

**Endocrine Causes of Chronic Fatigue Syndrome (CFS)/Chronic Fatigue Immune  
Deficiency Syndrome (CFIDS):**

**A Brief Guide for Patients and Primary Care Physicians**

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### Patient Case

Mary is a 45 year old woman who has had progressive, debilitating fatigue for the past 3 years. She can now only work 3 hours a day at her job as a computer programmer. She takes frequent naps and is too tired to spend time with her husband and two children. She used to take her children Nat and Carol, ages 3 and 5, to the park every evening and is now too tired to go. Previously, she was very active and exercised 3 times per week. She has been depressed for the past 4 years. She used to be quite a positive person. She has gained 30 pounds, primarily in her waist and hips. Her diet is good with lots of fish, chicken and vegetables. Her periods are irregular and she has had only six periods in the past year.

Mary went to her family doctor at her HMO. He performed thyroid function tests which showed a free T4 of 0.9 ng/dl (normal is 0.8-1.9) and her TSH was 0.7  $\mu$ U/ ml (normal is 0.4-5.2). Her doctor told her that these were within normal limits. He did a CBC to look for anemia and an ESR to look for autoimmune disease and told her that these were normal. He told her that she was going through menopause and that she needs to exercise more, eat better and see a therapist. When she asked to see an Endocrinologist, his response was “Why? You are normal.”

Mary was not satisfied with her quality of life and still had a lot of questions about hormones. She sought out the services of Dr. Friedman. The endocrine detective work on Mary began with her free T4 and TSH. They were both relatively low (although in the normal range). If she had such a low free T4 due to thyroid disease, her TSH should be higher. Instead, Dr. Friedman suspected pituitary disease, especially considering her periods were irregular. He performed a TRH test, which showed a blunted response

consistent with pituitary disease. Her IGF-1 (marker of growth hormone secretion) was quite low at 89 ng/ml and she had an abnormal response to growth hormone dynamic testing. Dr. Friedman concluded that she was growth hormone deficient. Her pituitary MRI showed a small pituitary tumor. The pituitary is the master gland of the entire endocrine system, located at the base of the brain. She was treated with levothyroxine, an estradiol patch and growth hormone. She has lost 15 pounds, her energy is greatly improved and her mood is much better. Best of all she can now play with her children. Mary and Dr. Friedman are now considering the risks and benefits of pituitary surgery.

Mary's experience is typical. The human endocrine system is extremely complex. Even a subtle malfunction can cause major but frustratingly difficult-to-diagnose problems for a patient. Without access to the most up to date and highly specialized information, a non-endocrinologist physician may understandably but mistakenly dismiss hormones as the basis of a patient's complaints. In Mary's case, basic endocrine tests were within normal limits. However, a more thorough endocrine workup revealed a tumor on Mary's pituitary, causing hypothyroidism and growth hormone deficiency. While diet, exercise and counseling, as prescribed by Mary's primary care physician, are appropriate general recommendations for many patients, patients with endocrine disorders, such as pituitary tumors need specific treatments.

The prevalence of endocrine diseases as a cause of chronic fatigue is unknown, but we postulate that screening patients for these diseases will lead to successful treatment plans for many patients diagnosed with CFS/CFIDS.

## Introduction

Chronic Fatigue Syndrome (CFS), also called Chronic Fatigue Immune Deficiency Syndrome (CFIDS), is a group of disorders characterized by chronic fatigue and multiple symptoms. There are probably many causes of CFS/CFIDS, although doctors do not have a good understanding of what those causes may be or the correct treatment. The symptom of fatigue is quite common and may be extremely debilitating, forcing the patient to have altered lifestyle, work and personal patterns. The complaint of fatigue is a source of frustration and confusion for any physician. Part of the difficulty of obtaining proper diagnosis and treatment is the lack of blood tests or imaging studies to correctly characterize the patient as having CFS/CFIDS. Thus, the diagnosis is based on symptoms, unlike most diseases where blood tests and studies are used to define the diagnosis.

Our approach is that CFS/CFIDS is made up of many diseases (see Table 1) some of which are endocrinological and can be identified with proper and sometimes highly sophisticated blood testing. It is also important for the patient to be screened for other treatable diseases that may present as chronic fatigue and have these diseases excluded. Some of these treatable diseases that may present with symptoms similar to CFS/CFIDS are listed in Table 2.

**Table 1.** Theoretical causes of CFS/CFIDS

- Infectious (viral or retroviral)
- Immunological
- Allergic
- Environmental
- Endocrinological

**Table 2.** Specific diseases that may present with symptoms similar to CFS/CFIDS

- Malignancy
- Autoimmune Diseases
- Infections
- Psychiatric Disease
  - Depression
  - Schizophrenia
  - Seasonal Affective Disorder
- Neuromuscular Disease
  - Fibromyalgia
- Drug Dependency/Withdrawal
- Prescription Drugs
- Chronic Diseases
  - Anemia
- Nutritional Deficiency
- Sleep Disorders
- Endocrine Diseases

This review will concentrate on Endocrine Causes of Fatigue and discuss the presentation, recommended diagnosis and treatment for these diseases.

### **How do you know if an Endocrine Disease is Causing Chronic Fatigue?**

Patients with Endocrine diseases usually have other symptoms besides fatigue. These endocrine symptoms differ from the classic infectious symptoms associated with CFS such as fever, sore throat and swollen joints. Symptoms suggestive of an endocrine cause of fatigue as opposed to an infectious cause are listed in Table 3. If the patient has some of the symptoms listed in Table 3, an endocrine cause of chronic fatigue should be suspected. Some of the more common endocrine diseases that often present as chronic fatigue are listed in Table 4. A quick reference guide for symptoms complexes and their

Endocrine causes is provided in Question and Answer format below. Before a patient is sent to a counselor or the gym, a primary care physician should carefully consider a specialist who is current on the latest developments in Endocrinology and is experienced in its many nuances.

**Table 3.** Symptoms suggestive of an Endocrine Cause of Fatigue

Irregular periods in women  
 Depression  
 Dizziness on standing  
 Weight gain in spite of dieting  
 Weight loss  
 Body hair growth in women  
 Osteoporosis  
 Breast discharge  
 Sleep disturbances  
 Loss of memory  
 Trouble concentrating  
 Carbohydrate cravings  
 Decreased interest in sex  
 Trouble with erections in men

**Table 4.** Endocrine Causes of Fatigue

Thyroid disease  
 Impaired conversion of the thyroid hormone T4 to T3  
 Adult growth hormone deficiency  
 Adrenal insufficiency  
 Mineralocorticoid insufficiency  
 Metabolic syndrome (Insulin resistance)  
 Diabetes  
 Hypoglycemia  
 Vitamin D deficiency  
 Cushing's Syndrome  
 Androgen deficiency  
 Estrogen deficiency

**Questions and Answers**

Q. You keep talking about tumors. That sounds scary, like cancer?

A. Most endocrine tumors are not cancerous. Many of them grow very slowly and secrete a hormone. The excess hormone is usually the source of most of the symptoms. Some endocrine tumors are non-secreting, but still can cause problems. Only a very small percentage of endocrine tumors are malignant.

Q. I'm a 32 year old female with a 30 pound weight gain over the past 2 years, in spite of dieting and exercise. I'm constantly tired, yet I have trouble sleeping. I'm growing a moustache and have extra hair around my breasts, although I've always been on the hairy side. I've missed 3 periods this year and when they come they are light. I'm also depressed. What could I have, doc?

A. The endocrine diseases that come to mind are Cushing's Syndrome, the metabolic syndrome or adult growth hormone deficiency.

Q. What is Cushing's Syndrome and why do you mention it in this case?

A. Cushing's Syndrome (a specific cluster of symptoms) is often due to a tumor of the pituitary (Cushing's Disease). This tumor will cause the adrenal glands to make too much cortisol. Weight gain, fatigue, trouble sleeping, irregular periods, extra hair growth (hirsutism) and depression are common symptoms. Cushing's Syndrome may be very difficult to diagnose. Patients should be sent to an Endocrinologist who may collect urine for cortisol [urinary free cortisol (UFC) and 17-hydroxysteroids] or collect nighttime salivary cortisol levels.

Q. My doctor has never heard about the metabolic syndrome. What is it?

A. The metabolic syndrome (also called Syndrome X or insulin resistance) is a newly identified syndrome associated with the symptom of fatigue. These patients have elevated insulin levels and central obesity. They often have hypertension, hyperlipidemia, men have gout, and women may have polycystic ovarian disease. A high carbohydrate diet may be involved in this disease. These patients are at risk for having heart disease. In addition to weight loss and exercise, these patients may also benefit from a low carbohydrate diet or treatment with agents that improve insulin action, such as metformin (Glucophage). Your Endocrinologist may want to measure a fasting insulin level to make the diagnosis. A simple blood glucose level or even a GTT are not sufficient to detect Insulin Resistance.

Q. I know children can become growth hormone deficient. Can adults also become growth hormone deficient and how is it related to chronic fatigue?

A. Adults with growth hormone deficiency have severe fatigue, weight gain especially around the abdomen, are often depressed, and have poor quality of life. Children, but not adults, with growth hormone deficiency are short. Most cases of adult growth hormone deficiency are due to damage to the pituitary, often the result of a tumor (usually not malignant). Symptoms of growth hormone deficiency may be the first manifestation of a pituitary tumor. However, a tumor is not always present even though a patient is truly growth hormone deficient. Growth Hormone therapy is effective only for patients who are truly GH deficient. Patients with other causes of CFS will not be helped by Growth Hormone therapy and some may be harmed by it. It is very important to be correctly diagnosed. You should not take growth hormone unless you are found to be growth hormone deficient.

Q. So I should have my growth hormone measured?

A. Not exactly. Growth hormone is secreted in pulses so a single measurement of blood levels is not helpful. Rather your Endocrinologist will probably screen you by measuring a plasma IGF-1 level. If it is low, your doctor may do sophisticated tests that stimulate growth hormone secretion and measure its levels. These tests should only be performed by personnel experienced with GH testing.

Q. I'm post-menopausal and ever since my gynecologist put me on Premarin and Provera, I've felt very tired. Any thoughts on why?

A. Estrogen replacement is a complex subject as estrogens can interact with many other hormonal systems. Even the form of the estrogen is important. Oral estrogen can alter thyroid requirements and actions of growth hormone. Yet estrogen delivered by patch does not interfere in the same way. The effects of different preparations of estrogen even vary from patient to patient. The body itself makes different estrogens, including estradiol and estriol. The symptom of fatigue may be relieved with more specific estrogen preparations. Relying solely on the common but rather generic Premarin, which is a broad preparation from the urine of pregnant horses, may be suboptimal for many women.

Q. I was diagnosed with hypothyroidism due to Hashimoto's thyroiditis and am now taking Synthroid (a form of T4). My TSH is normal (5.1  $\mu$ U/ ml, nl 0.4-5.2), yet I'm extremely fatigued. I've lost 15 pounds, only want to eat salty foods and have noticed that my skin appears more tan. I'm dizzy when I stand up. What should I do?

A. First of all, although your TSH is within normal limits, it is not optimal. I would increase your thyroid hormone replacement until your TSH is between 1 and 2  $\mu$ U/ ml. You may want to ask your Endocrinologist about taking a small amount of T3 (Cytomel) in addition to T4.

Secondly, I'm concerned that you may have adrenal insufficiency (Addison's disease). Hashimoto's thyroiditis is an autoimmune disease and patients with one autoimmune disease often develop another. In this case, it could be Addison's disease. Patients with adrenal insufficiency can have severe fatigue, weight loss, excess skin pigmentation and salt craving. They often have low blood pressure when they stand. This is due to a deficiency of the adrenal mineralocorticoid hormone, aldosterone. This may give them their fatigue. Your Endocrinologist may want to measure hormones such as cortisol, ACTH, DHEAS, renin and aldosterone. You may be treated with replacement hormones including hydrocortisone, Flurinef and DHEA.

Q. How do I find out more about Endocrine causes of chronic fatigue?

A. Visit Dr. Friedman's website at <http://www.goodhormonehealth.com>. Doctors and patients are both welcome to an easily readable table of symptoms associated with excesses and deficiencies of various hormones. For those wishing more in-depth information, e-chapters and e-articles are also available. Some material is available for purchase.