OCTOBER 2010

Common Sense Pathology

A REGULAR CASE-BASED SERIES ON PRACTICAL PATHOLOGY FOR GPs

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TIRED all the TIME

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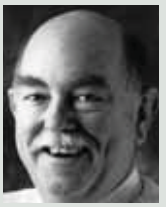
"Tired all the time"



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Introduction

Fatigue is a common and extremely vague presenting symptom in general practice. BBC's Radio 4 program *Case Notes* introduced its 11 October 2005 program thus:

"Being 'tired all the time' is now such a common reason for a GP visit that TATT has become a universal acronym."

Fatigue is also an important generator of pathology requests and for this reason this subject has been chosen as the first of this series of Common Sense Pathology.

Assessment of a patient with fatigue relies upon physical diagnosis: a careful history and a focused but thorough physical examination. The laboratory should be used selectively, guided by the clinical findings in every case presenting with fatigue.

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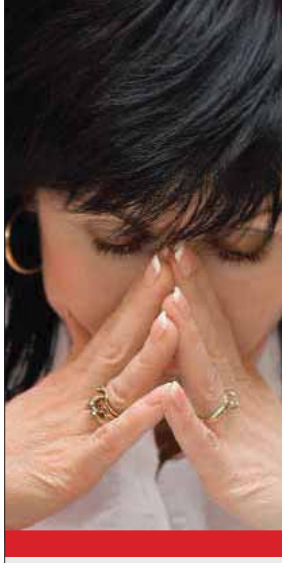


Clinical Scenario 1

Jane G, a 33-year-old lawyer, presents with feeling "tired all the time". She is having trouble coping with returning to work after maternity leave, as well as having three children under the age of five, the youngest of whom is six months old.

Jane finds that she fatigues easily, no longer enjoying her usual sporting activities. She says her house is "a mess" despite her usual meticulous standards. She has difficulty concentrating on even small tasks in a part-time capacity at work. She comments that she is impatient with clients, and during the clinical interview is often close to tears. Even when not woken by the children, she sleeps poorly, often waking unrefreshed.

Discussion

The finding of fatigue in a young mother raises iron deficiency as the first possibility. Nevertheless, the emotional lability, anhedonia and sleep disturbance that this patient evinces raises the possibility of depression as the cause of her fatigue. Thyroid disease is another consideration in a young female.

Initial assessment is by history and physical examination. Questioning should establish whether her sleep disturbance is of the type more commonly associated with depression (early waking associated with ruminating thoughts). Enquiring about menstruation, known iron deficiency in pregnancy or the past, diet and any change in weight would also be important, as would any symptoms suggestive of inflammatory or infectious conditions.

Physical examination should include looking for any signs of thyroid disease or anaemia.

Initial laboratory investigations should include full blood count, C-reactive protein (CRP) to quantitate any inflammatory response, simple biochemical tests looking for electrolyte disturbance, renal impairment or liver function abnormalities and in this case should also include iron studies in view of her multiparity.

Iron deficiency is the most common cause of anaemia worldwide, even in developed nations like ours. Iron deficiency affects about 10% of women during their reproductive years and 10%–20% of young children, depending on their age and recent growth rate.

Interpretation of iron studies is usually straightforward. The serum iron level is no guide at all to total body iron status. The most important parameter in iron studies is the serum ferritin level, which most closely reflects tissue iron stores. The majority of iron-deficient patients will have a diagnostically low serum ferritin level. If there is concurrent inflammation or chronic disease the ferritin may be misleadingly elevated. As it rises above 100µg/L iron deficiency becomes less probable. Expert guidance with interpretation of iron studies may be needed, guided by the CRP result.

Laboratories quote different reference serum ferritin ranges for females and children compared with males. This reflects the prevalence of iron deficiency in women and children, rather than a true difference in iron metabolism between these groups.

For practical purposes, serum ferritin level less than 15µg/L is diagnostic of iron deficiency,

whatever the blood count shows. In the presence of anaemia, a serum ferritin level in the range of 15µg/L-30µg/L suggests that iron deficiency is the cause of the anaemia, particularly if the anaemia is of the hypochromic, microcytic type.

In early iron deficiency the anaemia may be normochromic and normocytic. The mean corpuscular haemoglobin (MCH) is the red cell parameter most sensitive to incipient iron deficiency. Thalassaemia and the haemoglobinopathy HbE can also cause hypochromic microcytic anaemia, but not fatigue.

Non-anaemic tissue iron deficiency can also cause the characteristic triad of fatigue presented in this case. Iron, at the core of the haem molecule, is needed not only in haemoglobin for oxygen transport, but also in muscle myoglobin and intracellular cytochrome oxidase enzymes to capture and harness oxygen for energy production.[1] The brain depends on aerobic glycolysis for its energy supply. Tissue iron deficiency is manifest by physical fatigue with intellectual vagueness and emotional lability.

In pre-school children, tissue iron deficiency can cause not only difficulty with memory and concentration but it can also permanently impair cognitive development. Toddlers who are iron deficient and show disruptive behaviour will often return to normal behaviour with iron supplements.[2]

Every case of proven iron deficiency demands an adequate explanation for the iron deficit.

In children, it is usually the demands of rapid growth, resulting in increased blood and muscle mass depleting the iron stores, sometimes compounded by fussy eating, prematurity or bottle feeding.

In young fertile women it is usually due to menorrhagia and/or the demands of multiple pregnancies.

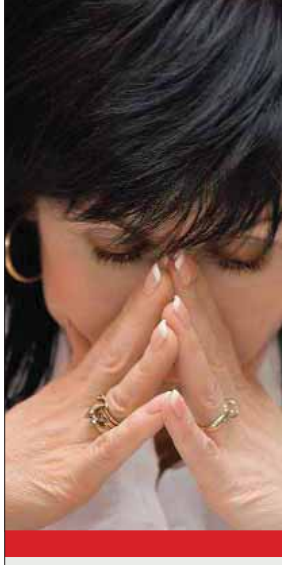
In iron-deficient adult males and postmenopausal females, a source of blood loss should be sought in the gastrointestinal tract. In 20% of this group, a colorectal cancer will be found to be the underlying cause of the iron deficiency. Other benign but important causes include upper GI ulceration, reflux oesophagitis and coeliac disease.

Thus adult males and postmenopausal females – even women who are still having regular but apparently normal menstrual losses in their 40s or 50s – should be referred for GI evaluation. Do not rely on faecal occult blood testing to rule out GI pathology. A negative stool occult blood test just tells you that whatever caused the iron deficiency was not bleeding at the time.

Follow-up testing is appropriate if the patient is significantly anaemic on presentation, or if the cause of GI blood loss was not found by routine upper and lower GI endoscopy.

The anaemia should be corrected by 2-3 months of oral iron supplementation at therapeutic doses. A further 3-6 months of iron therapy after correction of anaemia is generally required to replenish iron stores.

GI angiodysplasia is an important cause of iron deficiency in the elderly. In this case, after definitive iron replacement, the blood count and iron studies should be repeated every 3-6 months to ensure that the iron deficiency does not recur.



Case 2

Roger F, a 56-year-old accountant, presents with feeling "tired all the time".

Closer questioning reveals generalised fatigue and 3kg weight loss. He also admits to reduced libido and erectile dysfunction. He is exhausted after minimal exertion, but has had no difficulty with concentration or mood.

Examination reveals slight lid lag, a fine tremor of the fingertips and a warm, slightly tender goitre. Examination is otherwise unremarkable apart from a lean body habitus and reduced body hair.

Comment

This case illustrates one, and possibly two, endocrine causes of fatigue. Hyperthyroidism is manifest by the tremor and lid lag. The presence of a slightly tender goitre also raises the possibility of thyroiditis, and the sexual dysfunction raises the possibility of male hypogonadism.

Initial investigation should include FBC, with CRP, EUC and TSH. It would be reasonable to add thyroid antibodies in this case, although thyroid antibodies are not needed for all cases of suspected thyroid dysfunction (see the websites rcpamanual.edu.au or labstestonline.org.au).

Investigations revealed a suppressed TSH and a modestly elevated free thyroxine level, with a thyroid antibody profile suggesting acute thyroiditis of the de Quervain's type.

Both hyperthyroidism and hypothyroidism can present with fatigue. This particular case, with the hyperthyroidism a manifestation of acute thyroiditis, is an unusual presentation, but the inflammatory nature of the thyroiditis would be underscored by the elevation of the CRP on testing.

Suspected male hypogonadism is investigated initially by total testosterone levels and sex-hormone-binding globulin (SHBG) and a luteinizing hormone (LH) level.

Total testosterone level, complemented by the SHBG to estimate active (unbound) testosterone levels, is the best way to assess male hormone levels. The gonadotropin LH tests the pituitary feedback loop: if high, it confirms that the low testosterone level is indeed due to primary gonadal failure. In view of the implications of an abnormal finding, it is best to repeat the test on an early-morning specimen.

Effective testosterone replacement therapy in a man with primary gonadal failure has the poten-

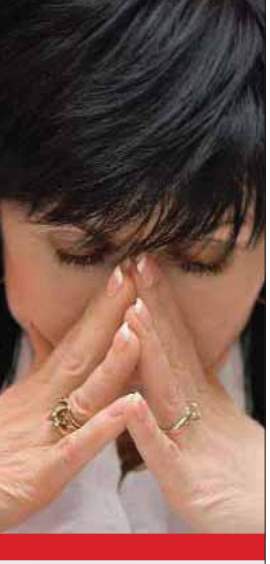


TABLE 1. Symptoms and signs suggestive of androgen deficiency in men
A. More specific symptoms and signs
Incomplete or delayed sexual development, eunuchoidism
Reduced sexual desire (libido) and activity
Decreased spontaneous erections
Breast discomfort, gynaecomastia
Loss of body (axillary and pubic) hair, reduced shaving
Very small (especially < 5mL) or shrinking testes
Inability to father children; low or zero sperm count
Height loss, low trauma fracture, low bone mineral density
Hot flushes, sweats
B. Other less specific symptoms and signs
Decreased energy, motivation, initiative, and self-confidence
Feeling sad, depressed mood, dysthymia
Poor concentration and memory
Sleep disturbance, increased sleepiness
Mild anaemia (normochromic, normocytic)
Reduced muscle bulk and strength
Increased body fat, body mass index
Diminished physical or work performance
From: Bhasin S et al. Testosterone Therapy in Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline. *J Clin. Endocrinol. Metab.* 2010, 95:2536-59.

tial to relieve a lot of distressing symptoms apart from fatigue. Testosterone replacement in these cases also rebuilds bone density, usually without the need for additional therapy.

Among the other endocrine causes of fatigue are electrolyte disturbance due to adrenal gland dysfunction and panhypopituitarism, which can directly cause fatigue. Most other endocrine disorders presenting with fatigue have other obvious symptoms or signs.

Case 3

Glenda P, aged 42, presents to a rural GP feeling "tired all the time".

Closer questioning reveals that she has been suffering from lethargy and poor stamina for the past six months. She also has poor concentration; unable even to pick up the local paper to read it. She has been aware of being snappy with her family and a little despondent.

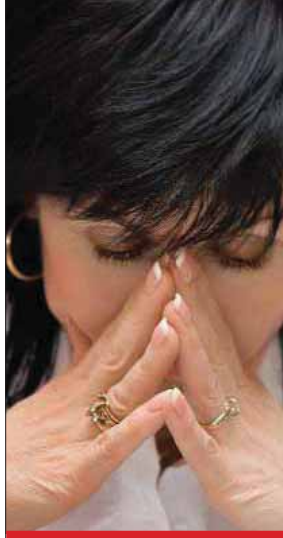
She sleeps for long periods each day but wakes feeling unrefreshed. Her weight has increased slightly. At its worst, her physical fatigue is accompanied by generalised myalgia and headache. She was diagnosed with "glandular fever" as a teenager, and had a febrile illness at the beginning of this current episode of lethargy, for which she was admitted to the local rural hospital and treated for pneumonia.

Six months ago, before the onset of the febrile illness, she had been working for three months as a meatpacker in a local abattoir. The abattoir handled sheep, pigs, cattle and goats from all around western NSW. She was not offered Q fever vaccination as her pre-employment skin test was read as positive.

Physical examination was unremarkable. She was clinically euthyroid and there was no enlargement of liver, spleen or lymph nodes, no abnormality was found on examination of the chest and heart.

Comments

This case illustrates the well-recognised entity of chronic fatigue syndrome. Chronic fatigue syndrome has been defined by the US Centers for Disease Control as follows:



"CFS is a debilitating and complex disorder characterised by intense fatigue that is not improved by bed rest and that may be worsened by physical or mental activity. People with CFS most often function at a substantially lower level of activity than they were capable of before the onset of illness. The cause or causes of CFS have not been identified and no specific diagnostic tests are available. Therefore, in order to be diagnosed with chronic fatigue syndrome, a patient must satisfy two criteria:

1. Have severe chronic fatigue for at least six months or longer, with other known medical conditions (whose manifestation includes fatigue) excluded by clinical diagnosis.
2. Concurrently have four or more of the following symptoms:
   - post-exertional malaise
   - impaired memory or concentration
   - unrefreshing sleep
   - muscle pain
   - multi-joint pain without redness or swelling
   - tender cervical or axillary lymph nodes
   - sore throat
   - headache.

The symptoms must have persisted or recurred during six or more consecutive months of illness and must not have predated the fatigue." (www.cdc.gov/cfs/)

This entity is probably the most common cause of fatigue lasting longer than six months presenting to GPs in Australia. It has a number of misleading alternative names, including myalgic encephalomyelitis and 'Yuppie Flu'.

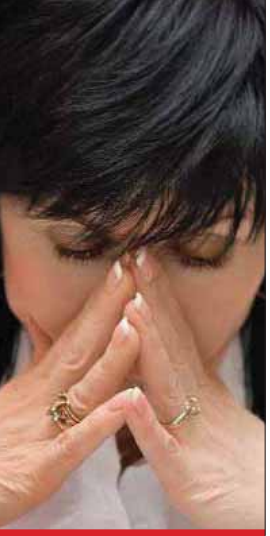
In this particular case, the CFS may be that which follows an episode of Q fever. The strains of Q fever prevalent in western NSW are associated with a significant rate of CFS following the acute infection. Harrison's *Principles of Internal Medicine* states:

In Australia and the UK, a fatigue state lasting 5–10 years has followed Q fever in 8–15% of cases. Low levels of *Coxiella burnetii* DNA have been detected in the affected patients 0.75–5 years after infection.[3]

Those working in the field think that western NSW strains of Q fever cause a higher than 15% rate of post-infectious CFS.

Although CFS can follow acute Epstein-Barr virus infection, asymptomatic Epstein-Barr virus infection is so common that there is no place for Epstein-Barr virus testing in suspected CFS. In the appropriate circumstances, however, Q fever serology may be helpful to help the worker establish a connection between their CFS and work-related exposure to Q fever.

If the core features of CFS are present on history and the patient is otherwise normal on examination, then the following tests will rule out cor-



rectable causes of fatigue lasting greater than six months: FBC with CRP, iron studies and thyroid function tests starting with TSH.

If autoimmune disease is suspected clinically, autoimmune serology including rheumatoid factor and antinuclear antibody can be ordered. It is usually possible to make a confident clinical diagnosis of autoimmune arthritis or polymyositis.

As stated in the CDC definition, there is no "diagnostic test" for confirmation of CFS. Thus there is no need to monitor any of the above results if they are normal on first testing.

Summary

We have dealt with three groups of illnesses that can present with chronic fatigue.

The first and most important is iron deficiency, which, even without anaemia can cause the characteristic triad of physical, intellectual and emotional fatigue. Fatigue is often confused with clinical depression, but the pattern of symptoms can help differentiate between the two. Most importantly, emotional fatigue is not accompanied by the early waking, rumination and poor self-image that is characteristic of true endogenous depression.

Of endocrine causes of fatigue, the most common are thyroid disorders. Most other endocrine disorders presenting with fatigue will have either clinical features (such as the example of male hypogonadism discussed) or some other clue in the basic biochemistry testing.

Finally we dealt with the most common cause of chronic fatigue presentations: chronic fatigue syndrome. This benign, self-limiting entity can go on for years and thus is a frequent source of frustration for patients and their medical attendants.

Key Points for GPs

- Patients presenting with the symptom of feeling tired all the time should firstly have a careful history taken and a directed physical examination before investigations are ordered.
- A basic set of tests including full blood count, CRP, biochemistry (including glucose, EUC, LFT and calcium levels), iron studies and TSH is appropriate in patients who have genuine fatigue.
- Iron deficiency, either with or without a hypochromic, microcytic anaemia, can cause debilitating fatigue in all age groups. In pre-school children iron deficiency is associated with permanent impairment of cognitive development.
- There are established diagnostic criteria for the diagnosis of thyroid dysfunction and thyroiditis.
- Male hypogonadism can present with fatigue, but is usually accompanied by specific symptoms of sexual dysfunction. It should not be diagnosed unless these symptoms are accompanied by confirmed abnormalities in serum testosterone levels.
- Some infective agents have been known to be associated with post-infectious CFS, but the majority of cases of CFS are truly idiopathic in origin.

In dealing with this frequent and vexing symptom, the GP should be alert to the possibility of rare disorders presenting as fatigue. By far the majority of patients presenting with fatigue lasting six months or longer will be able to have treatable disease excluded with the above series of tests and thus be confidently diagnosed with CFS and counselled appropriately.

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