TEACHING CASE REPORT

Fatigue: a practical approach to diagnosis in primary care

The case: A previously well 36-year old woman taking no medications presented to her primary care physician's office with a complaint of unusual generalized fatigue. It had progressed over 8 months, was exacerbated by physical and mental activities and was not relieved by rest. The patient had a history of anemia during a previous pregnancy without a specific clinical diagnosis. She reported regular menstrual periods and no sleep problems. Her weight was stable, and she had no gastrointestinal, musculoskeletal, neurologic or cardiovascular complaints. She reported no polyuria or polydipsia and no cold intolerance. She did not drink and had no history of trauma, recent viral illness, relationship change or situational stress. She denied having symptoms of depression.

On examination, the patient was alert and well groomed and was not pale or jaundiced. She was afebrile, and her heart rate and blood pressure were normal. The heart, lung, musculoskeletal and screening neurologic examinations yielded normal results, as did the abdominal examination. The patient had no lymphadenopathy. Results of a pregnancy test were negative, and those of initial laboratory tests, including a complete blood count, and creatine and electrolyte measurement, were normal except for elevated transaminase levels (alanine transaminase 83 U/L, aspartate transaminase 51 U/L [normal < 50 U/L for both]). The patient's random cortisol level was normal. The results of serologic testing for HIV infection, hepatitis C and B, and mononucleosis were negative.

The patient underwent abdominal ultrasonography, which revealed no liver or biliary tract abnormalities. Antinuclear antibody and smooth-muscle antibody tests yielded negative results, and the serum iron and total iron-binding capacity, α_1-antitrypsin and ceruloplasmin levels were all within normal limits. Because of the lack of an explanation for the persistent fatigue and elevated transaminase levels, a test for IgA antiendomysial antibodies was performed and gave a positive result. Endoscopy and small-bowel biopsy revealed a lesion consistent with celiac disease confined to the proximal small intestine.

Fatigue is a sensation of exhaustion during or after usual activities, or a feeling of inadequate energy to begin these activities. In national population surveys, 20%–30% of adults will report that they have significant fatigue at any given time.

For many patients, fatigue is related to a known severe illness or organ failure. In primary care practices, the underlying cause cannot be identified in one-third of patients, which can be frustrating for both the patient and the practitioner. However, the cause is identifiable in two-thirds of cases.[1] In a study conducted in the Netherlands, among 5915 patients who visited their primary care physician because of fatigue, the most common diagnoses ultimately made were viral illness, upper respiratory tract infection, iron deficiency anemia, acute bronchitis or bronchiolitis, adverse effect of a medication taken at the proper dose, and depression or other mental disorder.[1]

The fatigue's duration can be described as recent (onset within 1 month before presentation), prolonged (lasting 1–6 months) or chronic (lasting > 6 months). For patients with recent or prolonged fatigue, a history and physical examination often help to identify the cause, but we have found that these are often less helpful for distinguishing the cause of chronic fatigue.

The differential diagnosis of fatigue is broad (Table 1). Patients with chronic fatigue can have either chronic fatigue syndrome (Box 1) or, if the diagnostic criteria for the syndrome are lacking, simple idiopathic chronic fatigue.[2,3] The prevalence of chronic fatigue syndrome is higher among adults 30–39 years old than among those over 60 and affects more women than men.

Box 1: Diagnostic criteria for chronic fatigue syndrome

Chronic fatigue lasting > 6 mo
plus at least 4 of the following:

- Subjective memory impairment
- Tender lymph nodes
- Muscle pain
- Joint pain
- Headache
- Unrefreshing sleep
- Postexertional malaise (> 24 h)

We propose here an approach to evaluating fatigue in primary care practices:

1. History: Details about the fatigue's duration (recent, prolonged or chronic), onset (sudden or progressive), recovery period (short or long), type (physical or mental fatigue) and the patient's usual level of physical activity (sedentary or active) can point to the underlying cause. This history taking is particularly helpful in distinguishing chronic fatigue from chronic fatigue syndrome (Box 1), the latter often presenting with a sudden onset and a recovery period lasting hours or days. In addition, many patients with chronic fatigue are simply deconditioned or "out of shape" and will benefit from exercise therapy.
2. Physical examination: This occasionally identifies evidence of organ-based illness (Table 1); however, its value may be overrated. It can help to assure patients that their complaints are being taken seriously, especially the one-third of patients for whom no specific cause will be identified.[1] Some unusual

DOI:10.1503/cmaj.1031153

Table 1: Major underlying causes of fatigue

Cause	Symptoms or signs
Cardiorespiratory	
Heart disease, congestive heart failure	Dyspnea, crackles on auscultation, elevated jugular venous pressure, ankle edema, murmurs, extra heart sounds
COPD	Lip pursing, prolonged expiration, wheezing, hyperinflated chest, cyanosis
Endocrine	
Addison's disease	Hypotension, pigmentation in skin creases, scars and buccal mucosa
Diabetes mellitus	Polyuria, polydipsia, loss of sensation to light touch and vibration
Hypothyroidism	Temperature intolerance, weight gain, goiter or thyroid nodule, skin and hair changes, constipation, delayed relaxation phase of reflexes
Gastrointestinal	
Malignant disease	Melena, bright red blood in stool, anorexia
Celiac disease	Steatorrhea, weight loss, failure to thrive
Chronic liver disease	Jaundice, palmar erythema, Dupuytren's contractures, hepatosplenomegaly
Primary biliary cirrhosis	Pruritis, excoriations, xanthelasma, hepatosplenomegaly, clubbing
Hematologic	
Anemia	Menometrorrhagia, pallor, tachycardia, systolic ejection murmur
Autoimmune disease	Arthralgia, rash
Hemochromatosis	Slate-grey pigmentation, gynecomastia, hepatosplenomegaly, cardiac arrhythmias
Iron deficiency	Blue sclera
Lymphoma, leukemia	Lymphadenopathy, rash, hepatosplenomegaly, night sweats, weight loss
Infection	
HIV infection, viral hepatitis	History of injection drug use, unprotected sex
EBV infection	Sore throat, lymphadenopathy, hepatosplenomegaly
Viral illness	History of viral infection (e.g., gastroenteritis, influenza, cytomegalovirus infection, parvovirus infection)
Musculoskeletal	
Rheumatoid arthritis	Inflammatory arthritis, ulnar deviation, swan neck or Boutonnière deformity, rheumatoid nodules
Neurologic	
Cerebrovascular disease	Preceding cerebrovascular symptoms
Multiple sclerosis	Visual field defect, asymmetric deep-tendon or plantar reflexes, ataxia, nystagmus
Myasthenia gravis	Muscle fatiguability and weakness (worse with repeated activity, better with rest)
Parkinson's disease	Tremor, rigidity, bradykinesia
Amyotrophic lateral sclerosis	Upper motor neuron impairment
Other	
Malignant disease	Weight loss, lymphadenopathy, hepatosplenomegaly, mass in breast, testicle, skin or other area, post-treatment effect (radiation therapy, chemotherapy)
Systemic lupus erythematosis	Malar rash, joint deformity

Note: COPD = chronic obstructive pulmonary disease, EBV = Epstein–Barr virus.

causes of fatigue can be detected or suggested on physical examination (Table 1) and might be missed in a laboratory screening.[4] For example, multiple sclerosis, although rare, sometimes presents with asymmetric deep-tendon and altered plantar reflexes. Patients with physical signs of weakness, fasciculations, atrophy and altered reflexes may actually have a neuromuscular disease (e.g., botulism, Guillan–Barré syndrome, diphtheria or other myositis) rather than pure fatigue.

3. Medications and toxic exposures: The use of all medications (prescribed and over the counter) should be evaluated. Among the common medications often overlooked as causes of fatigue are long-acting antihistamines, corticosteroids, neuroleptics, antiarrhythmics (e.g., amiodarone), antidepressants and antihypertensives (e.g., clonidine, α-methyldopa and beta-blockers) and herbal remedies. Toxicity in renal or hepatic impairment (e.g., elevated levels of digoxin or anticonvulsants) can cause fatigue. Chronic and acute toxic environmental exposures (e.g., to carbon monoxide, lead, mercury and arsenic) should be considered.
4. Psychiatric assessment: About one quarter of patients presenting with unexplained fatigue in primary care have a depressive syndrome. Other common psychiatric causes include panic disorder and somatization disorder. Specific questions regarding drug abuse and alcohol consumption are also necessary.
5. Assessment for sleep disorder: Sleep apnea, excessive sleepiness and parasomnias are not uncommon. Preliminary data suggest that a new instrument, the Sleep Disorders Questionnaire, has a high sensitivity and specificity (95% and 87% respectively) when used in the primary care setting.[5]

Subsequent laboratory tests can actually be quite focused, with 2 primary goals: to rule out serious and common underlying diseases, and to identify patients with iron deficiency, a common and easily corrected cause of fa-

Box 2: Initial laboratory tests for patients with prolonged or chronic fatigue

- Complete blood count
- Erythrocyte sedimentation rate
- Serum urea, electrolyte and creatine levels
- Serum calcium and phosphate levels
- Liver transaminase levels
- Thyroid-stimulating hormone level
- Fasting blood glucose level
- Creatine kinase level
- Urinalysis for protein, blood and glucose
- Ferritin level
- Urine pregnancy test in women of childbearing age

tigue. We use a small battery of routine tests (Box 2). However, in the absence of a positive history or physical examination, laboratory tests are rarely helpful. Minor abnormalities in test results will be common, and most are unrelated to fatigue even in patients complaining of fatigue. Iron deficiency, even in the absence of anemia, can cause fatigue, and treatment of the deficiency with iron appears to help in many such cases. Additional directed tests (e.g., HIV antibody testing) should be considered based on the patient's history and the physical findings.

In the case of our patient with fatigue and elevated transaminase levels but without other typical features of celiac disease (steatorrhea, weight loss), the clinical index of suspicion (pretest probability) of celiac disease was estimated to be between 20% and 30%. Since the test for IgA antiendomysial antibody has a high sensitivity and specificity (about 90% and 95% respectively), the positive likelihood ratio is about 30. By using the Fagan nomogram, we found that the positive predictive value (post-test probability) for this patient increased to about 90%.

The differential diagnosis of fatigue in primary care is very broad, but an organized approach to the patient as we have described can identify key conditions of concern efficiently and reduce the expensive workups for obscure conditions that this undifferentiated complaint can sometimes generate.

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This article has been peer reviewed.

Competing interests: None declared.

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HEALTH AND DRUG ALERT

WinRho and disseminated intravascular coagulopathy

Reason for posting: WinRho is a human blood product, Rh_0(D) immune globulin, widely used to treat immune thrombocytopenic purpura (ITP) and to prevent Rh alloimmunization in pregnant women who are Rh-negative. Recently, however, a case series[1] described 6 patients with ITP who were given WinRho who subsequently experienced severe hemolysis and disseminated intravascular coagulation (DIC); 5 of them died. The manufacturer, Cangene, has since issued "Dear Health Care Professional" letters in both Canada and the United States that warn of 9 international reports of this serious adverse effect.[2]

The drug: WinRho is a gamma globulin fraction of plasma containing antibodies to Rh_0(D) derived from blood donors. Donated plasma is stringently screened for known pathogens and then filtered to further reduce the risk of transmission of viruses such as hepatitis B and C, HIV and parvovirus.

WinRho is routinely given to Rh-negative women in their third trimester of pregnancy (28 weeks), postpartum (within 72 h) and after possible exposure to Rh-positive blood after pregnancy termination, amniocentesis or abdominal trauma, to prevent maternal Rh-antibody formation and hemolytic disease of the newborn in future pregnancies. WinRho is also used to treat ITP, an autoimmune disorder of increased splenic platelet destruction.

Pregnant women are treated with 120–300 μg of WinRho, administered intravenously or intramuscularly. Patients with ITP are given a much higher dose, generally 25–50 μg/kg intravenously. Common adverse effects, which often occur within minutes to days after the infusion, include headache, chills and fever, back pain and shaking. Serious but rare adverse effects have included acute respiratory distress syndrome, acute renal insufficiency, acute anemia and hemoglobinuria.[3] The recent postmarketing case reports add DIC as another rare but potentially serious adverse effect, which likely starts as hemoglobinemia and hemoglobinuria.

The 6 cases[1] reported in the fall of 2005 were all submitted to the US Food and Drug Administration between 1999 and 2004. They involved 4 males and 2 females 12–85 years of age with ITP; all received doses of 48–75 μg/kg. Although most patients were discharged

DOI:10.1503/cmaj.060201