

THE CFS RESEARCH REVIEW

Providing up-to-date information on research, diagnosis and treatment of CFS for medical professionals

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Research Q&A

Cardiac Output Linked To Severe CFS Cases

By Mark
Giuliucci

Article: “Abnormal Impedance Cardiography Predicts Symptom Severity in Chronic Fatigue Syndrome.” *The American Journal of the Medical Sciences*. 2003; 326(2):55-60.

Synopsis: While the cause of chronic fatigue syndrome (CFS) remains unknown, researchers have noted circulatory irregularities in many patients. These include autonomic nervous system dysfunction, often manifested as orthostatic intolerance; neuroendocrine abnormalities (see story on p. 4); reduced plasma volume; and low red blood cell mass. In combination, some researchers believe, these factors could create deficiencies in blood flow to organs and muscles — with resultant symptoms, such as post-exertional fatigue, that are hallmarks of CFS.

New research from the CFS Cooperative Research Center at the University of Medicine and Dentistry of New Jersey has tested the possible link between CFS symptoms and cardiac output (the amount of blood pumped by the heart each minute). Thirty-eight CFS patients participated in the study, along with 27 matched, sedentary controls. All subjects were tested for cardiac output using impedance cardiography, a noninvasive procedure based on the principle that electrical impedance of tissues is

proportional to their blood flow. Subjects were tested during a 10-minute resting supine period and a five-minute quiet standing period.

Results showed that patients with severe cases of CFS (those who had more symptoms and rated them as substantial or greater in severity) had significantly lower cardiac output than either controls or patients with less-severe CFS — even though mean arterial blood pressure and heart rate did not vary significantly among the groups. Moreover, post-exertional fatigue and flu-like symptoms were predictive of lowered cardiac output ($p < 0.0002$).

The authors say their work suggests that “in some patients with CFS, blood pressure is maintained at the cost of restricted flow, possibly resulting in a low flow circulatory state.” CFS patients with lower cardiac output may not be able to meet the demands of everyday physical activities, leading to fatigue and other symptoms.

Lead author Arnold Peckerman, PhD, discusses the study’s findings:

Q: *What led to the hypothesis that CFS patients may have reduced cardiac output?*

Dr. Peckerman: Many of the symptoms
(continued on next page)

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*Chronic fatigue syndrome
(CFS) is also known as chronic
fatigue and immune dysfunction
syndrome (CFIDS) or myalgic en-
cephalomyelitis (ME). For a case
definition of the illness, see page 16.

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of CFS, such as post-exertional fatigue, are also symptoms of low cardiac output. A person can have low cardiac output for a number of reasons, but the result is the same — circulation slows down and some organs may not get enough blood flowing through them. If cardiac output falls to the point that it is unable to meet metabolic demands, this is called hypoperfusion. Clinical signs of hypoperfusion include lowering of pulse pressure, cool extremities, altered mentation, rapid resting heart rate, breathing that alternates between deep and shallow, and high blood urea nitrogen relative to creatinine. To be sure, most CFS patients do not show clinical signs of hypoperfusion, and they couldn't. If you have symptoms like these, you get referred for cardiological evaluation and treated appropriately. You would not be diagnosed with CFS. The point I am making is that the criteria for defining hypoperfusion are conservative. However, if you lower the bar, meaning you entertain a possibility that reduction in blood flow of a lesser degree than that may still be clinically

significant, and you pull together the many indications from different research and clinical observations in CFS pointing in this direction, it becomes a reasonable question to ask.

Q. The gap in cardiac output between controls and severe CFS cases was wider when subjects were supine than when they were standing. Why might that be?

Dr. Peckerman: When you are lying down, blood flow to the heart (venous return or preload) is generally higher compared to what it is when you are standing. Normally, having high blood flow to the heart is good. It helps the heart to work better. But if heart muscle is not working properly, if it is compromised and may become overloaded. Then you have the opposite effect. The more blood goes to the heart, the more the function goes down.

This is what happens with heart failure patients. When they're lying down, their heart's pumping capacity is reduced. When they stand up, the preload becomes reduced because much of the blood goes to the legs. Normal people have reduced cardiac

performance when standing. In these people, it's the opposite; it improves.

In a sense, this is what we found with severe CFS patients. When we looked at the lying position, the difference between controls and the severe patients was greater than when they were standing. If you start with the presumption that these people have orthostatic intolerance due to low blood volume, you'd expect to see larger deviation from the norm when standing. What actually happened was the opposite; it was smaller.

Q: Are you saying that some people with severe CFS may have heart failure?

Dr. Peckerman: Any such conclusion is really beyond the scope of this study. But what we may be seeing here is a more subtle form. Present medicine is slowly realizing that there are many people with heart failure that is not clinically evident but which may be progressing in that direction. They walk around with an unrecognized disease that is not being treated. Unfortunately, when the symptoms appear, it already may be irreversible.

Of course, there could be many other explana-

tions for what we observed in this study. We could not make a statement about heart failure with any certainty based on these preliminary findings. More recently we did a follow-up study that included cardiac stress testing, and the preliminary data we reported at the Experimental Biology conference in April were consistent with this possibility. But much more work still remains to be done.

Q. Cognitive dysfunction was not found to be predictive of reduced cardiac output?

Dr. Peckerman: That's true. But this does not mean that cardiac output cannot affect cognitive abilities. It may very well be happening. In fact, patients with severe CFS who had reduced cardiac output rated their problems with memory and concentration quite high.

What our analysis did show was that reduced cardiac output was more likely to be found in patients whose main symptoms were some combination of post-exertional fatigue and infectious symptoms such as fever and chills. This was after controlling for headaches, muscle aches, sleep, and other symptoms included

in the case definition.

The same analysis also found that those patients whose main symptoms related to cognitive functioning had less likelihood of having lowered cardiac output. The most plausible explanation for this is that primary problem in those people is not with low cardiac output, but may lie elsewhere, possibly in the brain.

A major stumbling block in studying CFS has been heterogeneity, meaning that different patient groups have different causes for their symptoms — and no reliable means of separating them. This study suggested one way it possibly can be done. Mind you, we wouldn't find what we found if we didn't separate our patients into the severe and less severe subsets. However, just looking at symptoms probably would not be sensitive enough. One needs to look for combinations of clinical and physiological markers. The combination we identified was that of low cardiac output, plus high post-exertional fatigue, high fever-chills, and low cognitive problems. This approach seems promising.

Q: Can you see any treatments for CFS arising from your findings?

Dr. Peckerman: Right

now, it's premature to talk about treatments. We're looking at a phenomenon that could have a number of different causes.

Unless you know the cause, treatment would be a shot in the dark. In fact, it can do harm. For example, if the problem is with the heart it is one thing, but if the problem is with low blood volume it is another. In people with heart failure, blood volume is not low, it is high. So if you assume that low cardiac output is due to low blood volume, and you give someone treatment to increase their blood volume, this isn't going to make matters better — it may make it worse. Our observations so far have been more consistent with a problem with the heart, but it is too early to tell for sure.

The good news is that there are ways to treat the problem of reduced cardiac output if the mechanisms are understood. If you can identify what's causing it, it's certainly possible to treat it. Unfortunately, we are nowhere near that point yet in CFS cases.

Mark Giulucci is editor of The CFS Research Review. ■

Grant Report: Corticotropin-Releasing Hormone in Chronic Fatigue Syndrome

By Dimitris
Papanicolaou, MD

Editor's note: The following is a preliminary report from a study funded by a grant from The CFIDS Association of America. The Association has issued a new Request for Applications for studies relating to chronic fatigue syndrome (CFS). For more information, see p. 9.

Low cortisol and high interleukin-6 (IL-6) have been associated with the symptoms of chronic fatigue syndrome (CFS). The purpose of this study is to investigate the role of endogenous IL-6 in the pathogenesis of all or part of the CFS symptom complex.

Hypocortisolism in CFS

Over the past few years increased emphasis has been placed on the hypothalamic-pituitary-adrenal (HPA) axis activity in patients with CFS. Adrenal insufficiency shares several symptoms with CFS (such as flu-like symptoms, fatigue, malaise, arthralgias, myal-

gias, sleep abnormalities, headaches, dizziness and decreased memory).

Given the similarity of the symptomatology of these two disorders, the HPA axis of CFS patients has been studied by several investigators.

Hypoactivity of the HPA axis, resulting in low cortisol production, has been implicated in the pathogenesis of this disorder. Investigators showed that patients with CFS had subnormal adrenal response to different doses of ACTH, indicating chronic HPA axis underactivity. These findings were supported by a subsequent study by Scott *et al* who demonstrated that patients with CFS had small adrenal glands compared to normal controls using computed axial tomography, suggesting adrenal atrophy.

Such findings have led many investigators to believe that CFS is a state of “functional” hypocortisolism. Patients with CFS showed a normal cortisol response when “stronger” stimuli of the HPA axis

were applied, such as insulin-hypoglycemia. These data indicate that, while patients with CFS suffer from chronic hypocortisolism, they do not suffer from Addison's disease, which is a near-complete destruction of the adrenal glands. The chronic hypocortisolism, though, can have profound effects on several immune and endocrine systems, further complicating the clinical picture of these patients. Specifically, hypocortisolism can lead to overproduction of inflammatory cytokines (such as IL-6), which in turn can further precipitate the symptom complex of CFS.

Interleukin-6 in CFS

Glucocorticoids have a suppressive effect on the production of inflammatory cytokines, such as IL-6. Conversely, glucocorticoid deficiency can result in overproduction of inflammatory cytokines. We have shown that in cases of adrenal insufficiency (a condition characterized

by hypocortisolism) there is significant increase in IL-6 production. The increased production of inflammatory cytokines is responsible — at least partially — for the symptom complex of adrenal insufficiency, which greatly overlaps with the symptom complex of CFS.

Overproduction of inflammatory cytokines, such as IL-6 has been reported in states of CFS. However, others have failed to find such elevation of basal production of inflammatory cytokines in CFS. A possible explanation for such a disagreement in the literature may be that CFS is an illness of remission and relapses and tends to have a fluctuating clinical course.

Moreover, while patients with CFS may be “functioning” at baseline, they clearly have difficulty functioning under physical or mental stress. They typically try to limit their activities and their exposure to stressful stimuli, so as not to trigger a CFS relapse.

Therefore, evaluation of biological parameters, such as IL-6, at basal conditions may not be the best way to approach this illness diagnostically. Rather, a provocative test

needs to be applied. Provocative testing is not uncommon in endocrinology; for example, the diagnosis of adrenal insufficiency or that of growth hormone insufficiency cannot be made on the basis of basal sampling, but rather requires the application of a provocative test, such as an ACTH stimulation test for the former and an insulin-tolerance test for the latter. Similarly, a stimulation test would be more appropriate for the diagnosis of CFS. To date such a test does not exist.

The source of circulating IL-6 in humans has been an enigma for some time. Recent studies have shown that adipose (fat) tissue contributes significantly to the circulating IL-6 levels in humans. For example, several groups, including ours, have found that IL-6 is produced by human adipocytes *in vitro*.

We are investigating the role of endogenous IL-6 in the pathogenesis of all or part of the CFS symptom complex. The major advantage of this approach is that the cytokine under investigation (IL-6) will not be administered exogenously as a pharmacological agent. Instead, corti-

cotropin-releasing hormone (CRH) will be administered to the subject. This will lead to a modest elevation of endogenous IL-6 concentration, which will approximate more closely than exogenous IL-6 administration the cytokine status of patients with fatiguing illnesses.

CRH: a direct stimulant of IL-6

We chose corticotropin-releasing hormone (CRH) as a stimulus for endogenous IL-6 production. CRH is known primarily for its role as the major hypothalamic factor stimulating cortisol secretion. During stress (immunological, physical, or psychological) CRH is secreted from the hypothalamus, and stimulates the pituitary to secrete ACTH, which — in turn — stimulates the adrenal glands to secrete cortisol.

Several lines of evidence suggest that CRH exerts actions independent of its effects on cortisol secretion: i) CRH participates in the inflammatory response in a mouse model; ii) in humans it has been shown to interfere with

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“Our hypothesis is that chronic hypocortisolism leads to increased production of inflammatory cytokines.”

normal sleep, however, it is unclear whether these effects are due to CRH *per se* or due to the concomitant increase in circulating cortisol; iii) recently, CRH was shown to affect fat metabolism in humans; iv) administration of antalarmin (a CRH receptor type-1 antagonist) to non-human primates resulted in a decrease in serum leptin concentration; and v) we recently found that incubation of primary human adipocytes with CRH for 48 hours resulted in induction of lipolysis and stimulation of interleukin-6 (IL-6) and leptin production by these cells. Thus it appears that fat (one of the major sources of circulating IL-6) is also a major site of CRH action.

The stimulation of IL-6 secretion by CRH is intriguing and may be an important link between the HPA axis and the inflammatory cytokines in the pathogenesis of CFS-like symptoms. Thus patients with CFS may have an exaggerated IL-6 response to peripheral CRH, which would

in-turn lead to or exacerbate the symptom complex of this illness.

Our hypothesis is that chronic hypocortisolism leads to increased production of inflammatory cytokines. Such chronic overproduction of inflammatory cytokines can subsequently lead to the development of CFS symptoms.

Study Design

In the pilot study funded jointly by the U.S. Centers for Disease Control and Prevention (CDC) and The CFIDS Association of America, we sought to determine whether CRH administration results in increased plasma IL-6 in humans *in vivo*. To do so we infused CRH to healthy volunteers in a double-blind, placebo-controlled pilot study. The pilot study also served to determine the appropriate dose of CRH infusion for future studies on CFS patients. The study was conducted at the Emory University Hospital General Clinical Research Center (GCRC). Clinical Research Centers are designed to provide an in-patient setting in which

research protocols are strictly adhered to by highly trained and experienced staff, minimizing errors which may compromise study results.

Recruitment of subjects for the pilot study was restricted to certain groups in order to increase statistical power. To eliminate gender-related variability and because CFS affects primarily middle-age women, only female subjects (age 30–50) were included in the pilot study. In addition, hypothalamic-pituitary-adrenal (HPA) axis physiology varies among races. To eliminate race-related variability, which would have a negative impact on the statistical power of the study, only Caucasian subjects were recruited to the pilot study.

To eliminate the variability due to the effects of the menstrual cycle on the HPA axis and circulating cytokines, all subjects were required to have normal menstrual cycles and were studied during the early follicular phase (Days 4–7 of the menstrual cycle, Day 1 being

the first day of the menstrual bleeding). They were free of medical illnesses, had no history of psychiatric illnesses and were on no medications. In addition, all subjects were off any treatment with glucocorticoids (oral, topical, or inhaled) for at least one year prior to entering the study; they were off any treatment with any estrogen or progesterone-containing medications for at least two months before entering the study; they were off any non-steroidal anti-inflammatory medications for at least one week prior to entering the study; and acetaminophen-containing medications — if taken — were discontinued at least 48 hours prior to entering the study.

Caffeine and alcohol ingestion were discontinued 72 hours before being admitted for the inpatient part of the protocol. Only non-smokers were admitted to the study. Because the adipose tissue is one of the major sources of circulating cytokines and to increase the sensitivity of the study we studied overweight, but not obese, subjects (BMI: 27–30 kg/m²). Obese (BMI > 30 kg/m²) subjects were not studied because

they were not considered to be “healthy” volunteers, as obesity is — by definition — an illness.

CRH administration: CRH was administered as a 24-hour intravenous infusion instead of an IV bolus injection. The 24-hour infusion was preferred over the bolus administration for the following reasons: i) our preliminary *in vitro* data using primary cultures of human adipocytes indicated that a prolonged infusion rather than an IV bolus administration would be needed for biological effects to occur; ii) a prolonged infusion would most likely result in a rather prolonged stimulation of IL-6 production, which would better resemble the chronic characteristics of CFS and related illness.

CRH dosing: The optimal dose of CRH for stimulation of IL-6 production was unknown. Thus a dose-response study design was implemented. The study was conducted in a double-blind fashion. The subjects received a bolus (over 1 min) injection of placebo (normal saline) or ovine CRH (oCRH) at doses of 0.01, 0.03, 0.1, 0.3 and 1 mcg/kg, recon-

stituted in normal saline. This was followed immediately by an infusion of placebo or oCRH at doses of 0.01, 0.03, 0.1, 0.3 or 1 mcg/kg/hr, respectively for 24 hours. The maximum dose was 100 mcg/hr regardless of body weight (100 mcg is the maximum FDA-approved dose for this medication). The Baxter Colleague Infusion Pump was used for the infusion. Five subjects were studied per dose (including saline placebo), totaling 30 subjects. The doses of CRH were selected based on earlier studies showing the minimum effective dose for the HPA axis to be 0.03–0.1 mcg/kg, and the maximum 1–3 mcg/kg.

Blood was drawn hourly for 48 hours (24 hours before CRH infusion and 24 hours during CRH infusion). Study parameters included: hourly measurements of plasma cortisol, IL-6, tumor necrosis factor-alpha (TNF-alpha), and C-reactive protein.

Results

Preliminary data showed that CRH infusion at the dose of 1 mcg/kg/hr resulted in a significant increase in

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plasma IL-6 concentration. C-reactive protein (C-RP, which is a major index of systemic inflammation and is considered as a surrogate marker of IL-6 action) increased after 1 mcg/kg/hr infusion compared to placebo. Plasma TNF-alpha (also known to be secreted by adipocytes) was not increased during CRH administration. Plasma cortisol levels and urine free cortisol excretion were increased in dose-dependent manner as expected.

Study outcomes

We have shown that 24-hour CRH infusion at 1 mcg/kg/hr results in elevation of circulating IL-6 levels in healthy volunteers. We have also shown that CRH stimulates IL-6 secretion by human adipocytes *in vitro*. We believe that systemic CRH administration has a dual effect on IL-6: a direct stimulatory one, and an indirect inhibitory one, the latter through stimulation of cortisol release, which — in turn — suppresses IL-6 release.

Low doses of CRH failed to raise IL-6 levels significantly, most likely due to the antagonistic effects of cortisol, which

was stimulated at the same time. However, CRH exerted its maximum effect on cortisol at the dose of 0.3 mcg/kg/hr, as 1 mcg/kg/hr did not result in a further increase in circulating cortisol levels, nor in a further increase in urine free cortisol. CRH, therefore, had a stimulatory effect on circulating IL-6 and C-reactive protein at 1 mcg/kg/hr.

We believe that at that dose CRH further stimulated IL-6 release by target organs, such as the adipose tissue, whilst it did not stimulate cortisol release any further. The fact that the cortisol response to CRH reached a “plateau” at 0.3 mcg/kg/hr, whereas the IL-6 response did not, confers an independent role of CRH in a net increase in IL-6 release at 1 mcg/kg/hr. The concomitant increase in circulating C-reactive protein further demonstrates the physiological significance of the IL-6 increase. The effects of CRH on IL-6 appear to be specific, since tumor necrosis factor (TNF)-alpha levels (another inflammatory cytokine produced by fat) were not stimulated at any CRH dose. In fact, plasma TNF-alpha levels

were decreased at the two highest CRH doses, most likely due to the known suppressive effect of cortisol on TNF-alpha production.

In summary, these preliminary data suggest that peripheral CRH administration resulted in an increase in peripheral IL-6 levels. The CRH effect on systemic IL-6 concentration may have resulted from a direct CRH effect on IL-6 release by adipose cells. Our next study should help clarify the role of CRH-IL-6 interaction in the pathophysiology of CFS. Our long-term objective is to develop a diagnostic tool for CFS and design new treatment strategies, targeting the HPA-cytokine axis.

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Association. ■

Association seeks research applications

The CFIDS Association of America is pleased to announce the availability of chronic fatigue syndrome (CFS) research grants for pilot projects in the following general priority areas:

- Possible cause(s) and diagnostic markers of CFS;
- Underlying pathophysiology of CFS;
- Efficacious treatments for CFS; and
- Epidemiology, natural history and pathophysiology of CFS in adolescents and children.

Letters of intent are due no later than Dec. 31, 2003. Investigators proposing projects reviewed as falling within funding priorities will be asked to submit a complete application. Awards will be announced in June 2004. The earliest date funding may begin is July 31, 2004.

The purpose of the Association's peer-review Research Grants Program is to provide financial support for the highest-quality pilot CFS research studies and to enable

investigators to collect sufficient data to expand their studies with support from government or private funding sources. Since 1987, the Association has provided \$3.7 million in grants to CFIDS researchers.

Research grants are generally made to cover the direct costs of such items as salaries for professional and technical personnel, patient costs, equipment, supplies, travel and other miscellaneous items. These projects will have a one-year period of performance, beginning on or after July 31, 2004. Grants typically range from \$30,000 to \$80,000 per year, including institutional indirect costs not to exceed 10 percent.

Researchers interested in applying for a CFIDS Association Research Grant should submit a pre-application letter of intent to the Association briefly describing the research study, including hypotheses, objectives and goals; methods to be employed; preliminary studies; estimated budget; and qualifications of the principal investigator (and key collaborators, if applicable).

If the research project described in the letter of intent is determined to fall within the funding priorities of the Association's Research Grants Program, the principal investigator will be invited to submit a Research Grant Application.

All applications are evaluated by a peer-review Scientific Advisory Committee. The Committee assesses each application on the basis of: support for the hypothesis, relevance to CFS, innovation and originality, appropriateness of the budget, expertise and experience of the principal investigator and other staff and overall scientific merit.

Eligibility. Grants are awarded to non-profit research institutions located primarily within the United States and its territories.

Please see "Guidelines for Conducting CFS Research Studies" at www.cfids.org/resources/association-grants.asp for recommendations on important factors to consider when writing a CFS research protocol. For more information, contact the Association's Research Grants Officer, Kristina Hopkins, at e-mail kphopkins@cfids.org or tel. 704-364-0016, ext. 105. ■

Exercise test could yield CFS marker

Exercise challenge in people with chronic fatigue syndrome (CFS) appears to lead to increased production of a specific immune system protein — a finding that could lead to a diagnostic marker for the illness.

Researchers at the National Jewish Medical and Research Center and the University of Colorado looked at post-exercise immune changes in 32 CFS patients and 29 age-matched, normal control subjects. Both groups exercised for 20 minutes on stationary bicycles at 70 percent of their predicted maximum work loads. Blood samples were taken prior to exercise, and additional samples were collected at four intervals after the test was completed.

A significant increase in the split complement protein C4a was detected in the CFS group at the six-hour post-exercise measuring point. Complement proteins are a key component of the immune system response; they perform tasks ranging from stimulation of phagocytosis to initiating inflammation and B-cell activation.

In normal subjects, C4a generation is only stimulated at much higher exercise levels, and levels return to normal within three hours of the cessation of exercise.

The authors note that the exercise challenge allowed them to study CFS patients in an exacerbated state of illness. It is worth mentioning that the patients showed significant increases in symptoms following the challenge; this is consistent with post-exertional relapse, a hallmark symptom of CFS. Symptom diaries revealed significant increases in “reduced activity” and “mental fatigue” after the exercise challenge; the control subjects reported no adverse effects as a group.

The increases in C4a also correlated with the post-exercise symptom reports. The authors state: “The detection of this single protein (C4a) after exercise in conjunction with increased symptoms makes the development of a diagnostic test with an exercise challenge a real possibility.”

Sorensen B et al. “Complement activation in a model of chronic fatigue syndrome.” J Allergy Clin Immunol. Aug 2003; 112:397-403.

Muscle structures altered in patients with CFS

Rapid muscle fatigue and ensuing muscle pain are hallmarks of CFS. A new study from Italy has found more support for the hypothesis that altered structures within muscles may play a role in the development of these symptoms.

Researchers examined biopsied samples of striated muscle from four CFS patients and four other subjects with fibromyalgia, looking specifically at sarcoplasmic reticulum (SR) membranes. These structures release calcium ions that induce muscle contraction, and also re-absorb the ions to elicit muscle relaxation.

The authors report increased fluidity in the SR membranes (confirming earlier results). This could result in changes in the flow of ions across the membranes. In addition, there are also changes in the actions of dihydropyridine receptors, which control the release of calcium ions. Other changes noted affect the activity of enzymes that catalyze the release and re-absorption of calcium ions.

Many of these changes mimic the behavior of muscles in aging people. The authors speculate that oxidative tissue damage may occur at an increased rate in CFS patients, a

phenomenon that has been reported in other research.

Fulle S et al. "Modification of the functional capacity of sarcoplasmic reticulum membranes in patients suffering from chronic fatigue syndrome." Neuromuscular Disorders. 2003; 13: 479-484.

Another study from New York Medical College and Washington State University related to oxidative stress finds that protein carbonyl levels — a measure of overall protein oxidation — were significantly higher in the sera of patients with CFS when compared to control subjects. The total protein levels in the patients, by contrast, were similar to controls. The authors state that the findings are consistent with the theory that elevated nitric oxide/peroxynitrite levels play a role in CFS pathology.

Smirnova IV et al. "Elevated levels of protein carbonyls in sera of chronic fatigue syndrome patients." Mol Cell Biochem. Jun 2003; 248(1-2): 93-5.

Reaction times linked to motor deficits in CFS

Along with muscle fatigue, patients with CFS often exhibit slower sim-

ple reaction times (SRT) and simple movement times (SMT). New research from Imperial College in London shows that this phenomenon may be related to deficits in the motor preparatory areas of the brain, according to a study published in *The International Journal of Clinical Practice*.

The study's authors tested 10 CFS patients twice over a period of two years, measuring both SRT and SMT. Transcranial magnetic stimulation was applied to the palms of test subjects to measure the level of corticospinal excitability at the times of the tests.

The results show that corticospinal excitability often varied in subjects from one testing period to the other. This variability correlated with changes in SRT and SMT; the more stimulus required to provoke corticospinal excitability, the lower the overall reaction time scores. The authors say their work "provides evidence that the changing motor deficits in CFS have a neurophysical basis."

Davey NJ et al. "Deficit in motor performance correlates with changed corticospinal excitability in patients with chronic fatigue syn-

drome." Int J Clin Pract. 2003; 57(4): 262-264.

REM sleep differs in CFS subjects

Patients with CFS appear to have a higher percentage of rapid-eye movement (REM) sleep than their non-CFS monozygotic twins, according to research from the University of Washington.

Twenty-two sets of CFS-discordant twins were used in the study. All subjects completed the Sleep Disorders Questionnaire prior to the testing, and then were given continuous polysomnography tests, which measure physiological activity during sleep. A post-polysomnography survey also was completed by each of the participants.

The twin pairs did not differ significantly on most objective measures of sleep, including total sleep time, sleep efficiency and percentage of Stage 1, 2 or 3-4 (delta) sleep. However, the CFS twin showed statistically significant increases in the percentage of REM sleep compared to the non-CFS twin (27.7% of overall sleep vs. 24.4%).

On the post-test survey, the CFS twins generally reported worse subjective results, including sleeping
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fewer hours (6.2 vs. 6.7) and feeling less well rested. Because the subjective reports did not match the objective findings, the authors suggest that the CFS patients “suffer from an element of sleep-state misperception.” The higher percentage of REM sleep in the CFS twins may play an unknown role in this phenomenon, and in the illness in general, according to the study.

Watson NF et al. “Comparison of subjective and objective measures of insomnia in monozygotic twins discordant for chronic fatigue syndrome.” Sleep. 2003; 26(3): 324-8.

Exercise test could stratify CFS patients

CFS research efforts are complicated by the heterogeneity of the patient population. Attempts are being made to stratify patient groups based on a number of factors, from immune system anomalies to severity and onset of illness. A new study from the University of the Pacific points to exercise testing results as a possible means to stratify patients in hopes of better studying and treating them.

The study looks at 189 people with CFS, ranging

in age from 19 to 60 years. All were recruited for another study on the efficacy of the immunomodulatory drug Ampligen. The patients were tested on a treadmill, with increasing difficulty settings over a 22-minute period, and asked to continue until they felt they could no longer maintain their position on the device.

Results show that nearly half the subjects tested (n=92) were classified under American Medical Association guidelines as having moderate to severe functional impairment. Worth noting is that 10 percent of subjects showed no impairment and 35 percent showed mild impairment. Multiple measurements factor into the AMA classifications, including peak and predicted VO₂.

Three other measurements reached statistical significance when differentiating the four subgroups: peak heart rate, peak systolic blood pressure and total respiratory quotient. Peak heart rate was lower in groups that showed more impairment, as was peak systolic blood pressure. The authors note that the blunted heart rate and blood pressure responses are similar to those found in patients

with chronic heart failure (an exclusionary criteria in the current study).

Gender differences also were apparent. A higher percentage of women than men fell into the moderate and severe categories. But the women in these groups consistently achieved a peak VO₂ level that was closer to the maximal predicted levels. The authors say these gender differences warrant further study.

Exercise testing may eventually help clinicians determine the etiology and pathogenesis of individual cases of CFS, the authors note. Because each category displayed unique cardiovascular profiles, cardiac autonomic dysfunction could play a role in some CFS cases. But the authors say that other factors, ranging from neuroendocrinological or metabolic function to postviral immune system activation, could also be factors in the exercise test results.

Vanness JM et al. “Subclassifying Chronic Fatigue Syndrome through Exercise Testing.” Med Sci Sports Exerc. 2003; 35(6): 908-13. ■

Flu vaccines: Balance risks against benefits

Care management for patients with chronic fatigue syndrome (CFS) presents unique issues for both providers and patients. Due to the lack of published data on various treatments, patients are approached on an individual basis and care management decisions are often tested by trial and error. When a patient inquires about annual influenza vaccination, therefore, it is important to balance the potential benefits against concerns that the inoculation will exacerbate CFS symptoms.

Charles Lapp, MD, director of the Hunter-Hopkins Center in Charlotte, N.C., says that his clinical experience with thousands of CFS patients suggests that relapse or worsening of symptoms often follows the shot. Based on his own observation, the Hunter-Hopkins Center generally does not recommend that patients with CFS receive the vaccine.

“Not only do some patients relapse after the flu vaccination, many do not develop antibodies to the vaccination,” Dr. Lapp says. “Thus, you may suffer the discomfort of a shot plus the misery of a

relapse, and not even develop immunity.”

However, Dr. Lapp does acknowledge two exceptions to his rule: if the patient has taken the vaccine and tolerated it, or if the patient has a serious chronic illness (such as emphysema, diabetes, or heart disease) in addition to CFS.

Other viewpoints

Many clinicians share Dr. Lapp’s views about the judicious use of influenza vaccinations. “I think the benefits outweigh the risks because the effects of true influenza for CFS patients are devastating and may last a long time,” says **Joseph F. John, MD**. “There may be some downside from the vaccine but it really has not been studied. That would make a good project.”

Charles Shepherd, MD, says his clinical experience shows that a substantial percentage of his patients experience mild to moderate relapse episodes following inoculation.

Dr. Shepherd says it remains impossible to determine exactly which patients are more likely to suffer an adverse reaction to the vaccine. But his experience shows that

CFS patients with ongoing infective-type symptoms such as sore throats and enlarged glands fare worse than others, as do those who have recently developed CFS.

Internist **Alan Pocinki, MD**, says that many CFS patients appear to have greater viral resistance. “Most patients fall into the ‘As sick as I am, I hardly ever get a cold’ group, and it appears that some of the antiviral part of their immune system is upregulated. For them I think the risks of an adverse reaction to the shot outweighs the potential benefit, unless they are at high risk for some other reason, e.g., volunteer in a nursing home.

“Others who get frequent colds or bronchitis, smoke or have asthma probably should get it. I know there are people in the CFS community strongly for or against vaccinations in general, but I’m in the ‘every patient is different camp.’”

— *Kasia Faryna*

EBV titer: Limited value

In the mid-1980s, several researchers reported slightly higher levels of antibodies to Epstein-Barr virus (EBV) in patients

(continued on next page)

with CFIDS-like symptoms compared with healthy individuals. Subsequent investigations showed that elevated EBV titers are not diagnostic for CFS.

It is inappropriate to initially test for antibodies to EBV in people with CFS symptoms even though EBV can be associated with a prolonged infection that has all the features of CFS. Diagnosis requires a complete clinical evaluation and cannot be accomplished by merely testing for antibodies. Since 95 percent of adults have been infected with EBV, most adults will show antibodies to EBV from infection years earlier. High or elevated antibody levels may be present for years and are not diagnostic of recent infection. Studies have shown that EBV antibodies can be present in 20 percent of healthy individuals for years so this is not always definitive (U.S. Centers for Disease Control).

Exercise: Avoid boom/bust

CFS symptoms tend to worsen with physical and/or mental activity, and a prolonged relapse can be triggered by overexertion. Exercise

and activity plans must be highly individualized. CFS patients are best advised to balance gentle activity with frequent rest periods. The primary care provider can discuss the benefits of activity and the adverse effects of deconditioning and assist the patient in setting realistic goals to optimize physical conditioning. The provider can also tactfully discourage excess rest and social withdrawal.

Recommended activities include stretching, light calisthenics, light weights (1–2 pounds), walking, bicycling or swimming. Most patients can start with 2- or 3-minute periods of such activities interspersed with frequent rest periods. Finding the correct balance is a trial and error process, but it is important that activity levels are stabilized to prevent the “boom or bust” cycles that are common for CFS patients. Careful planning of duration and distance allows the patient to stop the activity before becoming overexerted. The exercise duration is then increased very slowly over time, but may have to be reduced or withheld temporarily during periods of relapse.

It may be practical to consult a physical therapist experienced in treating CFS patients who are severely incapacitated.

Consider alternative diagnosis

If the patient has had more than six months of fatigue and indicates that it has not had a major effect on activities of daily living, then the patient should be diagnosed with non-syndromic chronic fatigue. Symptomatic and supportive treatment with periodic follow-up is appropriate. Note that the treatment of CFS and non-syndromic chronic fatigue does not differ. Crucial to clinical care of patients with CFS and other unexplained fatiguing illnesses is continued interest and evaluation by the health care provider. The provider should remain vigilant about other possible conditions that may not be apparent at first.

Material for this section is adapted from “Chronic Fatigue Syndrome: A Diagnostic & Management Challenge,” a self-study CFS course offered for continuing education (CE) credit to health care providers. For more information, see p. 15. ■

Provider education project offers CE, Spreads word about CFS management

Health care providers can learn more about recognizing and treating chronic fatigue syndrome (CFS) — and earn continuing education (CE) credits at the same time — by participating in a collaborative education program run by The CFIDS Association of America and the U.S. Centers for Disease Control and Prevention.

“Chronic Fatigue Syndrome: A Diagnostic & Management Challenge” is offered as a self-study course, and is available in three formats: video, print and online. All formats are based on the curriculum developed by a group of CFS experts from across the United States and offer a basic overview of the illness. Topics include case definition, history, theories of etiology, myths surrounding CFS, diagnosis, management, disability and prognosis.

For more information, call 704-364-0466, or send an e-mail to meded@cfids.org. Details also are available online at The CFIDS Association Web site, <http://www.cfids.org/>

[profresources/print-self-study-module.asp](http://www.cfids.org/profresources/print-self-study-module.asp).

The curriculum is part of a larger provider education project created by the Association and CDC. Project representatives attend major medical conferences across the country, staffing a CFS information exhibit, sponsoring speakers and facilitating other CFS-related events.

This year, the project was promoted in advertisements placed in major medical journals — including *The Lancet*, *Annals of Internal Medicine*, the *New England Journal of Medicine*, *Mayo Clinic Proceedings* and the *Journal of Family Practice*. Promotional banner ads also have appeared online, on WebMD and other outlets. A sample advertisement appears on this page.

A curriculum for ancillary health care providers is now in development. It will target multiple disciplines, including occupational and physical therapy, counselors and other professionals in the behavioral health community.

This new curriculum will be based on the medical provider course, yet will offer an increased focus on management options for the ancillary practitioner. The new program will be available in 2004. Contact meded@cfids.org for further information. ■

Help the PERSON behind the SYMPTOMS

INCAPACITATING FATIGUE, PROFOUND EXHAUSTION, EXTREMELY POOR STAMINA, PROBLEMS WITH CONCENTRATION AND SHORT-TERM MEMORY, FLU-LIKE SYMPTOMS SUCH AS PAIN IN THE JOINTS AND MUSCLES, UNREFRESHING SLEEP, TENDER LYMPH NODES, SORE THROAT, HEADACHE, COGNITIVE PROBLEMS SUCH AS DIFFICULTIES WITH CONCENTRATION AND SHORT-TERM MEMORY, WORD-FINDING DIFFICULTIES, INABILITY TO COMPREHEND/RETAIN WHAT IS READ, INABILITY TO CALCULATE NUMBERS, IMPAIRMENT OF SPEECH AND/OR REASONING, VISUAL DISTURBANCES (BLURRING, SENSITIVITY TO LIGHT, EYE PAIN, NEED FOR FREQUENT PRESCRIPTION CHANGES), PSYCHOLOGICAL PROBLEMS (DEPRESSION, IRRITABILITY, ANXIETY, PANIC ATTACKS, PERSONALITY CHANGES, MOOD SWINGS), CHILLS AND NIGHT SWEATS, SHORTNESS OF BREATH, DIZZINESS AND BALANCE PROBLEMS, SENSITIVITY TO HEAT AND/OR COLD, ALCOHOL INTOLERANCE, IRREGULAR HEARTBEAT, IRRITABLE BOWEL (ABDOMINAL PAIN, DIARRHEA, CONSTIPATION, INTESTINAL

Chronic Fatigue Syndrome: A Diagnostic & Management Challenge

Chronic fatigue syndrome (CFS) affects at least 800,000 U.S. adults and teens with debilitating pain, exhaustion and cognitive problems.

Studies show that 80% of people with CFS have not been properly diagnosed by a medical professional. Even fewer receive appropriate medical care.

Earn Free Continuing Education Credits from CDC

Self-study courses about diagnosing and managing CFS are available in **Web-, print-, video-based formats.**

The CDC is an accredited provider of continuing education credits for various professions.

For more information:
704-364-0466
meded@cfids.org
www.cfids.org

A collaborative effort of
The Centers for Disease Control and Prevention (CDC)
and **The CFIDS Association of America**

1994 INTERNATIONAL RESEARCH CASE DEFINITION OF CHRONIC FATIGUE SYNDROME*

CFS is a syndrome characterized by fatigue that is:

- Medically unexplained
- Of new onset
- Of at least six months' duration
- Not the result of ongoing exertion
- Not substantially relieved by rest
- Causes a substantial reduction in previous levels of occupational, educational, social or personal activities

In addition, there must be four or more of the following symptoms:

- Impaired memory or concentration
- Sore throat
- Tender neck (cervical) or armpit (axillary) lymph nodes
- Muscle pain (myalgia)
- Headaches of a new type, pattern or severity
- Unrefreshing sleep
- Post-exertional malaise (lasting more than 24 hours)
- Multi-joint pain (arthralgia without swelling or redness)

Conditions that would exclude a diagnosis of CFS include other medical disorders known to cause fatigue, major depressive illness, medication that causes fatigue as a side effect, and alcohol or substance abuse.

**Fukuda et al, The chronic fatigue syndrome: a comprehensive approach to its definition and study, Ann Intern Med, 1994;121:953-59.*

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