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THE CFS
RESEARCH REVIEW

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

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AACFS Conference Highlights

New research and treatment options for chronic fatigue syndrome (CFS) were the focus at The American Association for Chronic Fatigue Syndrome's biannual scientific conference held February in Chantilly, Va.

The event featured presentations on breaking CFS research results and, for the first time, a day-long session on treatment strategies for clinicians with CFS patients. More than 190 researchers, doctors and other healthcare professionals from around the world attended the meeting.

Below is a summary of some of the key presentations given during the conference.

Epidemiology

Recent sleep research indicates that CFS patients experience true fatigue and not simply feelings of sleepiness. Elizabeth R. Unger, PhD, MD, of the U.S. Centers for Disease Control and Prevention (CDC), reported that 62.5 percent of study subjects with CFS showed non-restorative sleep, with 66.7 percent exhibiting restlessness during sleep and 33.3 percent showing insomnia. These figures compared to 2.4 percent, 9.8 percent and 0 percent of non-CFS controls who showed no signs of fatigue.

A study from the University of Medicine and Dentistry of New Jersey found that pain was a greater limiting factor than fatigue in CFS patients who report chronic impairment in their ability to perform routine domestic and work-related tasks.

Biochemistry

Suzanne Vernon, PhD, a CDC research microbiologist, and Wilhemina Behan, MD, of Glasgow University in Scotland, presented an overview of gene expression profiling. They reported that it is now possible to take blood or other tissue and apply it to a small glass slide containing more than 20,000 gene identifiers. When the samples are processed and scanned, scientists can determine which genes are turned on, off or somewhere in between. The vast array of information is specific for various states of health and disease in each individual. For example, gene profiling can now distinguish between several types of lymphoma in a patient, thereby allowing more specific treatment for the patient.

Using 25 cases of CFS supplied by the CDC, Vernon could accurately distinguish CFS from healthy controls, and seven specific genes were identified as "turned on" in the disorder. Behan, meanwhile, studied muscle biopsies of three patients with CFS and found three genes upregulated and 33 genes downregulated. Twenty-four genes were positive in controls but absent in CFS.

Patrick Gaffney, MD, of the University of Minnesota also studied gene

INSIDE

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

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profiling and found 166 genes "different" in CFS when compared to normal controls. The implication is that gene profiling might some day provide a diagnostic test, as well as a means to distinguish infectious, immunological or other causes of CFS.

Infection and Immunology

Kevin Maher, PhD, of the University of Miami Medical School, described the molecular basis of immunological defects found in CFS, including activated T cells, elevated cytokines and immunoglobulins, reduced NK cell activity, and poor delayed skin hypersensitivity. His studies concluded that perforin and granzymes (used by T-cells for killing other sick or infected cells), were depressed in the T cells of people with CFS. Also, activation of T cells is correlated with increased Interleukin 4 and decreased Interleukin 6, as typically seen in CFS patients.

Immunity in some CFS patients may be disturbed by repeated or persistent bacterial infection, according to Olof Zachrisson, MD, PhD, of Göteberg University in Sweden. He treated 51 CFS patients with a staphyloccal (bacterial) vaccine for 12 weeks, and obtained a positive response in 16 patients. There were modest decreases in pain and fatigue that correlated with antibody production in the individuals. However, the response was not maintained unless the vaccine was continued monthly. The vaccine is produced privately in Switzerland, but is neither publicly nor commercially available.

Central Nervous System

Richard H. Gracely, PhD, of the University of Michigan, presented two papers on functional MRI (fMRI), which rapidly measures cranial blood flow in response to physical challenges such as pain. His group applied thumb pain either intermittently or constantly, and obtained fMRI scans of the fibromyalgia (FM) subjects every five seconds. This demonstrated that with intermittent pain the FM patients had decreased blood flow in the cingulated, secondary somatosensory cortex, cerebellum, and insula; only patients with FM showed activation (increased flow) in the thalamus and putamen.

With constant thumb pain, FM subjects showed increased cranial blood flow in the mid-frontal gyrus and inferior frontal gyrus (Broca's speech area); only FM subjects showed activation in the caudate and lentiform areas. Only control subjects, on the other hand, had activation when the pain stimulus was released. These studies confirm that people with FM respond differently to painful stimuli than do normal controls.

New Technology

Yoshi Yamamoto, PhD, from the Educational Physiology Lab at the University of Tokyo, demonstrated that autonomic symptoms can be improved modestly by distraction with extraneous noise or electrical stimulation. That is, abnormal autonomic responses were blunted when the subject was distracted. This fits clinically because many patients report that their symptoms are not as noticeable when they are distracted by noise, bright lights, activity, commotion or discomfort; however, it was not previously clear if such stimuli

simply distracted the subject or actually improved the dysautonomia.

Physiology

Daniel J. Clauw, MD, of the University of Michigan reported that patients with CFS and FM both show higher catecholamine levels — particularly norepinephrine — than controls while performing a series of activities. These activities included pain testing, cognitive challenges and sub-maximal exercise. Clauw noted that the catecholamine responses were consistently different between the CFS and FM groups during the testing, possibly a sign that the patients have slightly different responses of the hypothalmic pituitary adrenal (HPA) axis.

This report was compiled by Charles M. Lapp, MD, an AACFS board member and founder of the Hunter-Hopkins Center, P.A., in Charlotte, N.C.; and Mark Giuliucci, editor of The CFS Research Review. ■

CONTROLLING CFS PAIN: ONE DOCTOR'S ADVICE

During a presentation on pain management in patients with CFS, Benjamin Natelson, MD, professor of neurosciences at the University of Medicine and Dentistry of New Jersey, offered pharmacological advice based on his clinical experience. Natelson said he progresses through four stages of medication, choosing drugs appropriate to each patient's presentation.

Stage One

Nonsteroidal anti-inflammatory drugs (NSAIDs): **Includes ibuprofen at maximum doses or Celebrex (200 mg twice daily). "It's a reasonable thing to try," Natelson said. "The problem with NSAIDs is that they usually don't work."**

Tricyclic antidepressants (TCAs): **Amitriptyline can be effective, particularly in patients who have trouble sleeping. Use lower doses than prescribed for depression.**

Effexor (venlafaxine): **Try this antidepressant when mood disorder is also present. The long-lasting version is best; dosage may vary from 75 mg to 225 mg once daily.**

Stage Two — Anti-epileptics

Neurontin: **" Start low and go slow" with 100 mg at bedtime for 4-5 days, increasing to 100 mg four times per day and working to 300 mg four times per day. A dose of 1,200 mg per day is the first threshold where pain relief may be noticed. Can be increased to anywhere from 2,400 mg to three grams daily.**

If this is not effective, Neurontin can be combined with Lamotrigine starting at 25 mg per day at bedtime, then increasing to 25 mg three times per day, and then increasing again to 100 mg three times per day.

Trileptal: **Start with 150 mg twice daily, and increase to 600 mg twice daily.**

Topamax: **This can be useful in patients with weight problems.**

Dr. Natelson said he usually tries at least three anti-seizure medications before moving to the next stage.

Stage Three

Plaquenil: **Used as an anti-malarial agent during World War II, this drug can raise pain thresholds. But it carries a number of difficult side effects, and can take six months for patients to decide its effectiveness.**

Tizanidine: **Start with 2 mg per day, and progress to 2 mg twice per day and then 4 mg twice per day.**

Mexelitine: **Start with 150 mg per day, progressing to 200 mg and 300 mg per day. Can go as high as 10 mg per kilogram of body weight.**

Tramadol: **In doses up to 50 mg four times daily.**

Lidocaine: **Patches may help with localized pain.**

Stage Four — Opiates

Dr. Natelson advised staying away from short-acting opiates, but said he does sometimes start with Darvon. He also will use Methadone, which is inexpensive, and MS Contin (not OxyContin, which has "street concerns" due to illegal use).

Dr. Natelson said that doctors should be careful with opiates, but should not avoid prescribing them to patients with persistent, extreme pain. " You can't be frightened," he said. " You will definitely improve that person's quality of life."

He also stressed that more research is needed into pain relief for patients with CFS. "We desperately need trials," he said. " The drug companies don't understand our patients and their need for pain relief."

—Mark Giuliucci

Research Q&A

Tilt-Test Formula: A Diagnostic Marker for CFS?

Article: Naschitz JE et al. "The head-up tilt test with haemodynamic instability score in diagnosing chronic fatigue syndrome." *Q J Med.* 2003; 96:133-142.

Synopsis: Researchers in Israel have tested the haemodynamic instability score (HIS), a formula that uses measurements taken during a head-up tilt test, to see if it can accurately distinguish patients with chronic fatigue syndrome (CFS) from controls.

The HIS reflects blood pressure and heart rate changes during the tilt test, which is used to determine the functioning of a patient's autonomic nervous system. A majority of people with CFS display some degree of autonomic dysfunction.

In this prospective controlled study, the researchers examined 40 patients with CFS and compared their HIS scores to those of 278 non-CFS subjects with conditions that included fibromyalgia, syncope, generalized anxiety disorder, essential hypertension, non-CFS chronic fatigue and Familial Mediterranean Fever (FMF). Fifty-nine healthy subjects also were compared.

The results showed that the HIS was an effective tool in differentiating CFS patients from the other study participants. Specifically, 90.3 percent of the CFS patients who completed the tilt test scored above the threshold of HIS >-0.98. This compared to 21.4 percent of the non-CFS chronic fatigue group; 17.9 percent of the syncope group; 13.2 percent of the fibromyalgia group; 11.9 percent of the healthy controls; 8.0 percent of the FMF group; and 3.6 percent of the hypertension group ($p<0.0001$ in all comparisons). Only the anxiety group (45 percent) scored at a non-significant level.

The authors write that their results suggest a definable, CFS-characteristic autonomic dysfunction may exist. They further contend that "the presence of this distinctive dysautonomia in CFS, which is not usually observed in other fatigue syndromes, lends support to the concept that CFS is a separate entity among illnesses characterized by fatigue."

Below is a brief question-and-answer session with the study's lead author, Jochanan E. Naschitz, M.D., associate professor in medicine, Department of Internal Medicine, Bnai Zion Medical Center, Haifa, Israel.

Q: What are the potential benefits of your findings to both researchers and health care providers?

Dr. Naschitz: On the head-up tilt test (HUTT), a particular dysautonomia is revealed in CFS patients that differs from dysautonomia in several other disorders. This distinct abnormality can be identified by HIS >-0.98[1]. To further support the prospect of defining a characteristic dysautonomia in CFS patients, an additional methodology was proposed to assess the cardiovascular reactivity during the HUTT.

Beat-to-beat measurements of the heart rate (HR) and the pulse transit time (PTT) were rendered. Ten-minute recording with the patient supine was followed by recording 600 cardiac cycles on tilt, i.e., five to 10 minutes. Data were processed by recurrence plot and fractal analysis. Fifty-two variables were calculated in each subject. On multivariate analysis, the best predictors of CFS were determined, and, based on these predictors, the 'Fractal & Recurrence Analysis-based Score' (FRAS) was calculated[2]. The best cut-off differentiating CFS from a mixed control population was FRAS = +0.22. FRAS >+0.22 was associated with CFS (sensitivity 70% and specificity 88%).

The possibility of distinguishing the cardiovascular reactivity of patients with CFS, with the aid of the HIS and FRAS, from reactivity in patients with other functional somatic syndromes, such as fibromyalgia[3] and neurally mediated syncope, as described above, tends to support that a CFS-characteristic dysautonomia may be operative. In summary, four cross-sectional studies[1,3-5] converge to support the existence of a distinctive disease-specific dysautonomia in CFS patients.

Therefore, we submit that the HIS and FRAS may be used, in the appropriate clinical context, to support the diagnosis of CFS, which until now, could only be subjectively inferred. A pilot study suggested that midodrine treatment, directed at the autonomic nervous system in CFS, results first in correction of dysautonomia followed by improvement of fatigue. This finding implies that dysautonomia is pivotal in the pathophysiology of CFS, at least in a large part of the patients, and that manipulating the autonomic nervous system may be effective in the treatment of CFS.

Q: How did you develop the HIS concept?

Dr. Naschitz: This question brings about nostalgia. In the late 1990s we added to the standard head-up tilt test a capnography channel to enable diagnosis of hyperventilation and called this method "capnography head-up tilt test" (CHUTT)[6,7]. (Capnography involves measuring carbon dioxide levels in the expired breath.) The CHUTT was subsequently applied to the study of CFS patients, since dysautonomia and hyperventilation were the mechanisms supposed to be involved in the pathogenesis of CFS[8].

On CHUTT, vasodepressor reaction, cardioinhibitory reaction, orthostatic hypotension, postural tachycardia syndrome, or hyperventilation occurred in only half of CFS patients. Increased lability of blood pressure (BP) and heart rate (HR) was perceived in all subjects on HUTT. However, there was no appropriate measure to express these findings. The following study was undertaken in order to define objective and precise parameters of hemodynamic instability on postural challenge. Our proposed method involves computation of BP and HR changes during HUTT, followed by processing of the data by novel image analysis methods. An equation was deduced to calculate the hemodynamic instability score (HIS) in the individual patient: HIS = 64.3303 + (SYST-FD.abs x -68.0135) + (SYST-SD.cur x 111.3726) + (HR-SD.cur x 60.4164). The best cut-off differentiating CFS from healthy was –0.98. HIS values >-0.98

were associated with CFS (sensitivity 97% specificity 96.6%). The drawback of the HIS is the prerequisite that 30 minutes of HUTT is completed. If the tilt is prematurely terminated because of a symptomatic event, as it occurs in almost one third of CFS patients, the HIS cannot be computed.

Subsequent studies validated the HIS[3,4], improved the technique[5], shortened the duration of the tilt phase, thus practically eliminating tilt drop-outs[2].

Q: What comes next for you and your research team?

Dr. Naschitz: First, treatment of CFS by manipulating the autonomic nervous system. We hypothesized that midodrine treatment could benefit patients with the CFS. Ten patients with CFS and five control patients with non-CFS fatigue were studied. The patients were off medications for at least two weeks before entering the study. A dysautonomic reaction on HUTT (i.e., HIS >-0.98) was present in all CFS but not in the non-CFS control patients. With midodrine treatment, six of 10 CFS patients showed subjective and objective improvement, which was maintained during 12 months of treatment. On last HUTT the average HIS was -1.51 (range from -0.87 to -1.98). Non-CFS fatigue patients, with normal HIS at baseline, had no improvement in HIS and fatigue scores while taking midodrine[9]. Results of this pilot study spurs larger prospective studies on the principle of manipulating the autonomic nervous system to improve both dysautonomic phenomena and fatigue in CFS.

Second, separating fibromyalgia from CFS. Distinction between fibromyalgia and CFS could be possible based on their cardiovascular reactivities.

Third, developing an objective test in support of the diagnosis of FMF based on its specific cardiovascular reactivity. Finally, examination of additional groups of patients with "somatic functional syndromes" in searching for disease-specific cardiovascular reactivity patterns.

Editor's note: The authors acknowledge limits to their present study. Fifty-six HUTT examinations were terminated because of syncope or presyncope, including nine in the CFS group.

Notes

1) Naschitz JE et al. Hemodynamic instability in chronic fatigue syndrome: indices and diagnostic significance. *Semin Arthritis Rheum*. 2001;31:199-208.

2) Naschitz JE, Sabo E, Naschitz S, Rozenbaum M, Rosner I, Musafia-Priselac R, Shaviv N, Ahdoot A, Ahdoot M, Gaitini L, Eldar S, Yeshurun D. Fractal Analysis and Recurrence Quantification Analysis of Heart Rate and Pulse Transit Time for Diagnosing Chronic Fatigue Syndrome. *Clin Autonomic Res*. 2002;12:264-272.

3) Naschitz JE, et al. Cardiovascular response to upright tilt in fibromyalgia differs from that in chronic fatigue syndrome. *J Rheumatol*. 2001;28:1356-1360.

4) Naschitz JE, Sabo E, Naschitz S, Rosner I, Rozenbaum M, Fields M, Isseroff H, Musafia Priselac R, Gaitini L, Eldar S, Zukerman E, Yeshurun D. Hemodynamic Instability Score in Chronic Fatigue Syndrome (CFS) and non-CFS Chronic Fatigue. *Semin Arthritis Rheum*. 2002;32:141-148.

5) Naschitz JE, Rosner I, Rozenbaum M, Naschitz S, Shaviv N, Fields M, Isseroff H, Zuckerman E, Yeshurun D, Sabo E. The head-up tilt test with hemodynamic instability score in diagnosing chronic fatigue syndrome. *Q J Med.* 2003;96:133-142.

6) Naschitz JE, Gaitini L, Eridzhanyan L, Keren D, Sabo E, Yeshurun D, Hardoff D, Yaffe M. The capnography tilt test for the diagnosis of hyperventilation syncope. *Q J Med.* 1997;90:139-145.

7) Naschitz JE, Hardoff D, Bystritzki I, Yeshurun D, Gaitini L, Tamir A, Yaffe M. The role of the capnography head-up tilt test in the diagnosis of syncope in children and adolescents. *Pediatrics*. 1998:101:1-6.

8) Naschitz JE, Rosner I, Rosenbaum M, Gaitini L, Bistritzki I, Zuckerman E, Sabo E, Yeshurun D. The capnography head-up tilt test for evaluation of chronic fatigue syndrome. *Semin Arthritis Rheum*. 2000;30:79-86.

9) Naschitz JE, Rosner J, Rozenbaum M, Musafia Priselac R, Sabo E, Gaitini L, Eldar S, Zukerman E, Yeshurun D. Successful Treatment of Chronic Fatigue Syndrome with Midodrine: a Pilot Study. *Clin Exp Rheumato.* In press. ■

New Canadian CFS Guide Stresses Options for Clinicians

By Mark Giuliucci

A new clinical case definition for chronic fatigue syndrome (CFS) could speed patient diagnosis and help establish the illness as a distinct medical entity, according to the document's authors.

The expert consensus document was created under the auspices of Health Canada, the Canadian national health ministry. The 11 co-authors wrote the guidelines after soliciting advice and guidance from experts and patients across the world. The author list includes noted CFS researchers and practitioners such as Daniel L. Peterson, MD; Nancy Klimas, MD; Kenny De Meirleir, MD, PhD; and A. Martin Lerner, MD.

The new document is titled, "Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols." It is designed for use by primary care physicians, nurses, therapists and others who diagnose and treat patients with CFS. CFS is also known as Myalgic Encephalomyelitis, or ME.

Currently, the most widely accepted definition of CFS is the 1994 International Research Case Definition, also known as the Fukuda Criteria (see back page). It was intended for use by researchers to standardize study populations and protocols, but also is used by clinicians to diagnose CFS in patients. The Canadian document seeks to replace the Fukuda standards in clinical settings.

The Canadian panel's clinical definition re-prioritizes many of the symptoms in the 1994 case definition. According to the new definition, patients must meet each of these four criteria:

- ***Fatigue.*** Must have a "significant degree" of new onset, and be unexplained, persistent, or recurrent physical or mental fatigue that substantially reduces activity level.
- ***Post-Exertional Malaise and/or Fatigue.*** Patients must show "inappropriate" loss of physical and mental stamina, among other factors. There also must be a "pathologically slow" recovery period, usually lasting at least 24 hours.
- ***Sleep Dysfunction.*** Patients must exhibit unrefreshing sleep, or have disturbance in either sleep quantity or rhythm.
- ***Pain.*** There must be a significant degree of myalgia. It can be in muscles and/or joints, and may be accompanied by headaches of a new type, pattern or severity.

In addition, patients must have two or more "neurological/cognitive manifestations," including confusion, impairment to concentration and short-term memory, disorientation, perceptual and sensory disturbances and other symptoms.

Finally, the patient must exhibit symptoms from two of the following three categories:

- ***Autonomic.*** Includes, among other conditions, orthostatic intolerance, postural orthostatic tachycardia syndrome (POTS), extreme pallor, nausea and irritable bowel syndrome.
- ***Neuroendocrine.*** Includes loss of thermostatic

stability, sweating, marked weight change, loss of adaptability and worsening of symptoms with stress.

- ***Immune.*** Includes tender lymph nodes, recurrent sore throats and/or flu symptoms, and sensitivities to foods, medication or chemicals.

All of these symptoms appear in the 1994 case definition. But in that definition, fatigue is the only main symptom, and must be accompanied by four or more of a group that includes the other categories listed above. The secondary symptoms are not listed under headings such as "autonomic" or "immune" in the 1994 definition.

In both definitions, fatigue must persist for at least six months before a diagnosis of CFS can be considered.

The study's lead author says the new definition will save time and suffering in the patient population. "The clinical definition will enable clinicians to make an early diagnosis which may assist in lessening the impact of ME/CFS in some patients," said Bruce M. Carruthers, MD. "It will reduce the expensive problem of patients being sent to many specialists before being diagnosed and will allow patients to receive appropriate treatments in a timely fashion."

Emphasis on treatment

The main body of the new document deals with treatment protocols. The authors stress that patient support and well-being are the "top priorities" during treatment, and also call for ample patient education, individualized treatment plans and patient participation.

"The goal of a management/treatment program is to empower the patient by encouraging them to trust their own experiences, to enhance the patient's awareness of the activities and environments in which they can cope without exacerbating symptoms and pace themselves accordingly," the document says. "The program should aim at optimizing the patient's ability to maintain function in everyday activities, being as active as possible within their boundaries, and then gently extending those boundaries."

The guidelines also stress the importance of dietary, sleep and movement/ergonomic habits. In addition, the authors include an extensive drug protocol for dealing with various symptoms — including sleep disturbance, pain, fatigue, cognitive dysfunction, psychiatric co-morbidities such as depression and anxiety, and immune dysfunction.

The Canadian clinical case definition is the third created in the past year. Other versions were written under the auspices of the British and Australian governments. The British definition met with strong resistance from patient advocates after its release. They argued that the document over-emphasized psychological aspects of CFS/ME and treatments such as graded exercise therapy and cognitive behavioral therapy (CBT).

The Canadian version lists these therapies, but also mentions their shortcomings. While CBT can offer coping mechanisms to improve quality of life for CFS patients, claims that it could be potentially curative are "objectionable" and "far from being confirmed," the authors write.

Klimas says she is pleased with both the way the guidelines were created and the information they contain. "The process used to write the clinical definition was truly collaborative, involving representatives of the research

community, the medical profession, and patient advocates," she says. "I believe that it will be very useful in educating clinicians about the pathogenesis of CFS, thanks to the inclusion of sections on autonomic, neuroendocrine and immune-related symptoms. It should also help to validate patients' experience and the serious impact CFS has on their lives."

Research considerations

While intended mainly as a guide for health care practitioners, the Canadian document also may have long-term ramifications for the research community. The revised definition criteria tend to select a slightly different patient spectrum than the one created by the 1994 case definition.

DePaul University researcher Leonard Jason, PhD, has examined the new criteria and made some preliminary comparisons. In general, Jason says, the Canadian document selected patients with less psychiatric co-morbidity, more physical functional impairment and more fatigue/weakness, neuropsychiatric and neurologic symptoms than those identified by either the 1994 case definition or the earlier 1988 (Holmes) criteria.

Jason says the Canadian clinical criteria "appear to select a more symptomatic group of individuals than the CFS criteria, and these individuals do demonstrate less current and lifetime psychiatric impairment than those selected according to the CFS criteria."

The three patient groups showed no differences in sociodemographic levels, according to Jason's research, which was presented to the Dutch ME Foundation in April.

Both the 1994 and Canadian definitions would be improved if more attention was devoted to developing operationally explicit, objective criteria and standardized interviews, Jason says.

Mark Giuliucci is editor of The CFS Research Review.

Carruthers B et al. "Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols." J Chronic Fatigue Syndrome. *2003;11(1):7-115.* ■

CFS Case Study: Diagnostic Basics

Below is a case study adapted from "Chronic Fatigue Syndrome: A Diagnostic & Management Challenge," a CFS curriculum for primary care providers. The program can be used by physicians, nurses and physician assistants to earn continuing education credits. For more information on the program, visit http://www.cfids.org/resources/print-self-study-module.asp*, or contact Terri Lupton, coordinator for educational opportunities at The CFIDS Association of America, at* tlupton@cfids.org.

Patient description: Rita is a 57-year-old white female who works part time as a receptionist at a beauty salon.

Chief complaint: "I am always exhausted and never really feel well. I have difficulty remembering things, like what I need when I'm at the grocery store."

History of present illness: She describes the onset of her illness as occurring at age 43. Her symptoms began with a viral illness, e.g., fatigue, muscle and joint pain and upper respiratory symptoms. She also noted difficulties with concentration and increasingly severe allergies. Sometimes she feels nearly normal for months at a time, but then her symptoms return and she has difficulty managing family responsibilities. Spring and summer are her most severe periods. She has no history of depression, but states that her mood can be sad or even hopeless after several months of unremitting symptoms.

Currently, she has had a lot of symptoms and has been unable to work more than 20 hours a week. Forgetfulness, worsening pain in the hips, knees and lower back, difficulty falling asleep after waking during the night and awakening utterly exhausted in the morning are the most disabling symptoms. Light activity such as an hour of shopping or handling errands leads to increased fatigue and a sore throat for the next 1–2 days.

Question: What are some of Rita's symptoms that could indicate chronic fatigue syndrome (CFS), based on the 1994 international case definition (see back page)? *(Select all that apply.)*

A) Joint and muscle pain
B) Sore throat
C) Seasonal nature of symptoms
D) Disturbed sleep
E) Post-exertional malaise that lasts for 1–2 days
F) Lower back pain
G) Substantial impairment in short-term memory or concentration

Answer: A, B, D, E, G

Of the eight symptoms that are described by the 1994 case definition, Rita currently reports having six: joint pain, muscle pain, sore throat, disturbed sleep, post-exertional malaise and substantial impairment in short-term memory or concentration. The other two symptoms in the case definition, headaches of a new type and severity and tender lymph nodes, are elicited during the review of Rita's symptoms and the physical exam.

Question: Which one of Rita's symptoms is relatively unique to CFS?

A) Joint & muscle pain
B) Sore throat
C) Disturbed sleep
D) Post-exertional malaise that lasts for 1–2 days
E) Fatigue

Answer: D

Post-exertional malaise is one of the hallmarks that should lead a provider to suspect a diagnosis of CFS. Typically the patient describes 1–2 days of increased malaise and symptoms following even slight overexertion. Additional symptoms can indicate other illnesses ranging from Lyme disease to cancer, but the post-exertional malaise is fairly specific to CFS.

The provider taking the history should examine the nature of the "fatigue." In people with CFS, fatigue is typically exacerbated by physical or mental tasks previously achieved with ease. Recovery from periods of worsened fatigue can take days. Pathological fatigue can be differentiated from somnolence (because it is not relieved by sleep) and from neuromuscular weakness (because people with CFS can generate muscle strength and endurance when circumstances demand a response).

Question: Which one of these CFS symptoms contributes to worsening of others and should be addressed even before a firm diagnosis can be established?

A) Muscle pain

B) Sore throat

C) Disturbed sleep

D) Headaches

E) Fatigue

Answer: C

Disturbed sleep, described often as unrefreshing sleep, is very common in people with CFS and is shown in various studies to exacerbate other symptoms such as musculoskeletal pain, irritability and problems thinking.

Although patients with CFS usually report an increased total sleep time, sleep is typically broken and nonrestorative. Also common are frequent napping during the day and a change in circadian rhythm, i.e., a late-night to late-morning sleep cycle.

Restoration of refreshing sleep is a goal of management in the patient with CFS. This goal may be achieved by establishing proper sleep hygiene through:

- Avoiding daytime naps, especially late in the day
- Scheduling even gentle exercise activities at least 3–4 hours before bedtime
- Establishing a regular bedtime and waking routine
- Limiting food intake for the two hours prior to bedtime
- Using analgesics or non-steroidal anti-inflammatory drugs for relief of musculoskeletal pain or headache.

Review of symptoms

Headache: Occurs three or four times per week, usually begins at work, frontal pressure, takes Tylenol Sinus for headaches with modest relief.

Sore throats: Occasional, during episodes of most severe fatigue.

Cough: Occasional morning cough, nonproductive, and clears with the first morning coffee.

Chest: No wheezing or pain.

Cardiovascular: Palpitations at night occasionally, sometimes while standing for lengthy periods.

Abdomen: Diagnosed to have irritable bowel, reflux; taking both Axid (nizatidine) and Donnatal.

Genito-urinary: Frequent urinary tract symptoms, cultures always negative.

Extremities: Pain in lower extremity increases when standing for long periods, pain on right side on awakening, improved in one to two hours.

Neurological: Notes at the onset of the illness she had vertigo that persisted for two or three months.

Current Medications

Donnatal, Axid (nizatidine, Tylenol Sinus, Xanax (alprazolam) 0.5 mg hs, Prozac (fluoxetine hydrochloride) 10 mg, Synthroid (levothryoxine sodium) 0.125, antacids, multi-vitamins, vitamin C 4g, St. John's wort, ginkgo biloba, Echinacea.

Question: Given Rita's symptoms, what are some disorders and conditions that would need to be ruled out before making a diagnosis of CFS? *(Select all that apply.)*

A) Muscle weakness (neuromuscular disease)

B) Dyspnea and effort intolerance (cardiac or respiratory disease)

C) Somnolence (primary sleep disorders)

D) Autoimmune diseases

E) Major depression as the primary cause of fatigue and cognitive problems

Answer: All of the above.
Neuromuscular disease causing muscle weakness, and cardiac or respiratory disease causing dyspnea and effort intolerance, can present like CFS. Somnolence, primary sleep disorders and chronic sleep deprivation also cause some similar symptoms. Early symptoms of autoimmune diseases such as systemic lupus erythematosus, multiple sclerosis, Sjogren's syndrome and rheumatoid arthritis may mimic CFS symptoms and tend to evolve slowly. Providers considering a diagnosis of CFS should monitor changes in symptoms over time and should continuously rule out these and other serious illnesses in their patients.

Distinguishing CFS from major depression is one of the most difficult differential diagnoses to make. Major depression generally leads to a loss of motivation and pleasure and rarely includes physical symptoms such as sore throat, muscle and joint pain and fever. The 1994 international case definition recognizes that depression can occur with CFS but excludes those with a history of melancholic major depression or severe psychiatric disorders for research purposes.

Physical findings

Vitals: BP 140/85; pulse 78 sitting; temperature 98.4

Weight: 210 pounds (has gained 25 lbs. since hysterectomy)

Head, eyes, ears, nose, throat: Nasal turbinates boggy; slightly tender, enlarged lymph nodes

Lymphatic: Some axillary tenderness without adenopathy

Chest: Clear

Heart: No murmur

Abdomen: Nontender, hyperactive bowel sounds over right lower quadrant

Extremities: No edema, some numbness in median nerve

Musculoskeletal: 11 of 18 fibromyalgia tender points present; Thenar wasting right hand with pain on range of motion; osteoarthritis in left hand

Neurological: Mini mental exam score: low normal.

Cranial nerve: 2–12 intact, some difficulty with tandem gait, heel to toe. Reflexes normal throughout, muscle strength 3 of 4 in large muscle groups of legs, stands by pulling up from chair.

Question: What conditions may co-exist with CFS? *(Select all that apply.)*

A) Fibromyalgia

B) Exposure to chemicals or toxins causing increased sensitivity to these substances

C) Other adequately treated disorders, such as hypothyroidism

Answer: All of the above
All three of these conditions may co-exist with CFS,

even under the strict 1994 case definition. Fibromyalgia is associated with a number of symptoms that overlap with CFS, including prolonged fatigue, cognitive dysfunction and widespread muscle pain. A hallmark of fibromyalgia is the presence of at least 11 of 18 discrete tender points that hurt when mild pressure is applied.

Sensitivity to various chemicals and environmental toxins such as solvents, pesticides or heavy metals is often associated with CFS.

If a physician can verify that another disease process has been treated adequately and yet symptoms of CFS persist, a diagnosis of CFS should be considered. For example, if hypothyroidism is adequately treated with replacement thyroid hormones but relevant symptoms continue, an additional diagnosis of CFS may be made.

Question: Based on the history and physical exam, what laboratory tests are appropriate to rule out other causes of symptoms? *(Select all that apply.)*

A) Full blood count and ESR

B) Serum electrolytes, calcium and creatine

C) Liver function tests

D) Thyroid function tests

E) Urinalysis for blood, protein and sugar

Answer: All of the above
Full blood count and ESR can rule out anemia or trigger a search for other evidence of autoimmunity or chronic infection. Serum levels of electrolytes, calcium and creatine help rule out metabolic and renal disorders. Biochemical liver function tests help evaluate possible underlying liver disease. Thyroid function tests will help detect either hypothyroidism or hyperthyroidism as the cause of symptoms since either may present in a very similar fashion to CFS; however, hypothyroidism may co-exist with CFS. Urinalysis for blood, protein and sugar can assist in ruling out common medical conditions, which could explain fatigue and other symptoms.

Results of medical tests ordered after the initial patient visit

CBC: Hgb 12.2; HCT 39; MCV 89

Chem 23: normal with exception of mildly elevated SGOT

ANA: 1:20, rheumatoid factor negative, ESR=3

Thyroid function tests: normal

IgE: 125

IgG, A, M: normal range

Chest X-ray: no acute infiltrates

EKG: normal sinus rhythm, rate 73

Assessment

- CFS
- Fibromyalgia (although diagnosis confounded by overall use of medications)
- Dysuria (may be secondary to vitamin C excess)
- Allergic overlay likely, elevated IgE and allergic rhinitis/sinusitis on physical exam
- Overlay of depression
- Significant cognitive complaints warrant neurocognitive assessment

Management of patient should begin with treatment of allergies and sleep disturbances. Referral to specialist for neurocognitive assessment may yield findings important for any future disability claim, as well as rehabilitation strategies.

An understanding, empathetic approach by the provider can be very important in establishing coping strategies that help the patient to lead as full a life as possible within the limitations imposed by the illness. ■

No link between BHR, RNase L ratio

A CFS-related change in the body's antiviral pathway appears not to be responsible for the high percentage of CFS patients with bronchial hyperresponsiveness (BHR), according to new research from Belgium.

The study focused on 137 CFS patients, seventy-three of whom presented with BHR. This percentage is comparable to earlier research that found 60 percent of CFS patients showed signs of BHR.

All subjects were tested for the ratio between two different forms of RNase L, a key protein in the antiviral pathway. Many people with CFS have two forms, the normal 83 kilodalton (kDa) version and a lighter, 37 kDa type that is formed by the cleaving of the 83 kDa protein.

The researchers report no differences in the 83 kDa/37 kDa ratio between the BHR and non-BHR patients. There also were no differences in total lung capacity or forced expiratory/forced vital capacity measures. These results, the authors write, "refute any association" between the RNase L ratios and BHR.

Study results did indicate that CFS patients with BHR showed an overall higher immune system activation level than those without BHR.

Nijs J et al. "Associations Between Bronchial Hyperresponsiveness and Immune Cell Parameters in Patients with Chronic Fatigue Syndrome." Chest. *April 2003;123: 998-1007.*

Brain metabolism different in CFS

Research from Scotland finds that patients with CFS may show different metabolism characteristics than controls in the left basal ganglia region of the brain.

Eight patients with CFS and no psychiatric co-morbidity were tested for metabolic activity using proton magnetic resonance spectroscopy (H MRS), a relatively new tool for measuring brain function. Compared to controls, the patient group showed elevated levels of choline-containing compounds in the basal ganglia.

This could be an indication of higher cell membrane turnover or changes in the signaling process between separate membranes, the authors say. It is not understood why this may happen — although some researchers speculate that exposure to infectious agents or neurotoxins may result in such increased activity.

Chaudhuri A et al. "Proton magnetic resonance spectroscopy of basal ganglia in chronic fatigue syndrome." NeuroReport. *2003;14(2):225-8.*

Tilt-test studies show mixed results

Researchers may be able to differentiate female CFS patients from healthy controls using a measurement taken during the head-up tilt test.

The tilt test is commonly given to people with suspected autonomic disorders; a large percentage of CFS patients have such conditions. However, symptom presentation during the test has not proven effective in separating CFS patients from controls.

But new research has found that measuring heart rate variability (HRV), specifically a decrease in the aperiod fractal component of HRV, can be used to differentiate the patient population. In this study of 24 female CFS patients and 22 controls, researchers reached sensitivity and specificity measures of 90 percent and 72 percent, respectively.

Yamamoto Y et al. "A measure of heart rate variability is sensitive to orthostatic challenge in

women with chronic fatigue syndrome." Exp Biol Med. *Feb. 2003; 228(2):167-74.*

In a separate study, researchers conclude that CFS patients do not have a distinctive pattern of regional cerebral blood flow when placed under orthostatic stress.

This study, from Johns Hopkins University, looked at 26 patients with CFS and 23 controls. Researchers measured blood flow volume in the middle cerebral artery (MCA) at six points during tilt-table testing. The overall results found no significant variation between the two test groups.

Some researchers have speculated that changes in regional cerebral blood flow, as measured in the MCA, may be a hallmark of CFS. In general, CFS patients do show higher rates of neurally mediated hypotension and postural tachychardia syndrome than healthy controls on tilt testing.

Razumovsky AY et al. "Cerebral and systemic hemodynamics changes during upright tilt in chronic fatigue syndrome." J Neuroim. *Jan. 2003;13(1):57-67.*

For more information on tilt testing, please see the related story on p.4.

NIH to Host CFS Research Workshop

"Neuro-Immune Mechanisms and CFS: Will understanding central mechanisms enhance the search for the causes, consequences and treatment of CFS?"

The Office of Research on Women's Health (ORWH) of the National Institutes of Health (NIH) will host a scientific workshop designed to enhance understanding of chronic fatigue syndrome by examining the interface between the brain, immune system and symptoms of CFS and related disorders. The workshop will be held June 12-13, 2003 at the Bethesda Marriott Hotel. Dr. Leslie Crofford of the University of Michigan and Dr. Dedra Buchwald of the University of Washington will chair.

Scientists from NIH and academic institutions, representing diverse disciplines, will explore the mechanisms by which hormones, cytokines and other mediators act as intermediaries between the brain and other body systems. The potential application of new technologies in the study of these mediators and their central and peripheral actions will also be discussed. NIH intends for these deliberations to form the basis for future interdisciplinary initiatives.

Presentations will be given on the HPA axis, autonomic nervous system, neuroactive drugs, sleep, imaging studies (including PET and functional MRI scans), genomics and more. Dr. Vivian Pinn, ORWH director, will deliver opening remarks followed by introductory talks by Drs. Crofford and Buchwald.

The meeting has been organized by ORWH and the Trans-NIH Working Group for Research on CFS. Continuing medical education units will be available to medical professionals. For additional information, visit *www4.od.nih.gov/orwh/*. ■

NOTE TO READERS

Beginning with this issue, *The CFS Research Review* will be published on a twice-yearly schedule. The next issue will be mailed this fall. The *Review* also has changed from a 12-page to a 16-page format, to allow for more in-depth coverage of CFS issues. Thank you for your continued support.

—Editor

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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.*