

Neurological abnormalities in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome

MOST RECENT SCIENTIFIC EVIDENCE for Myalgic Encephalomyelitis/CFS as neurological disorder

There is growing evidence of significant abnormalities in the brain involving both structure and function. These findings are not consistent with the psychosocial model of causation that is favored by many psychiatrists.

Among the most important findings to date are two recent studies demonstrating a significant reduction in the volume of gray matter (de Lange et al 2005; Okada et al 2004) in the brain. de Lange et al reported that the decline in gray matter volume correlates to the reduction in physical activity. Okada et al reported that the reduction paralleled the severity of fatigue.

MRI brain scans demonstrating punctate areas of high signal intensity in the cerebral white matter. These are more common in patients who have no psychiatric co-morbidity (Keenan, 1999) and are significantly related to functional status (Cook et al, 2001).

Changes in the activity of brain chemical transmitters (neurotransmitters), in particular serotonin (Badawy et al, 2003) and dopamine modulation (Georgiades et al, 2003) and abnormalities involving brain chemicals such as carnitine (Kuratsune et al, 2002) and choline (Puri et al, 2002).

Blood flow studies demonstrating a significant overall decrease (Yoshiuchi et al, 2006) as well as a more specific perfusion defect to a part of the brain known as the brain stem (Costa et al, 1995).

Evidence of hypothalamic dysfunction, a key part of the brain that regulates a number of body functions including temperature control; hormonal output, in particular the production of cortisol from the adrenal glands (Papanicolaou et al, 2004); and the autonomic nervous system (Freeman, 2002).

Cerebrospinal fluid analysis demonstrating elevations of protein and/or white blood cells (Natelson et al, 2005) an abnormality suggesting immune system dysregulation within the central nervous system.

Myalgic Encephalomyelitis must now be RECOGNIZED AS A SERIOUS NEUROLOGICAL ILLNESS, RESEARCHED AS A SERIOUS NEUROLOGICAL ILLNESS, MANAGED AS A SERIOUS NEUROLOGICAL ILLNESS

Numerous studies cited below (some very recent cutting-edge research as well as other solid evidence in larger studies of serious neurological abnormalities:

Summary of Brain & Neurological Dysfunction at the 2007 IACFS-ME Conference, January 2007
(from Cort Johnson)

THE BRAIN

The brain imaging studies have brought some real excitement to the CFS research field. Among others they have suggested CFS patients have reduced blood flows to the brain, altered patterns of brain activation,

reduced grey matter volume, altered serotonergic neurotransmission, reduced acetyl carnitine uptake and others. Notice how often one area of the brain, the anterior cingulate, is mentioned in this section.

Introduction - Dr. Gudrun Lange

The brain imaging studies have brought some real excitement to the CFS research field. Among others they have suggested CFS patients have reduced blood flows to the brain, altered patterns of brain activation, reduced grey matter volume, altered serotonergic neurotransmission, reduced acetyl carnitine uptake and others.

Dr. Lange is a careful and conservative researcher and her talk brought us down to earth a bit. She noted that the brain is a difficult organ to study and elucidated a large number of possibly confounding variables (amount of resolution, different normalizing protocols, different types of brain slices, etc.) found in them. She noted that all the early brain imaging studies had poor methodology or sampling techniques. Her point was elucidated when a physician asked her about the remarkable similarity he had seen in the brain images of his CFS and MS patients. Dr. Lange replied that the CFS sample set must be very carefully assessed and gathered, that she sees no such similarities in her CFS patients, and that these kinds of findings are a big problem in CFS research.

This said, she gave us her view of what we can say with some assurance about the CNS research in CFS:

- The major cognitive problem seen is in 'information processing'.
- The studies showing reduced cerebral blood flows are starting to show consistency.
- There appears to be a problem with serotonergic neurotransmission in the hippocampus and anterior cingulate regions of the brain.
- The brain volume reductions appear to be relatively minor.
- There appear to be spinal fluid abnormalities
- fMRI studies are showing altered patterns of brain activation in CFS.

Dr. Lange believes CFS studies need to be more rigorous. She believes CFS patients need to be carefully screened and to be accompanied by appropriate control groups and they should be stratified according to sex, type of onset, presence of mood disorder (and probably others).

James Baraniuk. Proteomic biosignature of Chronic Fatigue Syndrome in cerebrospinal fluid.

Dr. Baraniuk didn't really give us any new information - he simply repeated the findings of his stunning cerebrospinal fluid (CSF) study but he did so in the context of other research efforts in CFS and in this light it was such a compelling presentation that it was, for me, a conference highlight. Look at how closely the protein signature he found appears to agree with other research findings.

- Two proteins suggest a protease - antiprotease imbalance is present. This implicates increased elastase production
- Several proteins suggest amyloid deposition in the blood vessels of the brain is causing microhemorrhaging
- One protein suggests altered rates of apoptosis are present
- Another suggests increased free radical production is present
- Another suggests problems with the vasoconstriction of the blood vessels and endothelial cell damage
- Another is associated with inflammation.

One protein found, keratin, is particularly interesting, as he said this is the first time in 25 years it has been found in CSF samples. It's associated with inflammation of the leptomeningeal cells that make up the membranes covering the brain and spinal cord.

A NEURO-IMMUNE CONNECTION?

A Garcia Quintana, I. Roca, A. Garcia-Burillo, J. Alegre-Martin, I. Mena, K. De Meirleir. Brain Spet quantification in CFS

Just about everybody believes that neuro-immune interface is disturbed in CFS but this is the first study I know of that has tried to unite immune findings with brain scans. This international collaboration between researchers from Spain, Belgium and Australia used a SPET scan to look at patterns of brain activity. Not surprisingly they found that areas of the frontal lobe including the anterior cingulate had reduced activity levels.

They then checked to see if these abnormalities were correlated with abnormal immune readings and they found that they were; they found that CFS patients with more abnormal RNase L measures, in particular, but also elastase levels tended to display the most altered brain activity patterns. The brain abnormalities were not, however, correlated with symptom expression, i.e. they were not accentuated in the most severely ill patients. Unfortunately there was no control group.

THE CFS BRAIN ON EXERCISE

A. Garcia Quintana, A. Garcia-Burillo, J. Alegre-Martin, I Mena, J. Garcia-Quintana. Brain SPET quantification in Chronic Fatigue Syndrome: comparison of basal and post-stress studies.

This group from Spain used a SPET scan to examine brain activity before and after an exercise session. This, again, is the first time, to my knowledge, that this has been done. It found that one area in particular, the Wernicke area, showed evidence of reduced activity after exercise. This area, which is found in the cerebral cortex, is thought to be 'essential for understanding and formulating coherent speech. *This certainly rings true for me.* Other areas in the temporal lobe were affected. Interestingly it was difficult to tell if the anterior cingulate region was affected because the activity in this region was too low to begin with.

THE EXHAUSTED BRAIN

Paul Nestad, Sanjay Mathew, Xiangling Mao, Kathryn Keegan, Susan Levine, Dikoma Shungu. A comparison of neurometabolites in chronic fatigue syndrome, generalized anxiety and healthy volunteers.

This study used proton resonance spectroscopy to compare brain metabolite levels in CFS patients with and without depression, anxiety patients and healthy volunteers. It found several things; first it found greatly increased lactate levels (about 300% higher!) in the CFS patients relative to the control groups. Many people know of lactate in connection with muscle fatigue but lactate is actually a general index of anaerobic energy production. Our cells switch from aerobic to anaerobic energy production when the aerobic system has become exhausted or is damaged. These high lactate levels appear to reflect the existence of a lot of really exhausted cells in the brains of CFS patients and suggest, Paul Nestadt said, problems with mitochondrial activity are present. Importantly these researchers found that people with high lactate levels were the most fatigued and they suggest that the increased lactate levels could be a biomarker for CFS.

Next, a reduced NAA to creatine ratio suggested an impaired metabolic process was present. That this ratio was significantly more reduced in CFS patients without depression than in those with depression buttressed Natelson's findings of greater brain abnormalities in CFS patients without mood disorders.

This looks like a really important study. It had highly significant findings, it contained several control groups, it implicated the mitochondria and the metabolism and it replicated Dr. Natelson's findings of increased brain abnormalities in CFS patients who do not have mood disorders. This group is now looking at much larger patient groups, this time using depressed patients and first degree relatives as control groups.

A KEY TO THE SLEEP PROBLEMS IN CFS?

Estimation of the fatigue state in patients with chronic fatigue syndrome using actigraphy and R-R interval power spectrum analysis - Saiki Tajima, M.D.

The actigraphy (activity) study found that there were four different types of fatigue; long sleepers (hypersomnia-like), severe insomnia, short sleep ('wired but tired' - hyposomnia), and delayed sleepers. When this researcher looked at heart beat variability he found that parasympathetic nervous system activation was significantly decreased during sleep in CFS patients.

This is an interesting finding given the number of sleep studies that have not found sleep problems in many CFS patients. Reduced HRV in CFS has now been found by Israeli, U.S. and Japanese researchers and is one of the few consistently found findings in CFS. It suggests that autonomic nervous system problems are present in CFS.

BRAIN DYSFUNCTION IS A KEY ABNORMALITY FOR UNDERSTANDING THE STATE OF CHRONIC FATIGUE SYNDROME

First Dr. Kuratsune pointed out several abnormal central nervous system findings that he thinks play a central role in CFS. Chief among these are reduced blood flows and reduced acetyl-carnitine uptake in areas of the brain (prefrontal cortices, anterior cingulate, cerebellum) involved in autonomic nervous system functioning, sleep and concentration, pain and motivation. Since acetyl-carnitine plays an important role in the synthesis of several neurotransmitters, reduced acetyl-carnitine uptake could be associated with reduced activity seen in those parts of the brain where it is found. He noted that low serotonergic activity in a specific area of the anterior cingulate produces pain. He believes this suggests that a similar problem in another part of the anterior cingulate could produce the fatigue in CFS. After this summary he presented his hypothesis regarding CFS.

A Hypothesis: The Neuro-molecular Mechanisms Leading to Chronic Fatigue

Dr. Kuratsune believes CFS starts with physical/chemical/biological stressors that perhaps in combination with inherited vulnerabilities cause an injury to the central nervous system (CNS). This CNS dysfunction causes the immune system to pump out cytokines (IFN/TGF-B) that disrupt serotonin activity in the brain and alter HPA axis functioning. Altered HPA axis functioning causes reduced acetyl-carnitine uptake in the brain and this further impairs neurotransmission, particularly in the anterior cingulate, basal ganglia and brainstem. This leads to profound fatigue, memory problems, autonomic nervous system problems (orthostatic intolerance, gastrointestinal discomfort) and the consequent circulation, breathing, muscle and temperature regulation problems in CFS. Immune dysfunction results in pathogen reactivation which further exacerbates the immune problems and - via cytokine production - further disrupts the central nervous system.

OTHER KEY REFERENCES

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Dr. Byron Hyde's description of the neurological abnormality in M. E./CFS:

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (M.E./CFS) is an endemic disorder, associated with an initial viral infection that occurs in both epidemic and sporadic forms.

M.E./CFS is an acquired brain dysfunction and results in a rapid and persistent exhaustion of both physical and cognitive abilities, an autonomic deregulation and a reduction of more than 50% of the individual's previous ability to carry out work, school or social activities. This Central Nervous System dysfunction can be exacerbated by levels of physical, sensory, cognitive, or emotional stress that would have been of no consequence in the same patient prior to the infectious or traumatic injury.

This neuroimmunological injury can usually be identified by studying SPECT or PET Scan Images of the patient's brain.

Neurological Dysfunction in Chronic Fatigue Syndrome, Journal of Chronic Fatigue Syndrome (The Haworth Medical Press, an imprint of The Haworth Press, Inc.) Vol. 6, No. 3/4, 2000, pp. 51-68.

Abhijit Chaudhuri, DM, MD, MRCP; Peter O. Behan, DSc, MD, FACP, FRCP

SUMMARY.

Chronic fatigue syndrome (CFS), popularly known in Europe as myalgic encephalomyelitis (M.E.), is a common but not a new illness. M.E./CFS was classified as a neurological disease by the World Health Organization in 1993. Neurological dysfunction is considered the principal mechanism of both physical and mental fatigue in this condition. This article reviews the neurological symptoms of the epidemic and sporadic forms of the illness. Paroxysmal changes in the severity of symptoms (fatigue and neuropsychiatric) are the hallmark features in the natural history of this disease. Ion channel abnormality leading to neuronal instability in selective anatomical pathways (basal ganglia circuitry) is proposed as the possible mechanism of fluctuating fatigue and related symptoms in CFS.

Gray matter volume reduction in the chronic fatigue syndrome

NeuroImage 26 (2005) 777-781; Floris P. de Lange,^{a,f} Joke S. Kalkman,^b Gijs Bleijenberg,^b Peter Hagoort,^a Jos W.M. van der Meer,^c and Ivan Toni^a

The chronic fatigue syndrome (CFS) is a disabling disorder of unknown etiology. The symptomatology of CFS (central fatigue, impaired concentration, attention and memory) suggests that this disorder could be related to alterations at the level of the central nervous system. In this study, we have used an automated and unbiased morphometric technique to test whether CFS patients display structural cerebral abnormalities.

We mapped structural cerebral morphology and volume in two cohorts of CFS patients (in total 28 patients) and healthy controls (in total 28 controls) from high-resolution structural magnetic resonance images, using voxel-based morphometry. Additionally, we recorded physical activity levels to explore the relation between severity of CFS symptoms and cerebral abnormalities.

We observed significant reductions in global gray matter volume in both cohorts of CFS patients, as compared to matched control participants. Moreover, the decline in gray matter volume was linked to the reduction in physical activity, a core aspect of CFS.

These findings suggest that the central nervous system plays a key role in the pathophysiology of CFS and point to a new objective and quantitative tool for clinical diagnosis of this disabling disorder.

Myalgic Encephalomyelitis/CFS Patients Have A Brain Defect Similar To AIDS Dementia

"SPECT Imaging of the Brain: Comparison of Findings in Patients with Chronic Fatigue Syndrome, AIDS Dementia Complex, and Major Unipolar Depression," Richard B. Schwartz, Anthony L. Komaroff, Basem M. Garada, Marcy Gleit, Teresa H. Doolittle, David W. Bates, Russell G. Vasily, B. Leonard Holman; American Journal of Roentgenology, Vol 162, 943-951, Copyright © 1994 by American Roentgen Ray Society

It has been known for some time that CFS patients have abnormal blood flow in their brains; that is, some areas of the brain are not getting as much blood as they should. Dr. Ismael Mena has studied M. E./CFS patients' brains using SPECT scans at the University of California-Los Angeles, where he is a professor of radiology (Ismael Mena, M.D., "Study of Cerebral Perfusion by NeuroSPECT in Patients with Chronic Fatigue Syndrome," The Cambridge Symposium on Myalgic Encephalomyelitis, 1990; 1: 21-22.)

Over several years' investigation, Dr. Mena has consistently reported that 71 percent of M. E./CFS patients have a diminished flow of blood in their brains. Dr. Mena has also commented, at scientific conferences, that M.E./CFS patients do not have equal blood flow on the two halves of their brains. That is, when the blood flow on the right and left sides (or hemispheres) of the brain were compared in individual M.E./CFS patients, the flow in the two halves of the brain can differ by twice as much as they do in healthy people.

This information suggests that some type of organic brain disease may be a component of M.E./CFS. While it has long been recognized that AIDS patients can develop very serious mental problems, sometimes labeled "AIDS dementia," only recently have such patients been studied using SPECT scans. The similarity between "AIDS dementia" patients' SPECT scans and those of CFS patients are striking.

SPECT scans in AIDS patients were discussed at the 1992 international AIDS meeting (in Amsterdam) by a research team from the Houston Immunological Institute. Rather shockingly, they found that exactly the same percentage of AIDS patients -- 71 percent -- as CFS patients had abnormalities in brain blood flow. The Houston research team also found that more severe cases of AIDS dementia showed greater abnormalities in brain blood flow, and they suggested that SPECT scans could provide a very important diagnostic tool for physicians treating patients with AIDS.

Other reported neurological findings:

Dr. Michael Goldberg, a UCLA pediatrician, is beginning to use SPECT scans to diagnose children suspected of having M.E./CFS. He found CBF to be variable in his patients and, based on this finding, hypothesized that some attention deficit disorder (ADD) patients are being misdiagnosed, and should actually be diagnosed with M. E./CFS. (See "Children with CFIDS" later in this article.)

Ottawa, Canada researcher Dr. Byron Hyde finds SPECT scans to be potent enough to alter the diagnosis of CFIDS (or M.E. – myalgic encephalo-myelitis -- as he prefers). "What we're going to tell the insurance companies from now on is not M.E., which they won't pay for, and not CFS, but major acquired brain dysfunction. And that is what these people actually have."

The difficulty with using SPECT scans as a diagnostic tool lies in their inaccessibility to most physicians. To get an accurate SPECT scan reading, a brain-dedicated scanner which uses either the ¹³³Xenon or the HMPAO radioisotope to measure CBF is needed. At this time there are only four such facilities in the United States. This situation should change very soon, as at least three companies are now offering software compatible with the SPECT scanners currently in hospitals across the country. This new software will enable physicians to do the ¹³³Xenon scans that Dr. Mena discussed at this conference. In a recent conversation, Dr. Mena estimated that within six months this technology will be widespread enough to be useful as a diagnostic tool for CFIDS.

MRI scans are unable to reliably show CFIDS-related brain defects, according to Drs. Stephen Lottenberg, Anthony Komaroff and Gunnar Heuser. However, Dr. Christopher Gallen presented a new type of brain scan which combines MRI (an anatomical scan) with the SQUID (Superconducting Quantum Interference Device) scan, a functional scan of electromagnetic fields. This magnetic source image (MSI) scan gives an extremely accurate picture of the brain's function. These electromagnetic fields are extremely subtle and must be differentiated from all the other electromagnetic "noise" in the environment. Trying to find the correct signal is like "listening to the footsteps of ants walking on soft

ground in the middle of a rock concert," according to Dr. Gallen, but this technology permits the researcher to isolate these minute signals.

MSI technology has been created with very stringent criteria for finding dysfunction. Because of this, Dr. Gallen and his team at the Scripps Institute estimate that they miss up to 30 percent of impaired people. In his very preliminary data, 50 percent of CFIDS patients show brain dysfunction with the MSI, primarily in the frontal, parietal and temporal lobes. Integrative and learning difficulties are often implicated by the MSI findings in CFIDS. Gallen stressed that more research needs to be done in this area before conclusions can be drawn, and that lack of funding alone has prevented these studies from being done.

Positron emission tomography (PET) scans measure glucose metabolism in the brain, another functional measure of brain activity. Dr. Lottenberg of U.C. Irvine has been able to "quantitatively evaluate brain function, especially for those who have more subtle findings that aren't as visually apparent" on MRI scans. "PET scanning is considered to be one of the gold standards in terms of evaluating whether there are functional problems that are causing [dysfunction]."

Abnormal brain SPECT & PET scan abnormalities are presented in Dr. Byron Hyde's landmark book, The Clinical and Scientific Basis for Myalgic Encephalomyelitis/CFS.

Here is an excerpt from a lecture by Dr. Byron Hyde at a recent Wisconsin conference on the disease Myalgic Encephalomyelitis/CFS:

From Dr. Byron Hyde's lecture at the Wisconsin AACFS conference as reported by Dr. Rich Vankonynen:

Comments on the Development of the Case Definitions

Dr. Hyde emphasized that his findings about M.E./CFS patients have been very different from the case definitions that were promulgated by the U.S. National Institutes of Health (NIH) and the Centers for Disease Control (CDC). He said that in his view, these definitions have totally failed us.

When the original board met at the CDC in 1988 to establish a case definition for CFS, Dr. Hyde was in attendance, because those interested in this type of diseases were invited to come. He said that "it was obvious to those who had actually seen M.E./CFS patients that the vast majority of the people on the board were researchers who had never seen an M.E. patient clinically."

Dr. Hyde said that the definition this board developed totally warped the whole concept of M.E./CFS-type disease, because the authors introduced the word "fatigue" into the name. Fatigue can be produced by many things, and it is a totally indefinable term in his view. Furthermore, in the 50 epidemics up to that time, fatigue had only occurred in one. What actually did occur in these epidemics again and again was central nervous system (CNS) derangement: sleep dysfunction, cognitive problems, and in general, difficulties with any tasks the brain is required to perform.

According to Dr. Hyde, the second factor that came into the picture in 1988 and was perpetuated as well in the development of the revised 1994 Fukuda et al. case definition process as well those carried out in other countries, was that they brought in more psychiatrists. The overall result was that the definitions were developed primarily either by epidemiologists who were in his view forced by the government to go and start looking at these patients and produce a definition, or by people who did not believe that there was any physical thing wrong with any of the people who had what they called CFS.

Dr. Hyde said that at a meeting initiating the development of the 1994 definition there was not a single clinician on the entire board, with one exception, and he therefore got up and said, "Why don't you put

some people on this board who have actually seen patients?" He said they accommodated by adding one more who had. Dr. Hyde said the people on the board were brilliant, but they had never seen a case of CFS. According to Dr. Hyde, bringing in so many physicians who had never actually seen CFS patients, and particularly psychiatrists, who wanted to say that these patients had depression or anxiety or some other psychiatric problem, and trying to accommodate these extremes in the definitions destroyed the reality in the definitions that resulted.

Dr. Hyde quoted a 1993 paper by Dr. William Reeves of the CDC, to wit, "Chronic fatigue syndrome has no confirmatory physical signs or characteristic laboratory abnormalities, and the etiology and pathophysiology remain unknown." In Dr. Hyde's view, any reasonable physician who did not actually deal with CFS would conclude from reading this that CFS had to be a form of psychiatric or somatizing illness. He said that we need to redefine what is going on, and that there is a lot of good evidence with which to do so.

He said that a good part of the 1994 CDC definition would just as well describe someone who had just finished climbing Mount Everest. He noted that this definition paper contains over 15,000 words, and suggested that those writing it could not have been very clear on what they were defining, to have to use so many words.

Dr. Hyde stated that he believes that "If a disease cannot be scientifically measured or appropriate tests made to confirm its presence, it cannot be defined or treated with any assurance of success. Without the ability to measure or test for a disease, most physicians will reject the concept entirely or state that the illness is psychiatric, psychological, or social in nature."

He went on to set forth his definition of M.E.: "M.E. is a measurable, diffuse post-encephalitic illness. The illness is characterized by (1) its acute onset, (2) the diffuse, non-focal persisting nature of the encephalopathy, and (3) the chronicity of the resulting symptoms. These symptoms consist of the rapid exhaustion or loss of stamina of motor, sensory, intellectual, cognitive and emotional abilities. It is of infectious/autoimmune origin and less commonly, a toxic/autoimmune origin. M.E. occurs in epidemics and sporadic cases."

Finally, the characteristic punctate lesions on MRIs of Myalgic Encephalomyelitis/CFS patients and neurocognitive abnormalities that have been reported by Dr. Myra Preston and also in the study cited below are other areas of solid evidence in the diagnosis of Myalgic Encephalomyelitis/CFS: A study showed patients with CFS have slowed reaction times, poorer short-term memory and reduced neural activity prior to movement compared to controls, suggesting that the central motor mechanisms accompanying motor response may be impaired. Gordon R et al. Cortical motor potential alterations in chronic fatigue syndrome. *Int J Molec Med.* 1999; 4: 493-99.

Neurocognitive Problems

Neurocognitive symptoms are reported with relatively high frequency in **the** syndrome. In addition to problems with memory and concentration, information processing functions appear to be abnormal. Many meritorious articles have been published, but at least one seems to be scientifically robust and has not been substantially challenged by other publications.

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Autonomic nervous system (including orthostatic intolerance)

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Other Neurological Findings

Neurology (CNS and brain)

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12. Peripheral cholinergic function in humans with chronic fatigue syndrome, Gulf War syndrome and with illness following organophosphate exposure. Faisal KHAN, Gwen KENNEDY, Vance A. SPENCE, David J. NEWTON and Jill J. F. BELCH Vascular Diseases Research Unit, University Department of Medicine, Ninewells Hospital and Medical School, Dundee DD19SY, Scotland, U.K. Clinical Science (2004) 106, 183189
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Brain Physiology

Buchwald D, Cheney PR, Peterson DL, Henry B, Wormsley SB, Geiger A, Ablashi DV, Salahuddin SZ, Saxinger C, Biddle R, et al. **A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpesvirus type 6 infection.** Annals of Internal Medicine 1992; 116(2): 103-13.

Abstract: OBJECTIVE: To conduct neurologic, immunologic, and virologic studies in patients with a chronic debilitating illness of acute onset. DESIGN: Cohort study with comparison to matched, healthy control subjects. PATIENTS: We studied 259 patients who sought care in one medical practice; 29% of the patients were regularly bedridden or shut-in. MAIN OUTCOME MEASURES: Detailed medical history, physical examination, conventional hematologic and chemistry testing, magnetic resonance imaging (MRI) studies, lymphocyte phenotyping studies, and assays for active infection of patients' lymphocytes with human herpesvirus type 6 (HHV-6). MAIN RESULTS: Patients had a higher mean (\pm SD) CD4/CD8 T-cell ratio than matched healthy controls (3.16 ± 1.5 compared with 2.3 ± 1.0 , respectively; P less than 0.003). Magnetic resonance scans of the brain showed punctate, subcortical areas of high signal intensity consistent with edema or demyelination in 78% of patients (95% CI, 72% to 86%) and in 21% of controls (CI, 11% to 36%) (P less than 10^{-9}). Primary cell culture of lymphocytes showed active replication of HHV-6 in 79 of 113 patients (70%; CI, 61% to 78%) and in 8 of 40 controls (20%; CI, 9% to 36%) (P less than 10^{-8}), a finding confirmed by assays using monoclonal antibodies specific for HHV-6

proteins and by polymerase chain reaction assays specific for HHV-6 DNA. **CONCLUSIONS:** Neurologic symptoms, MRI findings, and lymphocyte phenotyping studies suggest that the patients may have been experiencing a chronic, immunologically mediated inflammatory process of the central nervous system. The active replication of HHV-6 most likely represents reactivation of latent infection, perhaps due to immunologic dysfunction. Our study did not directly address whether HHV-6, a lymphotropic and gliotropic virus, plays a role in producing the symptoms or the immunologic and neurologic dysfunction seen in this illness. Whether the findings in our patients, who came from a relatively small geographic area, will be generalizable to other patients with a similar syndrome remains to be seen.

Cope H, David A. **Cognitive functioning with chronic fatigue** [Letter]. *British Journal of Psychiatry* 1995; 167: 818-819.

Cope H, David AS. **Neuroimaging in chronic fatigue syndrome** [Editorial]. *Journal of Neurology Neurosurgery and Psychiatry* 1996; 60: 471-473.

Cope H, Pernet A, Kendall B, David A. **Cognitive functioning and magnetic resonance imaging in chronic fatigue**. *British Journal of Psychiatry* 1995; 167: 86-94.

Abstract: **BACKGROUND.** This study examines whether cognitive dysfunction in chronic fatigue may be accounted for by depression and anxiety or is due to brain pathology evident on magnetic resonance imaging (MRI). **METHOD.** Twenty-six subjects with chronic fatigue, with and without coexisting depression, and 18 age-matched normal controls were recruited from primary care following a presumed viral illness six months previously. Comparison was made with 13 psychiatric controls with depressive illness on standardised cognitive tests. MRI determined the presence of cerebral white-matter lesions. **RESULTS.** No substantial differences in performance were shown between subjects with chronic fatigue, most of whom met the criteria for chronic fatigue syndrome, and controls. Subjective cognitive dysfunction increased with psychopathology. White-matter lesions were found in a minority from all groups. Improvement in fatigue and depression coincided with improved performance on cognitive measures. **CONCLUSIONS.** Subjective complaints of cognitive impairment are a prominent feature of chronic fatigue, but objective cognitive and MRI abnormalities are not. Such complaints probably reflect psychopathology rather than a post-viral process.

Costa DC, Brostoff J, Douli V, Eil PJ. **Postviral fatigue syndrome** [Letter]. *British Medical Journal* 1992; 304: 1567.

Costa DC, Brostoff J, Douli V, Eil PJ. **Brain stem hypo-perfusion in patients with myalgic encephalomyelitis - chronic fatigue syndrome**. *European Journal of Nuclear Medicine* 1992; 19: 733.

Costa DC, Tannock C, Brostoff J. **Brainstem perfusion is impaired in chronic fatigue syndrome**. *Quarterly Journal of Medicine* 1995; 88(11): 767-73.

Abstract: We looked for brain perfusion abnormalities in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). An initial pilot study revealed widespread reduction of regional brain perfusion in 24 ME/CFS patients, compared with 24 normal volunteers. Hypoperfusion of the brainstem (0.72 ± 0.05 vs. 0.80 ± 0.04 , $p < 0.0001$) was marked and constant. We then tested whether perfusion to the brainstem in ME/CFS patients differs from that in normals, patients with major depression, and others with epilepsy. Data from a total of 146 subjects were included in the present study: 40 normal volunteers, 67 patients with ME/CFS (24 in the pilot study, 16 with no psychiatric disorders, 13 with ME/CFS and depression, 14 with ME/CFS and other psychiatric disorders), 10 epileptics, 20 young depressed patients and 9 elderly depressed individuals. Brain perfusion ratios were calculated using ^{99}Tcm -hexamethylpropylene

amine oxime (99Tcm-HMPAO) and single-photon emission tomography (SPECT) with a dedicated three-detector gamma camera computer/system (GE Neurocam). Brain-stem hypoperfusion was confirmed in all ME/CFS patients. Furthermore, the 16 ME/CFS patients with no psychiatric disorders and the initial 24 patients in the pilot study showed significantly lower brainstem perfusion (0.71 ± 0.03) than did depressed patients (0.77 ± 0.03 ; ANOVA, $p < 0.0001$). Patients with ME/CFS have a generalized reduction of brain perfusion, with a particular pattern of hypoperfusion of the brainstem.

Douli V, Brostoff J, Costa CD, Kouris K, Ell PJ. **rCBFSPET in patients with myalgic encephalomyelitis**. Nuclear Medicine Communications 1992; 14,2:

Fischler B, D'Haenen H, Cluydts R, Michiels V, Demets K, Bossuyt A, Kaufman L, De-Meirleir K. **Comparison of 99m Tc HMPAO SPECT scan between chronic fatigue syndrome, major depression and healthy controls: an exploratory study of clinical correlates of regional cerebral blood flow**. Neuropsychobiology 1996; 34(4): 175-183.

Abstract: An explorative analysis of the relationship between symptomatology and cerebral blood flow in the chronic fatigue syndrome (CFS) as assessed with 99mTc HMPAO SPECT scan reveals statistically significant positive correlations between frontal blood flow on the one hand and objectively and subjectively assessed cognitive impairment, self-rating of physical activity limitations and total score on Hamilton Depression Rating Scale on the other. A pathophysiological role of frontal blood flow in the cognitive impairment and physical activity limitations in CFS is hypothesized. A comparison of cerebral blood flow between CFS, major depression (MD) and healthy controls (HC) has been performed. A lower superofrontal perfusion index is demonstrated in MD as compared with both CFS and HC. There is neither a global nor a marked regional hypoperfusion in CFS compared with HC. Asymmetry ($R > L$) of tracer uptake at parietotemporal level is demonstrated in CFS as compared with MD.

Goldberg MD, Mena I, Darcourt J. **NeuroSPECT findings in children with chronic fatigue syndrome**. Journal of Chronic Fatigue Syndrome 1997; 3(1): 61-67.

Abstract: BACKGROUND. NeuroSPECT studies have described specific abnormalities in cerebral perfusion in adults with criteria for Chronic Fatigue Syndrome. This reports findings in 13 children with criteria for Chronic Fatigue Syndrome. OBJECTIVE. NeuroSPECT findings in 13 CFS/CFIDS children. METHODS. Thirteen children meeting CDC criteria for CFS/CFIDS were evaluated using NeuroSPECT imaging utilizing Xenon 133 and Tc-99m-HMPAO (1). RESULTS. In 13 children, hypoperfusion was observed at 42 ± 10 ml/min/100g, $p < 0.0001$ in the left temporal lobe and at 45 ± 11 , $p < .001$ in right temporal lobe. Statistically significant hypoperfusion was also observed in both parietal lobes and at 50 and 53 ml/min/100g, $p < 0.05$ in the frontal lobe of the right hemisphere. Quantitated HMPAO demonstrated bilateral orbitofrontal and anterior temporal hypoperfusion. There was also hypoperfusion in the dorsal aspects of both frontal lobes and both parietooccipital lobes. CONCLUSION. NeuroSPECT is presented as a quantifiable, reproducible tool that can allow us to document a cohort of children defined as CFS/CFIDS.

Goldstein JA, Mena I, Jouanne E, Lesser I. **The assessment of vascular abnormalities in late life chronic fatigue syndrome by Brain SPECT: comparison with late life major depression disorder**. Journal of Chronic Fatigue Syndrome 1995; 1(1): 55-79.

Abstract: We report on brain SPECT analysis of regional cerebral blood flow (rCBF) in late life chronic fatigue syndrome (CFS) patients and compare their results with patients with late life depression and elderly normal controls 45 years and older. We attempted to distinguish CFS from normals and patients with depression and applied the findings to understand the pathophysiology of the illness. We studied 33 patients with CFS (55 ± 10 years), 26 patients with late life depression (62 ± 8 years), and 19 normal controls (66 ± 8 years); 43 other normal controls had

only $^{133}\text{(sup)Xe}$ rCBF measurements (66 ± 8 years). We evaluated rCBF quantitatively with $^{133}\text{(sup)Xe}$ images and qualitatively with high resolution imaging using $^{99\text{m}}\text{(sup)TcHMPAO}$. We found that rCBF in CFS measured by $^{133}\text{(sup)Xe}$ varied between 35 and 41 ml/min/100g in both hemispheres, $p < 0.0001$ and 0.05 ; similar findings were observed in depression.

Gonzalez MB, Cousins JC, Doraiswamy PM. **Neurobiology of CFS**. Progress in Neuropsychopharmacol Biological Psychiatry 1996; 20(5): 749-59.

Abstract: 1. Chronic fatigue syndrome (CFS) is characterized by a new onset of significant fatigue for a period of six months or longer usually following an infection, injury or period of high stress. 2. The exact etiology of CFS is not known and a diagnostic test is not available. Hence, the diagnosis is made by exclusion of other explanations for the patient's symptoms and by meeting the CDC research case definitions. Early studies supported an infectious or immune dysregulation hypothesis for the pathophysiology of CFS. 3. Subsequent studies documented that neurological, affective and cognitive symptoms also occur at high rates in CFS patients. Neuropsychological, neuroendocrine studies and brain imaging have now confirmed the occurrence of neurobiological abnormalities in most patients with CFS. 4. In this article, the authors review these findings in relation to the clinical neurobiology of CFS and their potential relevance to biological psychiatry.

Goudsmit EM, Howes S. **Cognitive functioning with chronic fatigue** [Letter]. British Journal of Psychiatry 1995; 167: 818.

Greco A, Tannock C, Brostoff J, Costa DC. **Brain MR in chronic fatigue syndrome**. American Journal of Neuroradiology 1997; 18(7): 1265-69.

Abstract: PURPOSE: To determine the prevalence of MR white matter abnormalities in patients with chronic fatigue syndrome (CFS). METHODS: Brain MR studies of 43 patients (29 women and 14 men, 22 to 78 years old) with a clinical diagnosis of CFS ($n = 15$), CFS with associated depression ($n = 14$), and CFS with associated other psychiatric disorders, namely, anxiety and somatization disorder ($n = 14$), were compared with brain MR studies in 43 age- and sex-matched control subjects. RESULTS: MR findings were abnormal in 13 (32%) of the patients in the study group (ages 34 to 78 years) and in 12 (28%) of the control subjects (ages 26 to 73 years). One patient with CFS had multiple areas of demyelination in the supratentorial periventricular white matter. Another patient with CFS and associated depression had a single focus of probable demyelination in the supratentorial periventricular white matter. In four patients with CFS (ages 34 to 48 years) MR abnormalities consisted of one or several punctate hyperintense foci in the corona radiata, centrum ovale, and frontal white matter. The remaining seven patients (ages 50 to 78 years) had frontoparietal subcortical white matter foci of high T2 signal. The prevalence of white matter hyperintensities was not different between the patients and the control subjects. CONCLUSIONS: Our findings suggest that no MR pattern of white matter abnormalities is specific to CFS.

Ichise M, Salit IE, Abbey SE, Chung DG, Gray B, Kirsh JC, Freedman M. **Assessment of regional cerebral perfusion by $^{99\text{Tc}}\text{m-HMPAO}$ SPECT in chronic fatigue syndrome**. Nuclear Medicine Communications 1992; 13(10): 767-72.

Abstract: Chronic fatigue syndrome (CFS) is a severely disabling illness of uncertain aetiology. It is characterized by a chronic, sustained or fluctuating sense of debilitating fatigue without any other known underlying medical conditions. It is also associated with both somatic and neuropsychological symptoms. Both physical and laboratory findings are usually unremarkable. Regional cerebral blood flow (rCBF) was assessed in 60 clinically defined CFS patients and 14 normal control (NC) subjects using $^{99\text{Tc}}\text{m}$ -hexamethylpropyleneamine oxime ($^{99\text{Tc}}\text{m-HMPAO}$) single photon emission computed tomography (SPECT). Compared with the NC group, the CFS group showed significantly lower cortical/cerebellar rCBF ratios, throughout multiple brain regions

($P < 0.05$). Forty-eight CFS subjects (80%) showed at least one or more rCBF ratios significantly less than normal values. The major cerebral regions involved were frontal (38 cases, 63%), temporal (21 cases, 35%), parietal (32 cases, 53%) and occipital lobes (23 cases, 38%). The rCBF ratios of basal ganglia (24 cases, 40%) were also reduced. ^{99}Tcm -HMPAO brain SPECT provided objective evidence for functional impairment of the brain in the majority of the CFS subjects. The findings may not be diagnostic of CFS but ^{99}Tcm -HMPAO SPECT may play an important role in clarifying the pathoetiology of CFS. Further studies are warranted.

Johansson G, Risberg J, Rosenhall U, Orndahl G, Svennerholm L, Nystrom S. **Cerebral dysfunction in fibromyalgia: evidence from regional cerebral blood flow measurements, otoneurological tests & cerebrospinal fluid analysis.** Acta Psychiatrica Scandinavica 1995; 91(2): 86-94.

Abstract: Measurements of regional cerebral blood flow (rCBF), analysis of cerebrospinal fluid, auditory brain stem responses (ABR) and oculomotor tests were performed in 19 patients with fibromyalgia. The results from the rCBF measurements showed a normal flow level with slight but significant focal flow decreases in dorsolateral frontal cortical areas of both hemispheres. The ABR results showed signs of dysfunction at least at the brain stem level and the oculomotor tests showed high frequency of pathology. The cerebrospinal fluid analysis showed discrete changes in the cell differential count. Possible explanations for the involvement of the central nervous system in fibromyalgia are discussed.

Natelson BH, Sisto SA, Tapp WN. **Gait abnormalities in chronic fatigue syndrome.** Journal of the Neurological Sciences 1995; 131(2): 156-61.

Abstract: To evaluate our clinical impression that patients with the chronic fatigue syndrome (CFS) did not walk normally, we assessed gait kinematics at slow walking speeds (i.e., 0.45, 0.89 and 1.34 m/sec) and 30 m run time speeds on CFS patients and on a comparison group of sedentary controls. Run time was significantly slower for CFS than control subjects ($p < 0.001$). There was a significant interaction ($p < 0.01$) between group and speed for maximum hip angle during stance and swing phase with hip angle being significantly larger at 1.34 m/sec for CFS than controls subjects for both cases ($p < 0.05$). Knee flexion during stance and swing phases was significantly larger for controls than CFS subjects at 0.45 m/sec ($p < 0.01$). Ratio of stride length divided by leg length was significantly larger for the control subjects than for the CFS subjects with differences occurring at 0.45 and 0.89 m/sec ($p < 0.01$) but not 1.34 m/sec. The data indicate that CFS patients have gait abnormalities when compared to sedentary controls. These could be due to balance problems, muscle weakness, or central nervous system dysfunction; deciding which will require further research. Evaluation of gait may be a useful tool to measure outcome following therapeutic interventions.

Natelson BH, Cohen JM, Brassloff I, Lee HJ. **A controlled study of brain magnetic resonance imaging in patients with the chronic fatigue syndrome.** Journal of the Neurological Sciences 1993; 120(2): 213-7.

Abstract: Two neuroradiologists compared the brain MR scans of 52 patients with the CDC criteria for the chronic fatigue syndrome (CFS) with those of 52 age and sex matched controls who had undergone imaging because of histories of head trauma or headache. CFS patients had significantly more abnormal scans than controls—27% vs 2%. Abnormalities seen were foci of increased white matter T2 signal in 9 CFS patients and one control and ventricular or sulcal enlargement in 5 CFS patients. Follow up of patients with subcortical signal hyperintensities revealed 3 who had symptoms suggestive of other known medical causes of what appeared to be CFS. The data indicate that some CFS patients have some organic problem manifesting itself on neuroimaging. But, finding MR abnormalities should warn the physician that the patient's symptoms may be secondary to some other medical illness and not simply primary CFS.

Pampiglione, Harris R, Kennedy J. **Electro-encephalographic investigations in so-called myalgic encephalomyelitis**. Postgraduate Medical Journal 1978; 54: 752-54.

Abstract: The main EEG features are described of thirty-six young adults who were examined at the Royal Free Hospital between 1960 and 1964 and twelve children seen at the Hospital for Sick Children, Great Ormond Street, London, between 1957 and 1977. It is important in the future, if a plan is considered for the study of a fresh epidemic, to include systematic EEG studies covering a period of 2 to 3 years. The EEG alterations found in this limited survey, though modest, would suggest that cerebral function was disturbed with somewhat variable distribution by an insidious illness which has not yet been identified.

Peterson PK, Sirt SA, Grammith FC, Schenck CH, Pheley AM, Hu S, Chao CC. **Effects of mild exercise on cytokines and cerebral blood flow in chronic fatigue syndrome patients**. Clinical and Diagnostic Laboratory Immunology 1994; 1(2): 222-6.

Abstract: Chronic fatigue syndrome (CFS) is an idiopathic disorder characterized by fatigue that is markedly exacerbated by physical exertion. In the present study, we tested the hypothesis that mild exercise (walking 1 mph [1 mile = 1.609 km] for 30 min) would provoke serum cytokine and cerebral blood flow abnormalities of potential pathogenic importance in CFS. Interleukin-1 beta, interleukin-6, and tumor necrosis factor alpha were nondetectable in sera of CFS patients (n = 10) and healthy control subjects (n = 10) pre- and postexercise. At rest, serum transforming growth factor beta (TGF-beta) levels were elevated in the CFS group compared with the control group (287 ± 18 versus 115 ± 5 pg/ml, respectively; P <0.01). Serum TGF-beta and cerebral blood flow abnormalities, detected by single-photon emission-computed tomographic scanning, were accentuated postexercise in the CFS group. Although these findings were not significantly different from those in the control group, the effect of exercise on serum TGF-beta and cerebral blood flow appeared magnified in the CFS patients. Results of this study encourage future research on the interaction of physical exertion, serum cytokines, and cerebral blood flow in CFS that will adopt a more rigorous exercise program than the one used in this study.

Rosenthal U, Johansson G, Orndahl G. **Otoneurologic and audiological findings in fibromyalgia**. Scandinavian Journal of Rehabilitation Medicine 1996; 28(4): 225-32.

Abstract: Patients with fibromyalgia were studied with otoneurological and audiological tests. Altogether 168 patients (141 women) participated. Vertigo/dizziness was reported by 72% of the patients. Sensorineural hearing loss was found in 15% of the cases. Auditory brainstem responses (ABR) and oculomotor tests were applied, and statistical comparisons between patients and controls were performed. Significant differences were found for the absolute latency of wave V and for the I-V and III-V interpeak latencies, indicating brainstem dysfunction. Abnormal ABR recordings were found in 30% of the cases. In the oculomotor study the mean velocity gain for the smooth pursuits and the mean saccadic latency were significantly different between patients and controls. Abnormal saccades were seen in 28% and pathological smooth pursuit eye movements in 58% of the patients. Electronystagmography was pathological in 45% of the cases. The findings indicate that CNS dysfunction frequently occurs in patients with fibromyalgia, although proprioceptive disturbances might also explain some of the abnormalities observed.

Samii A, Wasserman E, Ikoma K, Mercuri B, George MS, O'Fallon A, Dale JK, Straus S. **Decreased postexercise facilitation of motor evoked potentials in patients with chronic fatigue syndrome or depression**. Neurology 1996; 47(6): 1410-4.

Abstract: We studied the effects of exercise on motor evoked potentials (MEPs) elicited by transcranial magnetic stimulation (TMS) in 18 normal (control) subjects, 12 patients with chronic fatigue syndrome, and 10 depressed patients. Subjects performed repeated sets of isometric exercise of the extensor carpi radialis muscle until they were unable to maintain half maximal

force. MEPs were recorded before and after each exercise set and for up to 30 minutes after the last set. The mean amplitude of MEPs recorded from the resting muscle immediately after each exercise set was 218% of the mean pre-exercise MEP amplitude in normal subjects, 126% in chronic fatigue patients, and 155% in depressed patients, indicating postexercise MEP facilitation in all three groups. The increases in the patient groups, however, were significantly lower than normal. The mean amplitudes of MEPs recorded within the first few minutes after the last exercise sets in all three groups were approximately half their mean pre-exercise MEP amplitudes. This postexercise MEP depression was similar in all groups. We conclude that postexercise cortical excitability is significantly reduced in patients with chronic fatigue syndrome and in depressed patients compared with that of normal subjects.

Schwartz RB, Garada BM, Komaroff AL, Tice HM, Gleit M, Jolesz FA, Holman BL. **Detection of intracranial abnormalities in patients with chronic fatigue syndrome: comparison of MR imaging and SPECT.** American Journal of Roentgenology 1994; 162(4): 935-41.

Abstract: OBJECTIVE. Chronic fatigue syndrome is a recently characterized condition of unknown origin that is manifested by fatigue, flulike complaints, and neurologic signs and symptoms, including persistent headache, impaired cognitive abilities, mood disorders, and sensorimotor disturbances. This syndrome can be difficult to diagnose clinically or by standard neuroradiologic tests. We performed MR imaging and single-photon emission computed tomography (SPECT) in patients with chronic fatigue syndrome to compare the usefulness of functional and anatomic imaging in the detection of intracranial abnormalities. SUBJECTS AND METHODS. Sixteen patients who fulfilled the Centers for Disease Control, British, and/or Australian criteria for chronic fatigue syndrome had MR and SPECT examinations within a 10-week period. Axial MR and SPECT scans were analyzed as to the number and location of focal abnormalities by using analysis of variance with the Student-Newman-Keuls option. MR imaging findings in patients with chronic fatigue syndrome were compared with those in 15 age-matched control subjects, and SPECT findings in the patients with chronic fatigue syndrome were compared with those in 14 age-matched control subjects by using Fisher's exact test. The findings on MR and SPECT scans in the same patients were compared by using the Wilcoxon matched-pairs signed-ranks test. RESULTS. MR abnormalities consisted of foci of T2-bright signal in the periventricular and subcortical white matter and in the centrum semiovale; there were 2.06 foci per patient, vs 0.80 foci per control subject. MR abnormalities were present in eight (50%) of 16 patients, compared with three (20%) of 15 age-matched control subjects. Neither of these differences reached significance, although the power of the study to detect differences between groups was small. Patients with chronic fatigue syndrome had significantly more defects throughout the cerebral cortex on SPECT scans than did normal subjects (7.31 vs 0.43 defects per subject, $p < .001$). SPECT abnormalities were present in 13 (81%) of 16 patients, vs three (21%) of 14 control subjects ($p < .01$). SPECT scans showed significantly more abnormalities than did MR scans in patients with chronic fatigue syndrome ($p < .025$). In the few patients who had repeat SPECT and MR studies, the number of SPECT abnormalities appeared to correlate with clinical status, whereas MR changes were irreversible. CONCLUSION. SPECT abnormalities occur more frequently and in greater numbers than MR abnormalities do in patients with chronic fatigue syndrome. SPECT may prove to be useful in following the clinical progress of patients with this syndrome.

Schwartz RB, Komaroff AL, Garada BM, Gleit M, Doolittle TH, Bates DW, Vasile RG, Holman BL. **SPECT imaging of the brain: comparison of findings in patients with chronic fatigue syndrome, AIDS dementia complex, and major unipolar depression.** American Journal of Roentgenology 1994; 162(4): 943-51.

Abstract: OBJECTIVE. Chronic fatigue syndrome is an illness of unknown origin that begins abruptly with a flulike state and has symptoms suggesting both a chronic viral encephalitis and an affective disorder. We compared single-photon emission computed tomography (SPECT) scans of patients with chronic fatigue syndrome with those of patients with AIDS dementia complex and unipolar depression. SUBJECTS AND METHODS. We used ^{99m}Tc -hexamethylpropyleneamine

oxime to examine 45 patients with chronic fatigue syndrome, 27 patients with AIDS dementia complex, and 14 patients with major unipolar depression. Scans of 38 healthy persons were used as controls. Comparison of regional defects between groups, as well as midcerebral uptake indexes (an objective measure of global radionuclide uptake), was performed by using analysis of variance with the Student-Newman-Keuls option. Correlation between the number of regional defects and the midcerebral uptake index was determined by using the Spearman rank-correlation test. RESULTS. Patients with AIDS dementia complex had the largest number of defects (9.15 per patient) and healthy patients had the fewest defects (1.66 per patient). Patients with chronic fatigue syndrome and depression had similar numbers of defects per patient (6.53 and 6.43, respectively). In all groups, defects were located predominantly in the frontal and temporal lobes. The midcerebral uptake index was found to be significantly lower ($p < .002$) in the patients with chronic fatigue syndrome (.667) and patients with AIDS dementia complex (.650) than in patients with major depression (.731) or healthy control subjects (.716). Also, a significant negative correlation was found between the number of defects and midcerebral uptake index in patients with chronic fatigue syndrome and AIDS dementia complex, but not in depressed patients or control subjects. CONCLUSION. These findings are consistent with the hypothesis that chronic fatigue syndrome may be due to a chronic viral encephalitis; clinical similarities between chronic fatigue syndrome and depression may be due to a similar distribution and number of defects in the two disorders.

Tannock C, Costa DC, Brostoff J. **Look at M.E.** [Letter]. British Medical Journal 1994; 308: 1298.

Troughton AH, Blacker R, Vivian G. **^{99m}Tc HMPAO SPECT in the chronic fatigue syndrome.** Clinical Radiology 1992; 45: 59.

BRAIN POSITRON EMISSION TOMOGRAPHY (PET) IN CHRONIC FATIGUE SYNDROME: PRELIMINARY DATA.

Umberto Tirelli* MD, Franca Chierichetti° MD, Marcello Tavio* MD, Cecilia Simonelli* MD, Gianluigi Bianchin€ MD, Pierluigi Zanco° MD and Giorgio Ferlin° MD.

ABSTRACT

Background and objective: Chronic fatigue syndrome (CFS) has been widely studied by neuroimaging techniques in recent years with conflicting results. In particular, by single photon emission computed tomography (SPECT) and perfusion tracers it has been found hypoperfusion in several brain regions, although the findings vary across the research centres. Objective of the study was to investigate brain metabolism of patients affected by CFS, by using 18Fluorine-deoxyglucose (18FDG) positron emission tomography (PET). Methods: We performed 18FDG PET in 18 patients who fulfilled the criteria of working case definition of CFS. Twelve of the 18 patients were females; the mean age was 34 ± 50 (range 15-68) and the median time from CFS diagnosis was 16 months (range 9-138). Psychiatric diseases and anxiety neurosis were excluded in all CFS patients. CFS patients were

compared with a group of 6 patients affected by depression (according to DSM IV R) and 6 age matched healthy controls. The CFS patients were not taking any medication at the time of PET, while depressed patients were drug-free for at least one week prior to the PET examination. PET images were examined considering 22 cortical and subcortical areas.

Results: CFS patients showed a significant hypometabolism in right medium frontal cortex ($p = 0.010$) and brain stem ($p = 0.013$) in comparison to the healthy controls. Moreover, comparing patients affected by CFS and depression, the latter group showed a significant and severe hypometabolism of a medium and upper frontal regions bilaterally ($p =$ ranging from 0.037 to 0.001), while the metabolism of brain stem was normal.

Conclusion: Brain- ^{18}F FDG PET showed peculiar metabolism abnormalities in patients with CFS in comparison both with healthy controls and depressed patients. The most relevant result of our study is the brain stem hypometabolism which , as already reported in a perfusion SPECT study, seems to be an marker for the in vivo diagnosis of CFS.