CFSSI CIRCULAR

CHRONIC FATIGUE SYNDROME SOCIETY OF ILLINOIS, INC.

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CFS TREATMENT AND EVALUATION CENTER: THE FULL PICTURE

A CFSSI meeting was held August 1, 1993, at Mercy Hospital. The guest speakers were Audrius Plioplys, M.D. and Sigita Plioplys, M.D., who explained the details of the Chronic Fatigue Syndrome Evaluation and Treatment Center that was recently opened at Mercy Hospital.

Dr. Audrius Plioplys, the Director of the Center, indicated he is trained as both an adult and child neurologist. Having seen a number of CFS patients over the past two or three years, his interest in CFS was piqued when he saw dramatic improvement in these patients' level of functioning by trying various medications. After finding that two medications were successful in treating fatigue and lethargy, Dr. Plioplys became interested in setting up the Center, where these medications could be tried in a formal fashion.

An overview of the structure of the Center was given. Three goals were elucidated: 1)The provision of clinical services of the highest caliber, "that can't be beat in the United States or internationally." 2)The offering of research programs, which would include medication trials for patients (both formal and informal trials), and the investigation of the cause of CFS. 3)The dissemination of public and medical education regarding what CFS is and what can be done about it, as well as the elimination of misperceptions about the illness.

The clinical assessment procedure was explained. The first step would be a "thorough review of the medical history," which would include a review of any previous laboratory tests that may have been performed. This would be followed by a physical and neurologic examination. When necessary, a psychometric evaluation would be conducted. A determination would then be made of which laboratory tests and consultations are needed. The patient would subsequently return for a follow up visit, at which time a review would be made with regard to the diagnosis and elimination of other possible causes for the condition. Finally, the appropriate treatment regimen would be ascertained.

The standard laboratory tests Dr. Plioplys feels anyone with CFS-like symptoms should undergo include a urinalysis, chest x-ray, tuberculosis skin test, and a number of blood tests to rule out other illnesses where fatigue is generally an early symptom. These illnesses include thyroid disease, rheumatic conditions, hepatitis, carnitine deficiency, inflammatory muscle disease, HIV infection, and B12 deficiency.

Dr. Plioplys indicated additional tests can be run in the intitial evaluation, "and there's a tremendous rationale for doing them." For example, multiple sclerosis patients experience extreme disabling fatigue in the early stages, which usually run a few years, and MS can be diagnosed with an MRI scan of the brain. Additionally, CFS patients often show lesions in the brain when an MRI is run. For patients with sleep disorders, polysomnography, commonly known as a sleep study, may be arranged. Patients who may have been exposed to ticks would be tested for Lyme disease. Neopterin studies, which measure macrophage activity in the blood, might be ordered, as elevated neopterin may be indicative of an ongoing viral or inflammatory disease process.

The literature on viral causes of CFS was addressed, but, according to Dr. Plioplys, none of it is definitive, and none of it is conclusive. "Elevation in viral titers may be simply a secondary phenomenon of an abnormally activated immune system," continued Dr. Plioplys. Nevertheless, Dr. Plioplys believes it makes sense to screen for the implicated virsuses, which would include the Epstein-Barr virus, cytomegalovirus, and human herpes virus type 6 (HHV-6).

Immune system tests have been at the forefront of trying to understand CFS and finding diagnostic markers for the illness. None of the immune system tests, however, are specific to CFS. Since most researchers who have studied the immune systems of CFS patients have found abnormalities in certain areas, it makes sense to do a thorough immune system workup. "These kinds of workups are not easy to arrange because the assays are very non-standard and for the most part are run through research laboratories." Arrangements have, therefore, been made with two major immune system laboratories in California to get the studies done reliably and accurately. The blood would be drawn early in the morning at Mercy Hospital and immediately flown to Los Angeles.

Abnormalities detected in the immune system could give some supportive

evidence that a patient has CFS, especially if they coincide with abnormalities found in other reported studies. Immune system studies would include immunoglobulin subclasses, interleukins, interleukin-2 receptors, and alpha interferon. Elevations in any of these immune system measures might be indicative of an ongoing inflammatory condition.

Lymphocytes are white blood cells in the circulatory system that help fight infection. Abnormalities in the types and numbers of lymphocytes have been reported in quite a few studies. At the Center the entire battery can be done, which would include looking for abnormal elevations of activated lymphocytes and their ratios to other cells.

Dr. Plioplys believes the most exciting work that's been done recently relates to lymphocyte function, rather than the number of white blood cells and the categories they would fall under. Lymphocyte function pertains to whether or not the cells are working properly, and can be looked at in terms of responsiveness to three standard mitogens, as well as natural killer cell function. Dr. Plioplys feels that in the future these types of lymphocyte function abnormalities will be the most important ones in the assessment of CFS. Depending on the abnormalities observed in these lymphocyte function tests, it might someday be possible to select categories of medications that may be more beneficial to one type of CFS patient than another. Certain medications can affect lymphocyte responsiveness in certain ways.

At Mercy Hospital consultations with professionals from many specialties can be arranged, if necessary. These specialties include rheumatology, psychiatry, endocrinology, hematology, cardiology, infectious disease, and gastroenterology.

Treatment at the Center would, in part, include medications. The Center's general philosophy towards medications was summarized: "Not all CFS patients are the same, not all medicines are going to work the same." The choice of medication has to be individualized, based on the person, and the history of that person. If certain medications are tried and don't work out, other medicines can be tried. Medications will be used for improving specific symptoms, as there is not yet a "magic bullet" for CFS. Medications that are dangerous or prohibitively expensive will not be used. "On the other hand, we do want to maintain a very open mind to medication possibilities." There are many good medicines that have not yet undergone placebo controlled clinical studies. A specific medicine can help a specific person, and yet the same medicine might not have the same effect on a large group of patients in clinical trials.

Graded physical activity will be an important part of the treatment program. Physical activity will need to be maintained, but not to the point where it precipitates a relapse. Other components of the treatment will include a healthy general diet, as well as social and psychological support.

Kiki Richman, M.S.W., spoke briefly about her role as the psychosocial component in the Center, which is "really on the cutting edge of research and treatment, and inclusion of psychosocial supports." In addition, Ms. Richman views her role as that of an educator, in order to do away with misconceptions that CFS is the "yuppie disease" and that CFS is really depression.

Dr. Plioplys indicated there is a prospect for a future treatment approach to CFS through the Mind-Body Institute at Mercy Hospital, as the Center expands. "The Mind-Body Institute is a registered trademark from one of the Harvard affiliated institutions and basically deals with the issue, as the title of it states, of the interaction of the mind and the body and how to improve both." This approach involves physical therapy, occupational therapy, and psychological support. The Mind-Body Institute always utilizes a group therapy approach with a minimum of 12 or 15 individuals enrolled. When enough interest is generated, that resource will be made available.

Medication trials will be included in the research realm. These trials will be formal, as well as informal. If a patient tries one medication and it isn't successful and then tries another one that is successful, that information will be collected, put together, and analyzed on an ongoing basis. This will help define which treatments seem to work best for which patients. Basic research will also be included in the research realm. This might include the identification of muscular or immune system abnormalities.

Education will be an integral function of the Center. The educational efforts will be aimed at both the general public and the medical community. Lectures will be given to medical professionals and research findings will be submitted for publication.

Dr. Sigita Plioplys spoke on the clinical trials that are now in place at Mercy Hospital. Dr. Plioplys began by expressing her happiness over the fact that the Center is in operation, after a half year of very hard work and bureaucratic difficulties.

Part of the research activities at the Center will include an open label crossover pilot study to assess the efficacy of amantadine and L-carnitine in CFS patients. "Open label" means the subjects will know which medication they are taking while the trials are in progress. "Crossover study" means each patient will receive both medications through the course of the study. This research project was approved by the Institutional Review Board at Mercy Hospital in April, 1993.

Amantadine (commercially known as Symmetrel) is an anti-viral medication which inhibits penetration of viruses into host cells, but does not appear to have virucidal properties (virucidal properties would make it able to kill viruses). Amantadine does not suppress the immune system, but does seem to elevate dopaminergic activity. Dopamine is a neurotransmitter, which is an active chemical substance in the brain. The mechanism of action of amantadine in the central nervous system is not clear. It may be a nonspecific central nervous system stimulator.

Amantadine is effective for the treatment of the fatigue and chronic pain of multiple sclerosis. It is also used for the alleviation of symptoms (including fatigue) of withdrawal in patients with cocaine dependency. The

dose of this medication will be 100 milligrams twice a day, morning and noon, and this is a medium dose. Dr. Plioplys said amantadine is a "safe and very well tolerated medication."

L-carnitine (Carnitor) is a natural protein that transports long chain fatty acids into the mitochondria and removes potentially toxic and excessive short and medium chain fatty acids from the mitochondria. Energy production occurs in the mitochondria of the cells. Fatty acids are a necessary fuel for the production of energy in the body, especially in the heart and skeletal muscles. The main source of energy production, however, is glucose. When there is significant stress on the body from sources such as a viral illness, starvation or pregnancy, the amount of energy production from glucose is inadequate and fatty acids become much more important, especially for the muscles.

Abnormalities in muscle energy metabolism, as well as abnormalities in mitochondrial function, have been found in CFS patients. In fact, British researchers recently found structural abnormalities in almost 70% of the CFS patients they studied by examining muscle biopsies under the electron microscope. A similar research project is being planned at the Center.

L-carnitine has been found to be very effective in the treatment of muscle weakness and fatigue caused by other conditions, such as in the case of hemodialysis patients, inborn metabolic disorders, and seizures that require medications. This drug also improves alertness and arousability in patients with illnesses such as severe neurological handicaps, Rett syndrome and attention deficit disorder. The dose will be one gram three times a day, which is a medium dose, and L-carnitine is a "safe and well tolerated medication."

Thirty patients who meet the 1988 CDC Case Definition will be enrolled in the study. The basic recommended laboratory work-up, as described by Dr. Audrius Plioplys, will be performed on each patient before selection for the study. If there is documentation showing any of the necessary laboratory tests have already been performed within the last six months, the tests will not be repeated. Physical and neurological examinations will be performed on all patients. Differentiations from other illnesses will also be made for each case.

Psychometric evaluations will be performed before, during and after the treatment. The psychometric test battery will include the Beck Depression Inventory, Symptom Checklist-90, General Health Questionnaire, Fatigue Evaluation Questionnaire, Recovery Degree Questionnaire and Fatigue Severity Scale.

The treatment program will continue for four to five months. The first medication will be used for two months. A two-week washout period will follow, where the patient is not on any of the medications under study. Then the second medication will be administered for two months. Monthly visits will be required so that assessments can be made. Medicines will be dispensed during these visits.

During the study, patients will be allowed to take minor analgesics for pain and drugs for medical conditions not related to CFS. However, patients will not be allowed to take antidepressants, anxiolytics, beta blockers, anticonvulsants, or any intravenous medications. Any medications not allowed during the treatment trials must be discontinued two weeks before starting on the medications under study.

If side effects to the medications to be studied occur, the medications will either be reduced in their level of dosage or completely stopped. When a medication is stopped because of side effects, the alternate medication will be started after a two-week washout period.

All medications for the treatment study will be provided free of cost, and the commercial value of provided medications is approximately $600 per patient. Likewise, all evaluations during the program will be provided free of cost. However, the cost of the initial visit and laboratory workup will be billed to each patient's private insurance carrier. Medicare and Medicaid patients will be accepted.

Discontinuation from the treatment program will occur if there is non-compliance with medication intake, failure to keep follow-up visits, occurrence of pregnancy during the study, or intercurrent illnesses for which amantadine or L-carnitine would have to be stopped for more than two months. As Dr. Plioplys concluded, she expressed her hope that the information presented was interesting and useful.

--Ruth Robin

CDC CASE DEFINITION MEETING

A public meeting was held at the CDC in Atlanta on September 27, 1993. The purpose of this meeting was for the CFS medical panel to hear presentations by CFS researchers, support groups, and private citizens before reaching a decision on what should and shouldn't be included in the new case definition.

There was a strong consensus among the various researchers that the current case definition is not selecting homogeneous subjects for study. In other words, the scientists generally agreed that subjects who are being studied because they meet the current case definition for CFS are not all suffering from the exact same illness. [This is a serious problem, because if subjects being studied aren't suffering from the identical illness, results on the same measure from study to study will vary. If studies continually yield conflicting results, consistent commonalities among CFS patients will never be found. Such commonalities are important when uniform diagnostic markers and similar responses to treatment are sought.]

Considerable debate revolved around whether the minor criteria of the current case definition should be discarded or retained under the new case definition. Those researchers who favored discarding the minor criteria argued that they don't aid in the selection of a uniform group of subjects and serve to erroneously exclude a lot of people. Those who favored retaining the minor criteria argued that they do serve a very good function in differentiating patients who