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Review

Is the patient fatigued or weak?

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Abstract

Fatigue and weakness are terms that are often used as if the same thing, but in fact they describe two different sensations, both are nonspecific and in contrast to, weakness which usually indicates a medical disorder, fatigue may result from medical, psychiatric, or physiologic causes. Most patients with fatigue and weakness have self-limited conditions and do not seek medical care, nevertheless, patients who present with either of them as the sole or major complaint may represent a more difficult diagnostic and therapeutic problem. People suffering from certain medical conditions may describe feelings of total body weakness, referring to feelings of tiredness, even though no detectable loss of muscle strength is present. A precise understanding of the patient's description of fatigue or weakness is imperative because this help the clinician to narrow down the possible causes and help better management. The clinician should rely upon open-ended questions, encouraging the patient to describe the fatigue in his or her own words. Questions and comments such as "What do you mean by fatigue?" or "Please describe what you mean" may elicit responses that help distinguish fatigue from true weakness, asthenia, somnolence, shortness of breath, joint pain, limitation of motion or orthostatic hypotension. Extensive laboratory evaluations in the absence of a positive history or physical examination are of little diagnostic utility in the evaluation of the fatigued patient.

Keywords: Fatigue, Weakness, Asthenia, Sleepiness, chronic fatigue syndrome, idiopathic chronic fatigue.

INTRODUCTION

Fatigue and weakness are terms that are often used as if the same thing, but in fact they describe two different sensations, both are nonspecific and in contrast to, weakness which usually indicates a medical disorder, fatigue may result from medical, psychiatric, or physiologic causes. Most patients with fatigue and weakness have self-limited conditions and do not seek medical care, nevertheless, patients who present with either of them as the sole or major complaint may represent a more difficult diagnostic and therapeutic problem. People suffering from certain medical conditions may describe feelings of total body weakness, referring to feelings of tiredness, even though no detectable loss of muscle strength is present (Fauci et al., 2008). A precise understanding of the patient's description of fatigue or weakness is imperative because this help the clinician to narrow down the possible causes and help better management.

Yes, the patient is fatigued

Fatigue is a subjective feeling of tiredness, may be difficult for the patient to describe, and usually has a gradual onset. Other words that might be used to describe fatigue include: tiredness, lethargy, exhaustion, languidness, lassitude, listlessness, lack of energy, and malaise. Unlike weakness, fatigue can be alleviated by periods of rest and describes the inability to continue performing a task after multiple repetitions (Saguil, 2005). Fatigue is considered a symptom, rather than a sign because it is a subjective feeling reported by the patient, rather than an objective one that can be observed by others.

Patients could have physical or mental fatigue. Physical fatigue is a transient inability to maintain optimal physical performance, and is made more severe by intense physical exercise (Hawley and Reilly, 1997), whereas, mental fatigue is a transient decrease in maximal cognitive performance resulting from prolonged periods of cognitive activity (Marcora et al., 2009). In other words, fatigue incorporates 3 components, present to variable degrees: inability to initiate activity; reduced capacity to maintain activity (easy fatiguability); and difficulty with concentration, memory, and emotional stability (mental fatigue) (Markowitz and Rabow, 2007). Also fatigue can be graded using the following system: Grade Zero — no fatigue, Grade One — Fatigue relieved by rest, Grade Two — Fatigue not relieved by rest; limiting instrumental activities of daily living (ADL), Grade Three — Fatigue not relieved by rest; limiting self-care ADL (Common Terminology Criteria for Adverse Events, version 4.0, June, 2010).

Fatigue is a common complaint, with a prevalence of 6 to 7.5 % in Britain and the United States (Lawrie et al., 1997) and 21 to 33 % of patients seeking attention in primary care settings report significant fatigue. It is generally higher in women than in men (Fuhrer and Wessely, 1995) and females comprise 75 % or more of patients with chronic fatigue syndrome (CFS) (Prins et al., 2006).

Table 1. Major causes of chronic fatigue

Psychologic	depression, anxiety, somatization disorder, malnutrition or drug addiction
Pharmacologic	hypnotics, antihypertensives, antidepressants, drug abuse and withdrawal
Endocrine-metabolic	DM, apathetic hyperthyroidism, pituitary insufficiency, hypercalcaemia, adrenal insufficiency , chronic renal failure, hepatic failure
Neoplasdtic-haematologic	occult malignancy, severe anaemia
Infections	endocarditis , tuberculosis , mononucleosis, hepatitis , parasitic disease, HIV infection, cytomegalovirus
Cardiopulmonary	chronic heart failure, COPD
Connective tissue disease	rheumatoid disease
Disturbed sleep	Sleep apnea, esophageal reflux, allergic rhinitis, psychologic causes
Idiopathic(diagnosed by exclusion)	idiopathic fatigue syndrome, chronic fatigue syndrome, fibromyalgia

Table 2. Revised CDC criteria for chronic fatigue syndrome

A case of chronic fatigue syndrome is defined by the presence of
A. Clinically evaluated ,unexplained, persistent or relapsing fatigue that is of new or definite onset ; is not the result of ongoing exertion; is not alleviated by rest ;and results in substantial reduction in previous levels of occupational, educational, social, or personal activities
And
B. 4 or more of the following symptoms that persist or recur during 6 or more consecutive months of illness and that do not predate the fatigue:
Self-reported impairment in short term memory or concentration
Sore throat
Tender cervical or axillary nodes
Muscle pain
Multijoint pain without redness or swelling
Headaches of a new pattern or severity
Unrefreshing sleep
Post-exertional malaise lasting ≥ 24 hours

Fatigue can be a normal response to physical and mental activity as fatigue related to overwork, poor sleep, worry, boredom, or lack of exercise; in most normal individuals it is quickly relieved (usually in hours to about a day) by reducing the activity. Any illness, such as a cold, may cause mild fatigue, which usually goes away as the illness clears up. There are many contributing factors for fatigue; these include psychologic, pharmacologic, endocrine, metabolic, neoplastic, infectious, connective tissue diseases, idiopathic factors (Table1) (Gorroll et al., 1995), alcohol abuse and multiple sclerosis (MS) (Hossain et al., 2005).

60 to 80% of patients with chronic fatigue are suffering from Psychiatric illness. In one study, a psychiatric diagnosis was found in 74% of over 400 patients who presented to a chronic fatigue clinic with at least 1 month of fatigue. The 3 major psychiatric illnesses were major depression (58%), panic disorder (14%), and somatization disorder (10%) (Manu et al., 1993). In another large study of fatigue, at least 50% of patients with chronic fatigue attributed their fatigue to mainly psychological causes (Darbishire et al., 2003). There is debate, however, whether depression is the cause or consequence of fatigue (Fosnocht and Enge, 2013).

The prevalence of fatigue in patients with cancer ranges from 48 to 75 % (Piper and Cella, 2010) which increases to 85 % in patients with serious illnesses (Kutner et al., 2001) and possible contributors include pain, anxiety, depression, dyspnea, nausea, anorexia, cachexia, insomnia, treatment, anaemia, mood disorders, infection, deconditioning, hypoxia, dehydration, Neuroendocrine alterations (e.g., testosterone deficiency in men), Polypharmacy, Comorbidities (Renal, hepatic, cardiac), Autonomic dysfunction, Tumor byproducts, and inflammatory cytokines (Bruera and Yennurajalingam, 2013). However, fatigue is typically multi-dimensional (Munch et al., 2005).

CFS is an uncommon cause of chronic fatigue and for its diagnosis, the patients must have clinically evaluated, unexplained, persistent or relapsing fatigue plus 4 or more specifically defined associated symptoms. (Table 2) (Fukuda et al., 1994) CFS represents a small subset of those who complain of chronic fatigue, accounting for 1 to 9 % of patients with fatigue of at least 6 months duration

(Buchwald et al., 1995). It is important to distinguish between CFS, and idiopathic chronic fatigue as still there is a significant subset of patients has no identifiable cause of fatigue. If the fatigue persists for over 6 months and is debilitating, but does not meet criteria for the CFS, it is termed idiopathic chronic fatigue (ICF) (Fukuda et al., 1994). This is shown by a study conducted by Dutch family clinicians who failed to identify a specific diagnosis in 37.5 % of patients (Okkes et al., 2002)

Fatigue will be considered Recent if symptoms lasting less than 1 month, Prolonged if lasting more than 1 month and Chronic if lasting over 6 months. The history is the most important component of the evaluation of chronic fatigue. The clinician should rely upon open-ended questions that help distinguish fatigue from dyspnea, somnolence, and true weakness. Severity, onset, course, duration and daily pattern of fatigue, the quantity and quality of sleep, factors that alleviate or exacerbate symptoms, impact on daily life, ability to work, socialize and participate in family activities should be explored. History should include also details about medications, whether prescribed, over the counter, or recreational, including alcohol, any underlying medical or psychiatric disorder, and symptoms suggesting underlying occult medical illness such as weight loss or night sweats. The physical examination should note: General appearance, Presence of lymphadenopathy, splenomegally, evidence of thyroid disease, Cardiopulmonary and Neurologic examination (Fosnocht and Enge, 2013). A formal mental assessment of thought content, orientation, emotional status, memory, constructional ability, and abstract reasoning is vital. Loss of interest in daily activities and insomnia may indicate a depressive state. Recurring episodes of apprehension, tremulousness, and palpitations are seen with generalized anxiety. A psychiatric diagnosis should be based on the presence of positive findings and not simply on the absence of a medical explanation. When a diagnosis cannot be made, the patient should not be told that "there is nothing wrong"; instead, he should be advised that careful follow-up is necessary in order to collect additional data.

Reasonable laboratory investigations include: Complete blood count, ESR, Ferritin, electrolytes, glucose, renal and liver function tests, Thyroid stimulating hormone (TSH), and Creatine kinase (CK). Some other investigations like HIV testing, Mantoux test, EBV, CMV, or Lyme titers, immunoglobulins, inflammatory markers as ANA or rheumatoid factor, and antibody studies for celiac disease may be requested (Fosnocht and Enge, 2013) Serum testosterone, in men if the history suggestive of hypogonadism (Escalante et al., 2003).

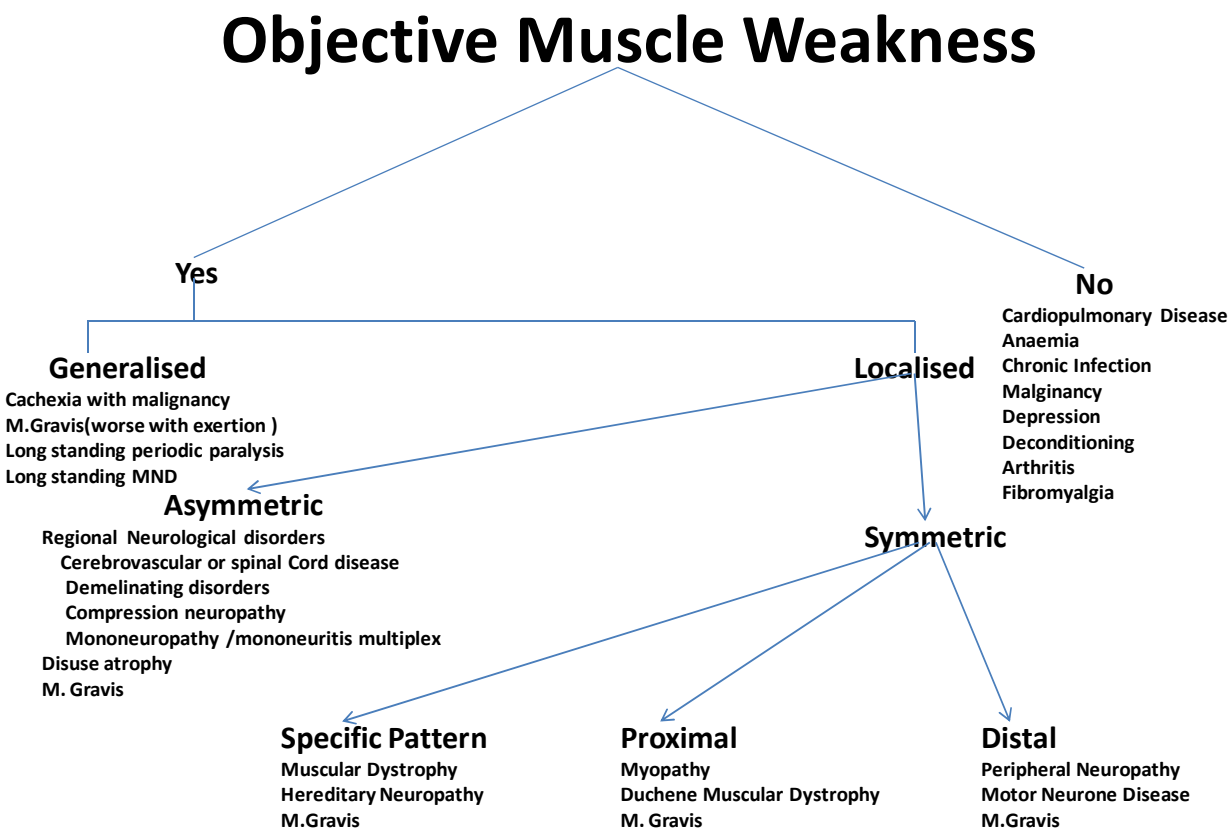
For treatment of fatigue, establishing a trusting clinician-patient relationship, and defining appropriate therapeutic goals, is important. These goals should include: accomplishing ADL, returning to work, maintaining interpersonal relationships and performing some form of daily exercise. Treatment is usually directed towards its cause. A trial of antidepressant drugs should be offered to patients whose illness has features of depression. Patients should be advised that immediate response to antidepressant therapy is not expected, and that treatment for several weeks needed before response could be assessed. However, Antidepressants may provoke or exacerbate fatigue and should be discontinued if no demonstrable improvement within a reasonable time frame (6-8 weeks) (Fosnocht and Enge, 2013). In one study of patients with unexplained symptoms, including patients with chronic fatigue, full dose antidepressant therapy was associated with 80 % of the overall response to a multidisciplinary treatment plan (Smith et al., 2006).

Either ICF or CFS should be managed either by cognitive behavioral therapy (CBT) or graded exercise therapy (GET) (Whiting et al., 2001). In a study of outpatients with over 3 months of unexplained fatigue, 25 % of patients who met criteria for CFS and 60% of patients who did not meet these criteria responded to treatment with either CBT or GET (Ridsdale et al., 2004). A randomized trial demonstrated that CBT and GET lead to significantly reduced fatigue (White et al., 2011).

A number of medications have been evaluated and used in treatment of patients with CFS include immune serum globulin, rituximab, acyclovir, galantamine, antidepressants, methylphenidate, modafinil, glucocorticoids, amantadine, doxycycline, magnesium, evening primrose oil, vitamin B12, Ampligen, essential fatty acids, bovine or porcine liver extract, dialyzable leukocyte extract, ranitidine, interferons, exclusion diets, BioBran MGN-3, and removal of dental fillings (Gluckman, 2013). Other measures include: Provision of general sleep hygiene advice, discouraging over-sleeping, patient education, referral to support groups, Iron therapy in nonanemic patients with low serum ferritin (Fosnocht and Enge, 2013), moderate exercise and yoga (Bruera and Yennurajalingam, 2013).

There are a number of pharmacologic agents that are effective in fatigue treatment in palliative care. Glucocorticoids decrease fatigue, possibly by reducing IL-1, IL-6, and TNF-alpha and by an effect on hypothalamic-pituitary axis (Agarwal and Marshall, 2001). Oral Dexamethasone appears to be the most intensively investigated and it significantly improved fatigue in a randomized controlled trial of 84 patients with advanced cancer (Yennurajalingam et al., 2012). Megestrol acetate is another drug significantly improved appetite, activity, and overall well-being. Both fatigue and depression in patients receiving palliative care can be treated with the psychostimulants such as dextroamphetamine, methylphenidate, pemoline, or modafinil which act rapidly, and are generally well tolerated and safe. However, they should be used with caution in patients with heart disease or cognitive disturbances (e.g., delirium). In hypogonadal men, testosterone replacement

Figure 1. Approach to the adult patient with the complaint of weakness



improves quality of life and diminishes fatigue (Bruera and Yennurajalingam, 2013).

No, he is Weak

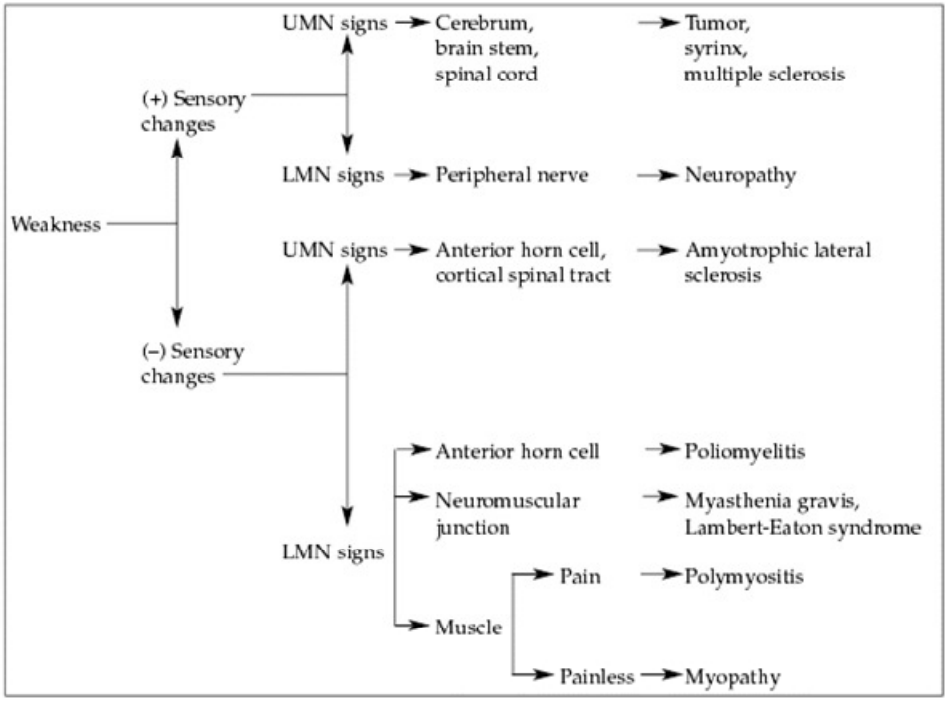
The patient feels weak if there is lack of strength in one or more muscles and he needs extra effort to move his arms, legs or other muscles. So, opposite to fatigue, patient with primary weakness is unable to perform the first repetition of the task (Saguil, 2005). Weakness may be generalized or may affect one muscle or muscle group exclusively (Fauci et al., 2008). Patients with true muscle weakness typically complain that they are unable to perform specific tasks, such as climbing stairs or combing hair. Weakness may or may not be associated with muscle atrophy, in the contrary, patients with cachexia have advanced generalized muscle atrophy despite muscle strength is relatively preserved. Also muscle pain is relatively uncommon in patients with many types of myopathy and true weakness (Miller, 2013). Recurring episodes of weakness should raise the question of periodic paralysis. Weakness exacerbated by effort and relieved by rest is characteristic of myasthenia gravis.

Formal muscle testing is required to document true muscle weakness. The strength of each muscle can be assessed by determining how much force is required by the examiner to overcome maximal contraction by the patient. A widely used system to measure muscle strength based upon a scale of zero to five: Zero — no muscle contraction, One — flicker or trace of muscle contraction, Two — Limb movement possible only with gravity eliminated, Three — Limb movement against gravity only, Four — power decreased but limb movement possible against resistance and Five — normal power against resistance (London Medical Research Council, 1981). The distribution of muscle weakness (i.e., generalized, distal, proximal, or localized) is essential followed by neurological examination to localize the site of the lesion and to narrow the number of possible causes (Figure 1, Table 3) (Miller, 2013). So checking muscle atrophy, tone and tenderness, deep tendon reflexes, pathologic reflexes, fasciculations, sensory deficits, and analysis of these findings allow the clinician to distinguish between cerebral, spinal, peripheral nerve, neuromuscular and myopathic processes (Figure 2) (Freeman et al., 2013). Proximal muscle weakness as with difficulty with combing hair and climbing stairs suggests a myopathy, whereas distal muscle weakness is more consistent with a peripheral neuropathy or pyramidal tract disorder. Upper motor neuron weakness is accompanied by increased tone, an increase in deep tendon reflexes, and a decrease in superficial reflexes, up going plantar response, relatively

Table 3. Differential diagnosis of weakness

Diagnostic category	Upper motor neuron	Anterior horn	Peripheral nerve	NM junction	Muscle
Genetic	Leukodystrophies and Demyelinating disease	Spinal muscular atrophy	Peroneal muscular atrophy	Myasthenia gravis	Muscular dystrophies
Inflammatory	Vasculitis	Amyotrophic lateral sclerosis	Guillain- Barre	Myasthenia gravis	Polymyositis, Dermatomyositis, Inclusion Body myositis, SLE, RA, Sjögren's syndrome, overlap syndrome, Vasculitis
Infectious	Brain and spinal cord abscess	Poliomyelitis	Leprosy	Botulism	HIV, influenza, parainfluenza, Coxsackie, cytomegalovirus, echovirus, adenovirus, Epstein Barr virus, Bacterial-pyomyositis, lyme myositis Fungal Parasitic- trichinosis, toxoplasmosis
Neoplastic	Brain and spinal cord tumor	Paraneoplastic syndrome	Myeloma/ amyloid	Eaton-Lambert syndrome	Malignancy- associated myositis
Toxic/drug	Radiation	Lead	Lead	Organophosphate poisoning	Steroid , Alcohol , Statin Penicillamine, Zidovudine, Cocaine, Heroin, colchicine, antimalarial drugs
Metabolic	Vitamin B12 deficiency	-	DM, Vitamin B12 deficiency	-	Hypothyroid , Hyperthyroid Cushing"s , Hypoglycemia, Disorders of carbohydrate, lipid, and purine metabolism
others	CVA				Hypokalaemia Hypophosphataemia Hypocalcaemia Hyponatraemia/hypernatraemia Rhabdomyolysis Malignant hyperthermia

Figure 2. Neurological Examination for Adult patient with the complaint of weakness



minimal atrophy, and do not lead to the fasciculations, nevertheless, some atrophy may occur of disuse nature and acute lesions may produce a period of diminished tone (shock stage). Lower motor neuron weakness result in decreased muscle tone, decreased reflexes, atrophy and, possibly, fasciculations especially with anterior horn cell lesions. Neuromuscular disease is characterized by fluctuating strength based on muscle use. For example, myasthenia gravis results in decreasing power with continuous contraction. On the other hand, Lambert-Eaton myaesthetic syndrome results increased strength with repeated contraction. Muscle diseases are generally proximal and symmetrical. There is usually minimal atrophy until late in the course and muscle stretch reflexes typically remain normal. An exception to this general rule is myotonic dystrophy, which tends to affect the muscle of the distal extremity and is associated with myotonia (inability to rapidly relax a muscle after tonic contraction) (Cohen et al., 2013). Patients should also be assessed for respiratory muscle weakness, particularly if there is evidence of ventilatory compromise or oropharyngeal muscle weakness (Miller, 2013).

Useful laboratory tests in identifying the causes of weakness include: serum electrolytes, calcium, magnesium, and phosphate; CK, aldolase, lactate dehydrogenase, aminotransferases, and TSH. If there are clinical features that suggest an inflammatory myopathy or associated connective tissue disease then serologic studies are warranted, including: antinuclear antibodies, antibodies against extractable nuclear antigens (anti-Ro/SSA, anti-La/SSB, anti-Sm, and anti-RNP), and "myositis specific" antigens (e.g., anti-histidyl-t-RNA synthase [anti-Jo-1]). Anti-neutrophil cytoplasmic antibody titers, hepatitis B and C serologies, and cryoglobulins should be obtained in patients with suspected vasculitis. A positive urine test for blood in the absence of red cells suggests myoglobinuria (Miller, 2013). Complete blood count, glucose level, ESR, protein electrophoresis, VDRL/RPR, HIV, vitamin B12 level, and testing of heavy metal exposure may be useful if peripheral nerve disease is anticipated. Antibodies against acetylcholine receptors may be indicated when myasthenia gravis is suspected (Cohen et al., 2013).

Magnetic resonance imaging, muscle biopsy and genetic testing help to identify the cause in case of myopathy. Nerve conduction and electromyographic (EMG) studies are requested when peripheral nerves, neuromuscular junction, or muscle lesions are suspected. The EMG is also of value in directing the site of muscle biopsy (Miller, 2013). Neuroimaging (for suspected cerebrovascular disease) or lumbar puncture (for possible meningitis, encephalitis, or multiple sclerosis) is indicated if central lesions are suspected (Saguil, 2005).

If an endocrinopathy is suspected, more specific assays can be performed based on clinical suspicion (e.g., 24-hour urine cortisol testing to rule out Cushing's disease; oral glucose load/growth hormone assay to rule out acromegaly; vitamin D assay to rule out osteomalacia) (Riggs, 2002).

Treatment of weakness is directed mainly toward treating the insulting cause, physiotherapy and rehabilitation.

Both fatigue and weakness should be differentiated from

Asthenia is common conditions that differ from weakness and fatigue, but often overlap with (Hinshaw et al., 2002). Asthenia is a sense of weariness or exhaustion in the absence of muscle weakness. This condition is common in people who have CFS, sleep disorders, depression, or chronic heart, lung, and kidney disease. Unfortunately, the distinction between asthenia, fatigue, and primary weakness often is unclear. Patients frequently confuse the terms, and the medical literature sometimes uses them interchangeably. In addition, a patient's condition may cause progression from one syndrome to another; for example, asthenia in a patient with heart failure may progress to true muscle weakness through deconditioning. Further, asthenia and fatigue can coexist with weakness, such as in patients with multiple sclerosis and concomitant depression (Saguil, 2005).

Fatigue should be distinguished from Sleepiness (somnolence), which is inability to remain fully awake or alert during the wakefulness portion of the sleep-wake cycle. If the problem is reported to be worse during sedentary, monotonous activities than during extended physical activity, sleepiness is more likely than fatigue (Braley and Chervin, 2010). The Fatigue Severity Scale can be combined with the Epworth Sleepiness Scale to objectively determine whether a patient is sleepy, fatigued, or both (Hossain et al., 2005). So, Fatigue is generally considered a more long-term condition than sleepiness (Shen et al., 2006).

Also, other symptoms should not be confused with fatigue or weakness . For example, some patients speak of fatigue or weakness when they are actually experiencing shortness of breath, joint pain or limitation of motion. So the clinician must explore exactly what does the patient mean? And a careful history and physical examination will permit the distinction between fatigue, weakness, shortness of breath, joint pain and limitation of motion, etc. Measuring the blood pressure in the erect position may document orthostatic hypotension as a cause of the weakness or fatigue.

CONCLUSION

The clinician should rely upon open-ended questions, encouraging the patient to describe the fatigue in his or her own words. Questions and comments such as "What do you mean by fatigue?" or "Please describe what you

mean" may elicit responses that help distinguish fatigue from true weakness, asthenia, somnolence, shortness of breath, joint pain, limitation of motion or orthostatic hypotension. Extensive laboratory evaluations in the absence of a positive history or physical examination are of little diagnostic utility in the evaluation of the fatigued patient.

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