bowel syndrome: qualitative study. *BMJ* 2004 Jun 5;328(7452):1354-7. [Epub 2004 May 28]
22. Ross SD, Estok RP, Frame D, Stone LR, Ludensky V, Levine CB. Disability and chronic fatigue syndrome: a focus on function. *Arch Intern Med* 2004 May 24;164(10):1098-107.
23. Blacker CV, Greenwood D, Wesnes K, Wilson R, Woodward C, Howe I, Ali T. Effect of galantamine hydrobromide in chronic fatigue syndrome: a randomized controlled trial. *JAMA* 2004;292:1195-1204.
24. Schacterle R, Komaroff A. A comparison of pregnancies that occur before and after the onset of chronic fatigue syndrome. *Arch Intern Med* 2004;164:401-404.
25. Smith S, Sullivan K. Examining the influence of biological and psychological factors on cognitive performance in chronic fatigue syndrome: a randomized, double-blind, placebo-controlled, crossover study. *Int J Behav Med* 2003;10(2):162-73.
26. Taillefer SS, Kirmayer LJ, Robbins JM, Lasry JC. Correlates of illness worry in chronic fatigue syndrome. *J Psychosom Res* 2003 Apr;54(4):331-7.
27. Vermeulen RCW, Scholt H. Chronic fatigue syndrome and sexual dysfunction. *J of Psychosomatic Research* 2004 Feb;56(2):199-201.
28. White PD, Thomas JM, Sullivan PF, Buchwald D. The nosology of sub-acute and chronic fatigue syndromes that follow infectious mononucleosis. *Psychol Med* 2004 Apr;34(3):499-507.
29. Woolley J, Allen R, Wessely S. Alcohol use in chronic fatigue syndrome. *J of Psychosomatic Research* 2004 Feb;56(2):203-206.