

Lab Updates

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Inside this issue:

Fatigue

Genomic Microarray Analysis

Featured Patient Service Center

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Fatigue

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I. Definition. Fatigue is a symptom in which patients describe a feeling of difficulty or exhaustion in pursuing or accomplishing activities. This article will consider idiopathic fatigue that has been present for longer than 1 month. Chronic fatigue refers to fatigue that has been present longer than 6 months.

II. Overview. Fatigue should be considered a symptom, not a diagnosis.

A. Etiology

- 1. Idiopathic fatigue.** Approximately 20% of cases have no identifiable cause.
- 2. Psychiatric disorders:** As many as 75% of patients with chronic fatigue have a psychiatric disorder. Depression is the most common of the psychogenic causes. Other causes include mood disorder, somatization disorder, and anxiety disorder.
- 3. Organic disease:** If fatigue develops in patients older than 40 years of age, the patient is twice as likely to have an organic disease as the cause.

B. Approach: Patients with fatigue often receive either excessive or inadequate medical evaluations. Therefore, a judicious approach is necessary.

- 1. The primary purpose** of evaluating a patient with fatigue is to identify and treat any underlying or contributing factors.



2. Exhaustive, unfocused evaluations are not likely to be revealing and in fact may be counterproductive, reinforcing that the patient has an insidious unidentified medical illness. This is particularly consequential in those with psychogenic components.
3. When assessing the causes of fatigue using a relatively standardized diagnostic approach, it is rare to overlook important medical diagnoses. This is particularly true when patients are assessed serially.

III. Differential diagnosis (Table 26-1)

- A. Physiologic fatigue** is found in situations that would cause most people to be fatigued. If a patient describes an overwhelming urge to sleep, even during the day, a sleep disorder should be suspected.
- B. Muscular fatigue** can produce decreased performance in the setting of muscle overuse. It is relieved with rest and accentuated with physical activity. It may be localized to specific muscle groups or occur in a generalized distribution. Overdemand in the workplace, overuse of muscles, deconditioning, or true weakness from neurogenic or myopathic disease would be examples of muscular fatigue.
- C. Medication-induced fatigue.** Fatigue is a common side effect of many medications, including prescription, over-the-counter, and drugs of abuse. A thorough medication history, including the temporal relation between the initiation of the medication and onset of fatigue is of paramount importance.

Differential Diagnosis of Fatigue

- **Physiologic causes**, including sleep disorders
- **Muscular disorders**, including fibromyalgia, neuromuscular disorders
- **Systemic medical disorders**
 - Endocrine (hypothyroidism, diabetes, adrenal insufficiency, hypopituitarism)
 - Cardiovascular (low output states)
 - Respiratory (chronic obstructive pulmonary disorder, asthma, chronic hypoxia)
 - Hematologic (anemia, myeloproliferative disorders)
 - Infectious (HIV, hepatitis, tuberculosis, Epstein-Barr virus, cytomegalovirus disease, subacute bacterial endocarditis)
 - Malignancy
 - Neurologic (multiple sclerosis, Parkinson's disease, dementia)
 - Rheumatologic (rheumatoid arthritis, vasculitis, systemic lupus erythematosus, Sjogren's syndrome)
 - Renal insufficiency
 - Electrolyte disturbance (especially hypercalcemia in the chronic setting)
 - Hepatic insufficiency
 - Obesity (body mass index > 45)
 - Malnutrition or eating disorder
 - Pregnancy
- **Pharmacologic causes**
 - Medication side effects, associated with over-the-counter medications, supplements, herbal medications, and prescription agents
 - Substance abuse
- **Psychogenic disorder** (most common)
- **Chronic fatigue syndrome**
- **Undetermined etiology**

TABLE 26-1



D. Psychogenic fatigue. Generally, the fatigue is present on awakening prior to getting out of bed. As the day progresses, or on weekends or holidays, it may improve. If this type of fatigue is found during the history, a thorough psychological assessment should be pursued.

E. Fatigue related to a systemic illness. This type of fatigue is generally absent upon waking but develops and progressively worsens during the day. Fatigue usually becomes worse unless the underlying disorder is diagnosed and treated. Relentlessly progressive fatigue may signal serious disease. Conditions in which fatigue may predominate are noted in Table 26-1.

F. Idiopathic fatigue. This type of fatigue is stable and does not change over time. If changes are noted, the patient should be reevaluated to identify intervening diagnoses. The approach to idiopathic fatigue is largely supportive, and patients may benefit from rescheduling activities and an exercise program.

IV. Clinical Evaluation

A. History. Eliciting important medical history or signs and symptoms of organic disease will permit a targeted evaluation, which will uncover the less common, yet potentially life-threatening medical causes of fatigue.

1. Define fatigue. It is very helpful to ask patients to define the fatigue they are experiencing. Fatigue has varying connotations such as weariness, weakness, fatigue with exertion, tiredness, boredom, lack of energy, and sleepiness. Asking why the patient feels fatigued can provide valuable insight into the meaning of fatigue for the patient.

2. Onset of symptoms: Explore medical and psychosocial circumstances present at the onset of symptoms. It is important to note that fatigue is rarely the only symptom present in medical conditions.

3. Sleep history: A detailed sleep history is mandatory, as sleep disorders are associated with excessive daytime somnolence. Questions that determine how many hours of sleep, quality of sleep, and daytime sleepiness can be revealing.

4. Psychiatric history: Obtain a relevant psychiatric history, including psychosocial stressors, major life changes, significant illness of family member or friend, current level of functioning, social supports, history of abuse (physical, mental, and substance), and coping skills.

5. Review of symptoms: A detailed review of symptoms, mandatory in all patients presenting with isolated fatigue symptoms, may be best obtained through the use of a standardized questionnaire.

B. Physical examination. Besides identifying important clues to underlying medical diagnoses, a complete physical examination also offers patients a message that their concern is being taken seriously. This is important not only diagnostically, but also as a tool when reviewing the syndrome with patients during the “therapeutic” interchange.

V. Diagnostic Evaluation (see Fig. 26-1 on page 6)

A. Laboratory evaluation. If the history and physical examination do not identify a specific etiology or psychiatric diagnosis, a rudimentary laboratory evaluation is pursued, including a complete blood count (CBC) with differential, liver chemistries, electrolytes, creatinine, glucose, calcium, thyroid-stimulating hormone (TSH), and urinalysis.

B. Supplemental studies. The following should be considered in limited circumstances:

1. Where **rheumatic, inflammatory, or muscular conditions** are suspected, creatine phosphokinase (CPK), antinuclear antibodies, rheumatoid factor (RF), and erythrocyte sedimentation rate (ESR) should be considered. ESR is not recommended as a routine study since the diagnostic yield is low and will often generate other studies, which may be misleading.
2. In **patients older than 50 years of age**, who are tobacco abusers, have known environmental exposures, and are at risk for occult pulmonary pathology (e.g., sarcoidosis, tuberculosis, neoplasm), a chest radiograph, intradermal tuberculosis test, and oximetry can be helpful.

3. **HIV testing** should be considered in any patient whose history or examination is suggestive of infection.

4. Patients should all be screened with age- and gender-specific **health maintenance recommendations**. Although identified pathology may not be causative of fatigue, the clinical presentation of fatigue affords the clinician an opportunity to pursue recommended screening procedures.

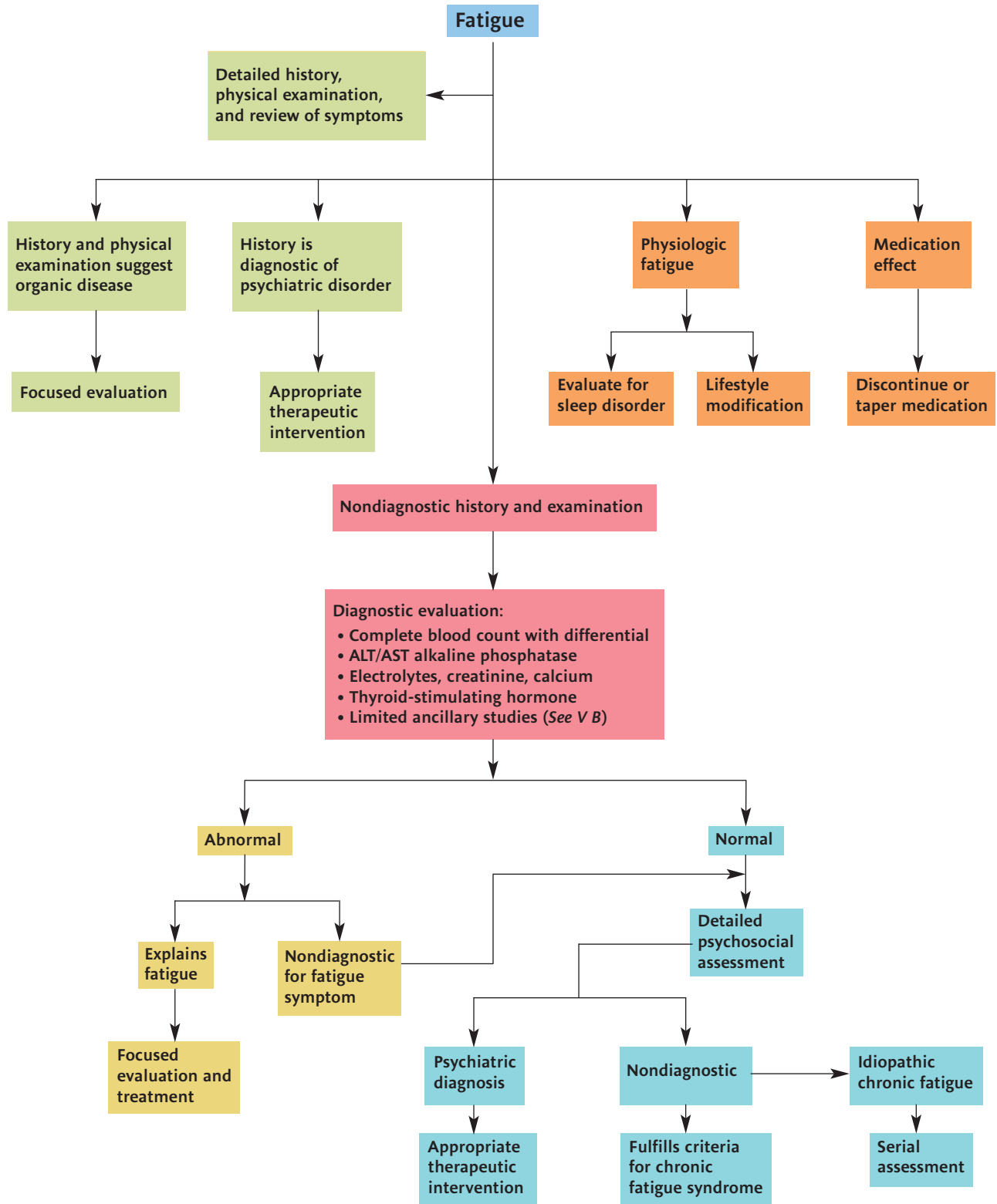
5. Where the clinical scenario is suggestive, an **overnight polysomnogram** should be considered.

Reference: Rebecca Spanagel, "Fatigue". *Guide to Diagnostic Testing*. pp 173-177.

If you have questions, comments or suggestions, please contact:
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Algorithm for the Diagnosis of Fatigue



ALT/AST = alkaline aminotransferase/aspartate aminotransferase

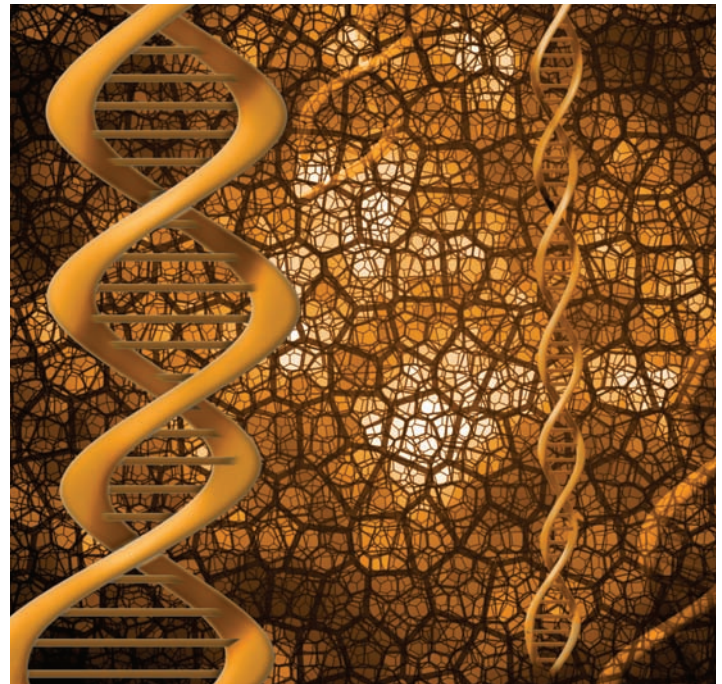
Figure 26-1

UMass Memorial Genomic Microarray Analysis

The UMass Memorial Laboratories is pleased to announce that we are now offering Genomic Microarray Analysis to complement our extensive test menu. Conventional cytogenetic analysis is limited in its ability to detect and/or characterize chromosome abnormalities of less than approximately 5–10 Mb in size, as well as larger changes that do not alter the standard G-banding karyotype pattern. Genomic microarray analysis can detect chromosome imbalances up to 10 times smaller than those found by conventional cytogenetics, as well as those that may be hidden by the limitations of G-banding. This test utilizes comparative genomic hybridization (CGH) with over 43,000 oligonucleotide probes to identify chromosomal imbalances. The array provides high-density probe coverage of all known microdeletion/microduplication syndrome regions, as well as both the subtelomeric and pericentromeric regions of the chromosomes. In addition, the UMass Memorial array has probes spaced at an average of 75 kb across the genome to identify duplications and/or deletions of ~500 kb or greater. Our oligonucleotide microarray chip is based on the design of the EmArray Cyto6000, developed at Emory Genetics Laboratory (Atlanta, GA) as part of the International Standard Cytogenomic Array Consortium (ISCA), and is manufactured by Agilent Technologies Inc. UML Cytogenetics Laboratory is a member of the ISCA, along with ~35 cytogenetics laboratories world wide.

The UML microarray analysis is appropriate testing for patients:

- (1) who have had a normal chromosome analysis but have an abnormal phenotype such as dysmorphic features or mental retardation because the analysis can uncover imbalances smaller than the resolution of a standard karyotype.
- (2) with features that overlap more than one known microdeletion/microduplication syndrome because the analysis targets and tests all such regions simultaneously, providing complete results after a single analysis.
- (3) with a cytogenetically detected unbalanced chromosome abnormality (such as a translocation or marker chromosome) because the analysis can precisely identify the unbalanced region(s) and define the size of the imbalance so that the involved genes may be examined.
- (4) with an “apparently balanced” chromosomal rearrangement and an abnormal phenotype because the analysis tests for possible cryptic deletions/duplications at the chromosomal breakpoints and across the genome.



There are limitations to microarray analysis. Microarray analysis will not detect balanced chromosomal rearrangements such as translocations or inversions. Microarray testing can not detect point mutations, copy number changes in areas of the chromosomes that are not represented by the oligonucleotide array (that is, in areas between probes), or low-level mosaicism. This technique detects imbalances that are relatively small by cytogenetic standards. However, duplications or deletions smaller than 500 kb will not be investigated or reported unless they encompass one of the genomic locations specifically targeted on this array.

Specimen Requirements: Whole blood in a green top (Sodium Heparin) tube. Adults: 10 ml; Children: 5 ml; Infants: 3 ml. Standard chromosome analysis should be considered prior to or concurrent with microarray analysis. A consultation with a Clinical Geneticist prior to testing is recommended.

If you have questions, comments or suggestions, please contact:

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We are one of the largest laboratory providers in New England

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The vision of UMass Memorial Laboratories is:

- To be a leading provider of laboratory services throughout New England, meeting the needs of patients and providers in the region, and
- To be one of the top ten academic medical center-based laboratories in the United States



West Boylston Street PSC **1 West Boylston St., Worcester, MA**

West Boylston PSC is located at 1 West Boylston Street, Worcester, MA. The hours are Monday through Friday 8:00am-5:00pm, closed 12:15pm-1:15pm. The phone number at West Boylston PSC is 508-853-1208.