

SICK AND TIRED

Imaging techniques help unravel the mystery of chronic fatigue syndrome

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— Benjamin Natelson, MD

*by Denise Leathers
RT Image Assistant Editor*

It all started out innocently enough back in September 1988. Priscilla deLeon, RT, had a bad case of the flu — aches and pains, sore throat, fever — the works. “Oh well,” she thought to herself, “nothing to worry about.” In fact, a few days of bed rest might be just what she needed to shake off the suffocating blanket of fatigue that suddenly seemed to have settled over her body.

But as the days stretched into weeks, the mysterious illness showed no signs of relenting; the antibiotics prescribed by her physician proved ineffectual against the potency of the disease. If anything, said deLeon, the sickness seemed

to have really taken hold, wresting control over her own body from her and robbing her of all energy. Clearly, this was no ordinary case of the flu.

“It got to the point,” she recalled, “that my alarm went off in the morning, and I opened my eyes to look at it but didn’t even have the energy to lift my hand and turn it off, let alone get dressed and go to work.

“I felt like I had been run over by a Mack truck and then flattened by a steam roller. Everything hurt.”

Each task, no matter how minute, came to represent an epic struggle between deLeon’s will and the sheer strength of her illness. But more often than not, she said, the disease won out.

Stairs were now a major source of concern, an obstacle that had to be overcome. Just the thought of writing out a check to pay a bill was often too overwhelming to even consider. And completing a load of laundry was a seemingly insurmountable task.

“When I had dirty laundry that just had to be done,” explained deLeon, “I would throw it over the balcony to get it from the second floor to the first floor. Then, I’d kick it down the cellar steps to where the washer and dryer were. Finally I’d sit down at the top of the stairs and slide myself down, step by step, to the basement. One load a day got done this way. Maybe.”

After tests for everything from strep throat to toxoplasmosis

came back negative, deLeon was finally able to put a name to the illness that had turned her life upside down. A test for the Epstein-Barr virus, which also causes infectious mononucleosis, came back positive.

Later that same year, however, when it was discovered that EBV is only one of many potential causes of the disease, the name of her illness was changed from chronic Epstein-Barr syndrome to chronic fatigue syndrome — a label that reflects the illness' most serious consequence.

Although outbreaks of CFS-like diseases have been reported around the world since as early as 1750, the first modern-day U.S. epidemic originated along the shores of Lake Tahoe in Incline Village, NV, in 1983. More than 200 people there suffered from an unexplainable debilitating illness characterized by persistent, crippling fatigue and accompanied by a wide variety of secondary symptoms.

Although tens of thousands of Americans have fallen victim to CFS over the past decade, no one knows exactly how many have contracted the baffling disease. The only study of its kind to date estimates that 4 of every 10,000 — or nearly 100,000 — Americans suffer from CFS. Surveillance studies currently underway in four U.S. cities should provide additional demographic information, although researchers have already discovered that three of every four CFS victims are female.

PHYSICIAN ATTITUDE. Called "the Rodney Dangerfield of dis-

eases" by some, CFS has traditionally gotten little respect from the medical community, some of whom have labeled it a mental rather than physical illness. Feminists have theorized that because the majority of CFS sufferers are women, physicians tend to dismiss their symptoms as little more than depression or hysteria. "It's all in your head," said deLeon, is an all-too-common diagnosis.

"I walked into a gastroenterologist's office for an exam," she reported, "because I'd been having symptoms of irritable-bowel syndrome — a common side effect of CFS. But after I told him my history, he practically laughed in my face. He told me that all I needed was more fiber in my diet and that I should become more socially active and just get on with my life."

One reason for physician skepticism is the lack of a "smoking gun," according to Benjamin Natelson, MD, director of the CFS Center at the New Jersey Medical School, one of three National Institutes of

Health-funded centers studying the causes of CFS.

Results of standard medical tests on even the sickest CFS patients — those so weak that they're confined to wheelchairs — often come back normal, said Natelson. "Physicians are so used to demanding something specific — a smoking gun — before making a diagnosis that when there's no usable lab test, they tend to dis-

miss the patient and his or her symptoms.

"That's an example of physician arrogance," he continued. "To me, it doesn't seem appropriate to discard a patient, to say there's noth-

ing wrong, just because you can't find an abnormal test."

SEARCHING FOR CLUES. The growing search for a smoking gun has led researchers in various directions, deepening the mystery while providing tantalizing glimpses into what may cause the disease. Some believe CFS represents an immunological dysfunction, others say it's infectious, while still others claim it's psychological.

According to Natelson, for example, there's growing evidence that CFS is caused by an immune system "gone a little bit wild." In certain patients with CFS, he explained, virus-killing cells activated by the onset of an infection fail to turn themselves off after the danger has passed, continuing to churn out immunologically active agents called cytokines. As a result, patients with CFS frequently display abnormally high levels of these immune proteins.

When given as drugs, explained Natelson, these same proteins reproduce many of the symptoms of CFS in healthy patients, leading researchers to believe that an overactive immune system may be the culprit.

In addition, NIH researchers have reported that some CFS patients have abnormally low levels of both cortisol and corticotroin-releasing hormones. Deficient amounts of cortisol, the hormone responsible for suppressing the immune system in healthy individuals, could account for the high levels of virus-killing cells among CFS sufferers. On the other hand, low levels of CRH, which may stimulate energy production, could explain the overwhelming sense of fatigue experienced by most CFS patients.

Other studies have pinpointed a number of viruses that may play a role in CFS. Researchers have found high levels of antibodies to the Epstein-Barr virus, once thought to be the cause of CFS, in

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Health-Care Workers and CFS: An Unlikely Pair?

If membership in various chronic fatigue syndrome support groups is any indication, CFS appears to be more prevalent among health-care professionals than the normal population.

A trend also observed by the national Centers for Disease Control and Prevention, which once planned to study the phenomenon after being flooded with reports of CFS among health-care workers, the apparently high incidence was recently studied by Leonard A. Jason, PhD, of DePaul University in Chicago.

According to Jason, health-care workers may be more susceptible to CFS because "health-care professionals often get involved in shift work. And in shift work, you're basically throwing your biological rhythms off, and that tends to be stressful to the immune system."

In addition, he remarked, those working in hospital settings are often exposed to a variety of viruses. Many researchers have implicated viruses as likely CFS causes. A third risk factor, according to Jason, involves the stresses associated with physician dominance and working in an environment where life-and-death situations are commonplace.

In a nationwide survey of several thousand nurses, a group believed to be at especially high risk for CFS, Jason discovered that the prevalence of the disease among nurses is at least 100 times the 4 to 6 cases per 100,000 reported by the CDC.

"We wanted to find a group that had a high rate of risk for CFS and we really picked it," said Jason. "We could write a book on the things that we're learning from nurses around the country."

Jason acknowledged, however, that his criteria were somewhat less rigorous than the CDC's. "The CDC's definition of CFS is beginning to be re-examined," he explained. "For research purposes, it is considered very narrow." Using a slightly broader definition of the disease, said Jason, prevalence among even normal populations is at least two times higher than previously believed.

One of the problems with CDC figures, said Jason, is the fact that they were solicited from physicians, not CFS sufferers themselves. "A lot of physicians don't believe that CFS exists," he remarked, "and a lot of people don't have physicians. If you base your rates on physicians as gatekeepers, you're going to underestimate the disease."

In his survey, Jason sampled nurses directly. Nearly 75 out of approximately 3,400 surveyed indicated that they may have the disease. "That doesn't mean that they do have it," he remarked, "but the point is that this isn't just a blip; there are a lot of nurses out there who are sick."

Reliable rates on CFS prevalence are important, said Jason, "because you can do public-health planning only if you have a sense of how many people are sick."

— Kevin Crawford

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the systems of some patients. Others have elevated levels of antibodies to different viruses, including the human herpes virus 6, which has been found in active form in 70 percent of all CFS sufferers vs. 20 percent of healthy individuals.

Additional viruses implicated as potential causative agents include the retrovirus HTLV-2, the Cocksackie B virus and a spumavirus not previously linked to disease in humans.

THE NUCLEAR MEDICINE CONNECTION. Although much of the

research into the causes of CFS has taken place in the laboratory, the growth of nuclear medicine has allowed imaging experts to play an active role as well, taking the study of CFS in an entirely new direction.

According to Ismael Mena, MD, director of nuclear medicine at Harbor-UCLA Medical Center and a professor of radiological sciences at the UCLA School of Medicine, SPECT brain scans of CFS patients indicate that the disease may be grounded in a neurological dysfunction.

In studies comparing the SPECT brain scans of elderly CFS sufferers to those of normal controls, Mena and colleagues found that CFS patients demonstrated markedly diminished cerebral blood flow in both the right frontal and right temporal lobes.

Cerebral blood flow is significant, said Mena, because it correlates directly with brain function. If blood flow to a particular area of the brain is reduced, he explained, the function of that area will likely be impaired. Conversely, if brain tissue has been damaged due to trauma, inflammation or a tumor, for example, blood flow will be down-regulated because the need for blood in that area, which is now functioning less, would be decreased.

"Very frequently," said Mena, "CFS patients exhibit symptoms — ranging from cognitive abnormalities, such as memory disturbances, to feelings of tiredness — related to the abnormalities in blood flow that we're seeing in the right frontal and right temporal lobes."

Mena and fellow CFS researcher Jay Goldstein, MD, director of the CFS Institute and a clinical instructor of medicine at UC Irvine and UCLA, are currently using SPECT to examine the neurological effects of exercise on CFS patients. Soon-to-be published results indicate that cerebral blood flow becomes even further diminished with exertion.

"What we've seen," said Mena, "is that many of the patients first

get abnormally tired after exercise. This then correlates with further diminution of function in the areas of the brain that are already impaired."

"The problem isn't with the heart, the lungs or the muscles," added Goldstein. "It's with the brain. The brain inappropriately perceives fatigue after only minimal exertion."

THE LIMBIC SYSTEM. According to Goldstein, CFS is essentially a regulatory disorder involving a part of the brain called the limbic system. It's this system that regulates blood flow to various regions of the brain.

"The limbic system works like a computer," said Goldstein. "It receives sensory information from outside the body and then integrates that data with one's experiences and attitudes to choose a response that would be most adaptive to a particular situation."

One of the limbic system's most important duties, said Goldstein, is maintaining homeostasis. In its efforts to keep the body on an even keel, he explained, the limbic system regulates various bodily processes including fatigue, pain, sleep, weight, appetite, temperature, pulse, respiration, moods, memory, the immune system and hormones.

"If the limbic system doesn't work right," continued Goldstein, "any or all of those processes could be disregulated."

But what causes the limbic system to break down in the first place? According to Goldstein, not one but a variety of different factors — ranging from a genetic predisposition or head trauma to a viral infection, physical or emotional stress or exposure to toxic substances — could result in damage to the limbic system.

"Whatever the cause," said Goldstein, "the mechanism for generating symptoms is limbic dysregulation." Symptoms can take such a variety of forms, he added,

"because the limbic system regulates so many different things.

"I think that would explain the many variations of the disease," said Goldstein, "as well as the spectrum of symptoms that includes everything from thyromyalgia and migraine headaches to allergies, asthma and even irritable-bowel syndrome."

THE NEXT STEP. Although SPECT is considered the most promising modality in the continuing study of CFS, PET and MRI have also added valuable information.

PET studies of the motor areas of the cortex, for example, have shown CFS sufferers to have decreased blood glucose metabolisms relative to normal controls, while MRI scans have revealed a comparatively high number of lesions.

According to Goldstein, MR spectroscopy of the brain, which would allow researchers to determine the concentrations of cerebral chemicals elsewhere in the body, will likely be the next step in CFS imaging.

Already used in the study of neurodegenerative disorders such as Alzheimer's disease, the new technique will provide researchers with even more pieces to the puzzle.

"Not only will we know whether or not the chemical concentrations are too high or too low and what areas are involved," said Goldstein, "but we'll also be able to superimpose the MR image onto SPECT or PET scans to see exactly where chemical abnormalities are and where they correspond to perfusion or metabolic abnormalities."

LIFE GOES ON. According to researchers, the future for CFS patients is still very uncertain. Five years after the Lake Tahoe outbreak, only about 20 percent of those afflicted had recovered fully. Many CFS sufferers, however, begin to feel somewhat better two to five years after onset, although they rarely recapture the level of energy they experienced prior to the disease. Others end up bedridden, permanently disabled, with little hope of ever recovering.

Treatments thus far have been largely palliative in nature, aimed at ameliorating individual symptoms. A number of experimental drugs are currently being studied in clinical trials across the country, but none promises to be the CFS cure-all.

As for deLeon, she began to feel a little bit better after a few years, although she was forced to give up her career as a radiologic technologist years ago, after first going on disability before finally winning social-security

benefits.

Over the past year, said deLeon, she's re-evaluated the profound effect CFS has had on her life and decided to adopt a fresh approach. "[CFS] has already taken away so much of my productivity, as well as the years I invested in my career, and my dreams for the future. I've decided it's not going to take anything else without a fight.

"If I have only a few hours of productivity a day," she continued, "I'm going to make that time as 'quality' as I can. It's taken a long time to get here, but I'm back in control now." ■

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