The Laboratory Investigation of Tiredness
Laboratory Investigation of Tiredness

Developed by bpac\textsuperscript{nz}
Level 8, 10 George Street
PO Box 6032
Dunedin

Phone 03 477 5418
Fax 03 477 2622
www.bpac.org.nz

Acknowledgement
bpac\textsuperscript{nz} would like to thank Professor John Campbell for his help and guidance on the development of this resource.

© bpac\textsuperscript{nz} February 2006

All information is intended for use by competent health care professionals and should be utilised in conjunction with pertinent clinical data.
Contents

Key points ........................................................................................................................................... 3
Introduction .......................................................................................................................................... 4
Causes of tiredness presentation ......................................................................................................... 5
  Lifestyle factors .............................................................................................................................. 5
    Life events ................................................................................................................................... 5
    Occupation or study .................................................................................................................... 5
    Diet .............................................................................................................................................. 6
    Alcohol and recreational drugs .................................................................................................. 6
    Exercise ....................................................................................................................................... 6
    Sleep disorders .......................................................................................................................... 6
  Psychosocial factors ....................................................................................................................... 7
Physical health .................................................................................................................................... 7
  Co-morbidities .............................................................................................................................. 7
  Medications ................................................................................................................................... 7
  New conditions presenting as tiredness .......................................................................................... 7
A suggested clinical framework ........................................................................................................ 8
  STEP 1: Defining the problem from the patient’s viewpoint ......................................................... 8
  STEP 2: Focused symptom review ............................................................................................... 9
  STEP 3: Focused examination ....................................................................................................... 9
  STEP 4: Focused laboratory investigations ................................................................................... 9
Approach to laboratory investigations .............................................................................................. 11
  Iron deficiency ............................................................................................................................. 11
  Thyroid dysfunction ...................................................................................................................... 12
  Urinary tract infection .................................................................................................................. 12
  Glandular fever ............................................................................................................................ 13
  Diabetes mellitus ........................................................................................................................... 13
  Haemochromatosis ....................................................................................................................... 14
  Vitamin B12 or folic acid deficiency .............................................................................................. 14
  Primary adrenocortical deficiency (Addison’s disease) ............................................................. 15
  Hypercalcaemia ............................................................................................................................. 15
  Liver disease .................................................................................................................................. 15
  Renal impairment ........................................................................................................................ 16
  Systemic autoimmune diseases ................................................................................................... 17
  Chronic fatigue syndrome .......................................................................................................... 17
    International diagnostic criteria for chronic fatigue syndrome ............................................. 18
References .......................................................................................................................................... 19
Key points

- The investigation of tiredness is a clinical rather than laboratory task.
- A focused approach to the laboratory investigation of tiredness is usually determined by clinical findings.
- When tiredness is the sole clinical finding, investigations are determined by patient demographics, presence of risk factors and duration of tiredness.
Introduction

Tiredness represents one of primary care’s most difficult challenges; it is a common presentation that is usually self-limiting but may, on occasions, have more sinister causes. This is demonstrated by the results of a Dutch study in which 12,292 people, who presented to Dutch general practitioners with tiredness as the reason for consultation, yielded the final diagnoses presented in the following table (Kenter, 2003). In this study 72% of the patients who presented with tiredness did not require a follow up consultation.

<table>
<thead>
<tr>
<th>Final Diagnosis</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>General weakness/tiredness</td>
<td>43.2</td>
</tr>
<tr>
<td>Upper respiratory tract infections</td>
<td>8.7</td>
</tr>
<tr>
<td>Viral disease - NOS</td>
<td>6.4</td>
</tr>
<tr>
<td>Psychological disorders</td>
<td>6.2</td>
</tr>
<tr>
<td>Lower respiratory tract infections</td>
<td>3.6</td>
</tr>
<tr>
<td>Iron deficiency anaemia</td>
<td>3.0</td>
</tr>
<tr>
<td>Social problems</td>
<td>2.7</td>
</tr>
<tr>
<td>No disease/prevention</td>
<td>2.2</td>
</tr>
<tr>
<td>Adverse effect medical agent in proper dose</td>
<td>1.7</td>
</tr>
<tr>
<td>UTI</td>
<td>1.0</td>
</tr>
<tr>
<td>Heart disease</td>
<td>0.8</td>
</tr>
<tr>
<td>Infectious mononucleosis</td>
<td>0.7</td>
</tr>
<tr>
<td>Presumed GI infection</td>
<td>0.7</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.3</td>
</tr>
<tr>
<td>Anaemia other/unspecified</td>
<td>0.3</td>
</tr>
<tr>
<td>Malignant neoplasm digestive system</td>
<td>0.2</td>
</tr>
<tr>
<td>Menopausal symptoms/complaints</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Note: Adapted from, Kenter, 2003

Although this document is about laboratory testing for tiredness, the investigation of tiredness is a clinical rather than laboratory task. Patient, clinician and contextual factors make every consultation different. Clinicians will have developed an approach to tiredness, which suits them, their practice and their patients. In this document, we make some suggestions that clinicians could incorporate into their own approach if they are not already part of it. When investigating tiredness, sound clinical judgement is important and laboratory tests should be guided by your judgement.

The diagnosis of tiredness is a clinical rather than a laboratory task.
Causes of tiredness presentation

Causes of tiredness presentation can be usefully divided into three overlapping groups. Many presentations will not fit into these groups and the cause will remain unknown. It is useful to explain to patients during the first consultation that you are considering these three groups as possible causes for their tiredness.

- **Lifestyle factors**

  Lifestyle factors can be a significant cause of tiredness. These may be a natural consequence of a busy life or related to a number of additional factors. Discussion and acknowledgement of these factors with the patient may be the most helpful approach.

  **Life events**

  Tiredness is common in people who have undergone significant life events and should be taken seriously. They can significantly increase the risk of serious illness in the following two years (Holmes, 1967, p. 607-8). Tiredness may be the ‘admission ticket’ for people who have had significant life changes and wish to discuss them.

  **Occupation or study**

  People may complain that their occupation or study is causing their tiredness; however, focusing on occupation exclusively to reduce fatigue may be inadequate (Bultmann, 2001). It is usually the complex relationship between occupation and other lifestyle factors, psychosocial issues and physical health which needs exploring to identify modifiable factors.
- Diet

Dietary extremes can cause tiredness. Initially, clinicians may think of deficient diets, particularly iron deficiency, but we are all familiar with the somnolence and lethargy that follow a heavy meal. Many people eat meals that are too heavy, too often; while those on fad diets may not be meeting their nutritional needs. Tiredness may also result from excesses of particular dietary ingredients such as the caffeine, guarana or sugar found in so-called energy drinks.

- Alcohol and recreational drugs

Use of alcohol or recreational drugs has a two-way relationship with tiredness. On one hand lifestyle changes or direct chemical effect related to alcohol or drug-use can cause tiredness. On the other hand tiredness can lead to alcohol or drug use and decrease motivation for reducing intake. Use of alcohol or recreational drugs is rarely volunteered and direct questioning of patients is usually needed.

- Exercise

Extremes of exercise can contribute to fatigue. Elite athletes and others doing high levels of exercise may present with tiredness. Possible causes, related to their high exercise levels, include non-fasting hypoglycaemia, iron deficiency and susceptibility to recurrent infections (Reid, 2004). At the other end of the extreme, those who under exercise can experience persistent lassitude. Increasing exercise can increase wellbeing and improve sleep.

- Sleep disorders

Sleep disorders are estimated to have a similar magnitude of effect on quality of life as chronic diseases such as COPD (Reimer, 2003). Patients may be surprised to learn that our sleep requirements are biologically determined and the amount of sleep we need and the best times for sleeping varies between individuals (Rivkees, 2003). Simple advice on sleep requirements may be all that is required.

Primary insomnia is generally associated with a state of hyperarousal related to poor sleep habits and environment. Assessment of sleep hygiene and behaviour modification may help (Roehrs, 2004). Secondary insomnia associated with physical causes, such as night pain or breathlessness, or psychological causes, such as depression or anxiety, are not always obvious to patients.

Obstructive sleep apnoea often presents with snoring, daytime sleepiness, witnessed apnoeas and nocturnal choking (Schlosshan, 2004). Central sleep apnoea is usually related to alveolar hypoventilation caused by defects in metabolic respiratory control or respiratory neuromuscular apparatus or by disorders, such as cardiovascular disease, which induce temporary instabilities in central respiratory drive (Kasper, 2005, p.1575).
Psychosocial factors

Lifestyle and psychosocial factors often overlap when people present with tiredness. Anxiety, stress and interpersonal difficulties affect quality of life and are often amenable to intervention. Depression needs early identification because of the morbidity and threat to life associated when left untreated.

Asking both of two screening questions reliably identifies depression (Arroll, 2003). These questions are:

1. During the last month, have you often been bothered by feeling down, depressed or hopeless?
2. During the last month, have you often been bothered by having little interest or pleasure in doing things?

A positive response to either of these questions indicates the need for a detailed assessment of the patient’s current mental health status, functional impairment and risk of harm to self or others. The PHQ-9 (bpac.nz, 2005) questionnaire may assist with this assessment.

Physical health

Physical illness can also make someone tired. These physical causes may not always be obvious.

- Co-morbidities

Pre-existing chronic conditions are easy to overlook as causes of tiredness. Examples of these are diabetes, rheumatoid arthritis, cancer, COPD, asthma and heart failure. It is worthwhile checking that any chronic conditions the patient has are under good control.

- Medications

Many medications can cause tiredness. Psychoactive drugs, antihypertensives, and hormone preparations are common culprits.

- New conditions presenting as tiredness

Many conditions cause tiredness but it is uncommon for patients to present with tiredness caused by a physical health problem that has not been previously diagnosed or that has no other associated signs or symptoms. Never the less some serious physical health problems may present with tiredness. A common example is type 2 diabetes and a rare one, Addison’s disease.
STEP 1: Defining the problem from the patient’s viewpoint

- What does the patient mean by tiredness?

As patients define what they mean by tiredness the underlying problem often becomes clear.

- Is tiredness the only issue?

In many cases tiredness is not a deciding factor in reaching a diagnosis; other features in the history may give stronger clues to the underlying problem.

- How is it affecting their life?

This helps define the duration and severity of the problem and may indicate some underlying psychosocial issues.

- What do they believe is causing it?

Often patients already have this sorted out and are merely attending for confirmation. On the other hand, misconceptions about the cause may be adding to the problem.

- What are their concerns?

All concerns whether or not they are realistic need addressing.
STEP 2: Focused symptom review

The focus of additional symptom review, especially looking for red flags, is determined by patient demographics and past history. For example, women will need to be asked about menstrual symptoms; elderly people about weight loss, appetite and bowel disturbance; and smokers about cough.

STEP 3: Focused examination

The focus of the examination will be determined by patient demographics and findings from the history. Clearly a 65 year-old man with tiredness and weight loss will need a different examination to an 18 year-old that presents with one week of fatigue and is clearly under stress and sleeping poorly.

STEP 4: Focused laboratory investigations

Similarly, we suggest a focused approach to laboratory investigations of tiredness, determined by clinical findings. When there are no other clinical signs or symptoms we suggest an approach based on demographics, the presence of risk factors and the duration of the tiredness. This is a consensus approach that has been suggested, because there are few clinical trials that assess laboratory testing using patient benefits as outcomes.

Laboratory testing cannot be used as a substitute for clinical assessment in the investigation of tiredness. These recommendations do not preclude the use of other accepted screening tests at the usual intervals.
When there are no other clinical signs or symptoms, laboratory tests are requested based on patient demographics, presence of risk factors and duration of tiredness.

### Patients under 50 years without other risk factors:

<table>
<thead>
<tr>
<th>Tests</th>
<th>Comments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- CBC</td>
<td>Searching for iron deficiency, macrocytosis, significant infections and leukaemias.</td>
</tr>
<tr>
<td>- Ferritin</td>
<td></td>
</tr>
</tbody>
</table>

### Patients over 50 years or tiredness lasting over one month:

<table>
<thead>
<tr>
<th>Tests</th>
<th>Comments:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- CBC</td>
<td></td>
</tr>
<tr>
<td>- CRP</td>
<td></td>
</tr>
<tr>
<td>- Ferritin, iron saturation</td>
<td></td>
</tr>
<tr>
<td>- LFT</td>
<td></td>
</tr>
<tr>
<td>- Creatinine with eGFR</td>
<td></td>
</tr>
<tr>
<td>- Electrolytes</td>
<td>This wide range of tests reflects the increased risk that older people have of many diseases and the difficulty of reaching a diagnosis in chronic tiredness.</td>
</tr>
<tr>
<td>- Calcium, phosphate</td>
<td></td>
</tr>
<tr>
<td>- TSH</td>
<td></td>
</tr>
<tr>
<td>- Fasting glucose</td>
<td></td>
</tr>
<tr>
<td>- Urinalysis</td>
<td></td>
</tr>
<tr>
<td>- ANA</td>
<td></td>
</tr>
</tbody>
</table>

### Patients under 50 years with additional risk factors may require the following extra tests:

<table>
<thead>
<tr>
<th>Type 2 diabetes</th>
<th>Fasting glucose</th>
<th>See page 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid dysfunction</td>
<td>TSH</td>
<td>See page 12</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>Creatinine with eGFR</td>
<td>See page 16</td>
</tr>
<tr>
<td></td>
<td>Electrolytes</td>
<td></td>
</tr>
<tr>
<td></td>
<td>TSH</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urinalysis</td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>LFTs</td>
<td>See page 15</td>
</tr>
<tr>
<td>Body fluid transfer</td>
<td>HIV</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatitis B &amp; C serology</td>
<td></td>
</tr>
</tbody>
</table>
Approach to laboratory investigations

The diagnostic challenge when investigating tiredness is to detect physical causes and serious disease without burdening the patients with excessive medical investigation. In a study performed in Australia (Gialamas, 2003), of 345 patients who presented to their GP with tiredness, 189 patients (55%) went on to have 1183 pathology tests performed. Of these tests 84% were considered normal. Of the 345 patients, 12 (4%) had a significant new clinical diagnosis made because of an abnormal pathology test. The most common diagnoses made from the tests were anaemia, diabetes mellitus and hypothyroidism.

Iron deficiency

Serum ferritin and CBC are appropriate for most people who present with tiredness. Iron deficiency is relatively common in people presenting with tiredness (Kenter, 2003) and has causes that extend across all demographic groups.

Those most at risk include menstruating and pregnant females, children, adolescents, people experiencing periods of rapid growth, and those with inadequate diets. It can result from intermittent blood loss of any kind and may be the first sign of a gastro-intestinal neoplasm. Iron deficiency may be the first indication of coeliac disease, as 0.5-1.0% of patients with this disease have no other suggestive symptoms (Collin, 2002).

In the ‘NZ Food NZ Children’ study (MOH, 2003) the New Zealand prevalence of iron deficiency in children was 1.6% and iron deficiency anaemia 0.3%. The highest prevalence was in females aged 11-14 years, Māori and Pacific peoples, and children from low decile groups. There is a lack of data available on the iron status in other age groups.

A small study in Auckland found much higher rates in children aged 6 to 23 months (Wall, 2002). 27% of the children were found to be iron deficient and no ethnic group was over represented. Associated factors included:

- Low intake of iron rich meats, and of fruits and vegetables rich in vitamin C
- Tea drinking
- The replacement of breast milk or infant formula with cows’ milk before 12 months of age

Ferritin is the best test of depleted iron stores and usually demonstrates iron deficiency before anaemia occurs. The average serum ferritin for adult males is approximately 100µg/L and for adult females 30µg/L. For adults the WHO standard for iron depletion is <15 µg/L (WHO, 2001), although it is recognised that patients with ferritin levels between 15-20µg/L have borderline stores, and these levels may be sufficient to cause symptoms. For children less than five years-old the WHO standard for iron depletion is <12µg/L.
Normal ferritin levels in a patient with inflammation do not rule out iron deficiency because ferritin is raised in the presence of inflammation.

**Thyroid dysfunction**

TSH testing is appropriate for people who are at increased risk of thyroid dysfunction and present with non-specific symptoms such as tiredness.

Increased risk of thyroid dysfunction is associated with:

- Increased age
- Autoimmune diseases, especially type 1 diabetes, pernicious anaemia and vitiligo
- Dyslipidaemias
- Chronic cardiac failure, coronary artery disease, arrhythmias, pulse >90 or <50 per min, hypertension
- Menstrual disturbance or unexplained infertility
- The postpartum interval or a previous episode of post partum thyroiditis
- Genetic conditions (e.g. Down, Turner syndromes)
- Drugs such as amiodarone, lithium, interferon
- A history of neck surgery or irradiation

In the majority of situations TSH should be the sole initial test of thyroid function. TSH is the most sensitive test of thyroid function and adding other tests is only of value in specific situations. When TSH is within the reference range, there is a 99% likelihood that the FT4 will also be in the reference range (Viera, 2003).

**Urinary tract infection**

While most people with a urinary tract infection (UTI) have classical features others may present with less specific symptoms. The elderly, in particular, may present with confusion, tiredness or just being ‘off colour’.

When a UTI is suspected antibiotic treatment is appropriate in the presence of:

- Classic UTI symptoms, or
- Positive leukocytes or nitrites on dipstick, or
- Positive urine culture.

A dipstick test negative to both nitrites and leukocytes accurately predicts the absence of UTI on an MSU (negative predictive value 92%), and therefore a negative urinalysis does not usually need following up with urine culture. However, a negative urinalysis does not predict response to antibiotic treatment (Richards, 2005); this means that antibiotic treatment is justified when the patient has classic symptoms even when both dipstick test and MSU are negative.
When the patient has non-specific symptoms and both dipstick test and MSU are negative the decision to use antibiotics must be made on a case-by-case basis.

Bacteriuria found incidentally in asymptomatic elderly women should not be treated unless co-existing conditions increase the risk of symptomatic invasive disease. In untreated asymptomatic bacteriuria, the organisms (especially *E. coli*) lose their virulence and become extremely susceptible to the bactericidal effect of normal human plasma. Large amounts of bacteria in the urine may therefore protect against symptomatic bacteriuria caused by more virulent strains (Merck, 2005).

**Glandular fever**

Diagnostic testing for glandular fever is unlikely to be helpful in people who present with tiredness and no other suggestive symptoms.

Ninety five percent of adults have been infected with Epstein Barr virus (EBV) in childhood and continue to have antibodies to EBV. While chronic EBV infection is sometimes suspected, reliable laboratory evidence is rarely found in patients who have been ill for more than 4 months. Beyond this time other causes are much more likely. On rare occasions reactivation of EBV occurs, but antibodies are an unreliable indicator of this.

**Diabetes mellitus**

Type 1 diabetes, because of its usually acute onset, is unlikely to present as tiredness alone. However, type 2 diabetes has an insidious onset and tiredness may well be the initial symptom. A fasting glucose is therefore worthwhile for people who present with tiredness and have risk factors for diabetes.

Risk factors for the development of type 2 diabetes include:
- Age over 50 years
- Age over 40 years for Māori, Pacific Island, or Asian people
- Central obesity
- Family history of diabetes
- History of gestational diabetes or having a baby over 4 kilograms
- Physical inactivity
- Adverse lipid profile
- Hypertension
- Polycystic ovary syndrome
Haemochromatosis

People with haemochromatosis are no more likely to be tired than the general population. The commonly associated symptoms of fatigue, diabetes, joint symptoms and sexual dysfunction were found to be no more frequent in people with haemochromatosis than in the general population. The reported incidence of tiredness for people homozygous for C282Y was 27.4%, people heterozygous for C282Y/H63D 26.54%, and controls 26.5% (Beutler, 2002).

Iron saturation is the most useful initial screening test and is raised in over 90% of patients with haemochromatosis, and is usually raised long before serum ferritin becomes elevated. The test should be performed fasting in the early morning when the patient is well. Although ferritin may also indicate increased tissue iron stores, it may also be increase due to inflammation and conditions such as fatty liver.

Gene testing for haemochromatosis is not recommended as an initial screen. It should be reserved for confirmation or further evaluation of patients with abnormal iron studies and those with a family history.

Vitamin B12 or folic acid deficiency

It is rare to find a patient with vitamin B12 or folic acid deficiency with a normal complete blood count (RCPA, 2004). Therefore, it is usually appropriate to reserve testing vitamin B12 and folic acid for when blood film examination shows a megaloblastic picture.

Deficiency of B12 is almost always due to malabsorption; in New Zealand this is usually associated with pernicious anaemia or achlorhydria, although it can also occur in those on long term vegan diets. Folic acid deficiency can also be caused by malabsorption but is most often caused by low dietary intake. Folates are widely distributed in food but are often destroyed during cooking. Low intake is associated with old age, poverty, alcoholism and diet fads.

Approximately 0.4% of the New Zealand population have inadequate intake of B12, and in 1997 approximately 7% of the population had inadequate folate intake. Inadequate intakes of folic acid are more common for females than males, while Māori females and people in the most deprived areas have the highest rates of inadequate intakes (MOH, 2003).

Vitamin B12 levels take approximately two years to deplete, therefore B12 deficiency is unlikely to be the result of a short term change in diet. Vegetarians have been found to have similar vitamin B12 levels to non-vegetarians (Harman, 1998). Women taking oral contraceptives frequently have “falsely low” vitamin B12 concentrations, probably a result of low cobalamin-carrier protein.

The recent trend to request red cell folate instead of serum folate is not warranted. While RBC folate is theoretically a more accurate measure of folate, it is a more laborious method and has poorer precision. In a large bench marking review performed in the UK (Galloway 2003), serum folate was found to be just as useful as red cell folate in most instances. In the small number of
cases where the serum folate is normal but there is high clinical suspicion of folate deficiency, a red cell folate is indicated.

**Primary adrenocortical deficiency (Addison’s disease)**

Although fatigability and weakness are characteristic in Addison’s disease, performing routine bloods on tired patients is unlikely to help in the diagnosis of Addison’s disease. In the early stages of the disease symptoms may be sporadic and worse at times of stress, and routine laboratory investigations, such as electrolytes, are likely to be normal.

Addison’s disease may be suspected when patients have a combination of suspicious symptoms such as fatigability, weakness, mild GI distress, weight loss, anorexia and a suggestion of increased pigmentation. An appropriate investigative strategy is to perform an early morning serum cortisol. A result above 450 nmol/L makes adrenal insufficiency unlikely, while a clearly low level strongly suggests the diagnosis. When the initial result is equivocal (e.g. in the low normal range), ACTH stimulation testing should be considered to rule out adrenal insufficiency.

**Hypercalcaemia**

Fatigue can occur with hypercalcaemia. Hyperparathyroidism and malignancy account for 90% of cases of hypercalcaemia.

More than half of patients with hyperparathyroidism are asymptomatic. Subtle presentations include fatigue, weakness, depression, confusion, GI upsets and frequent micturition. Other manifestations reflect involvement of the kidneys or the skeletal system.

Hypercalcaemia secondary to malignancy, usually occurs in those already known to have cancer and is a poor prognostic sign. However, it may occasionally be the first presentation of a malignancy and requires careful investigation (Kasper, 2005, p.2252-4).

**Liver disease**

Abnormalities of liver function may be found in asymptomatic people or those with mild symptoms such as tiredness. Marked abnormalities are likely to be accompanied by other symptoms and clearly need further investigation. Mild elevations in liver function tests can also be signs of serious pathology but may have benign transient causes.

Potential causes of mild abnormalities in liver function include viral hepatitis, alcohol use, medication, fatty liver and cirrhosis.
Risk factors for liver disease include:
- Alcohol excess
- Substance abuse
- Diabetes
- Obesity
- Body fluid transfer
- Polypharmacy

Gilbert’s syndrome is usually discovered incidentally when liver function tests are performed. People with Gilbert’s syndrome have an elevated serum bilirubin caused by a reduced ability to conjugate bilirubin. The serum bilirubin level fluctuates but no relationship exists between symptoms and serum bilirubin level. At least 30% of patients are asymptomatic, others complain of non-specific symptoms such as abdominal cramps, fatigue and malaise, some get intermittent jaundice.

**Renal impairment**

Chronic renal failure can develop insidiously with non-specific symptoms such as fatigue, anorexia or nausea. Appropriate initial investigations include serum creatinine and urinalysis for abnormal sediment and proteinuria. Glomerular filtration rate can be estimated from the serum creatinine. Traditional creatinine clearance measurement (using a 24 hour urine collection) is seldom indicated as it is subject to significant day to day variability and is usually poorly performed (Berger 2000).

There are several methods for estimating glomerular filtration rate (GFR). The Cockroft-Gault formula estimates GFR using body mass as well as serum creatinine. More recently, an estimated GFR has been reported by laboratories based on the serum creatinine, age and gender of the patient. Although both methods have limitations, they provide more information than a creatinine on its own because serum creatinine is affected by gender, muscle mass and physical activity.

Risk factors for chronic renal failure include:
- Hypertension
- Diabetes
- Autoimmune disease
- Family history of inheritable renal disease
- Past or current evidence of renal damage
- Increasing age
Systemic autoimmune diseases

Fatigue can be an early feature of some of the systemic autoimmune diseases such as systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Investigation for these diseases is done if they are suspected on clinical grounds or if fatigue becomes chronic.

The best initial test for SLE is antinuclear antibodies (ANA) as it is positive in over 95% of patients with SLE (Kasper, 2005, p. 1961). CRP is almost always elevated in the active stage of RA and a normochromic, normocytic anaemia is frequently present.

Rheumatoid factor is not a useful screening test for rheumatoid arthritis in tired people because less than one third of people with a positive test for rheumatoid factor will be found to have RA. Rheumatoid factor can be used to support the diagnosis in people with a suggestive clinical presentation, or as an indicator of prognosis; high titres are associated with risk for severe systemic disease (Kasper, 2005, p. 1972).

Chronic fatigue syndrome

Many patients with ongoing fatigue enquire about the possibility of chronic fatigue syndrome or Myalgic Encephalomyelitis (ME).

The status of the chronic fatigue syndrome as a separate diagnosis remains controversial since patients meeting the case definition for the syndrome do not differ substantially in demographic and clinical characteristics from other patients with fatigue (Morriss, 1998). Some authors consider chronic fatigue syndrome to be one end of the range of chronic tiredness with multiple symptoms, but others regard the syndrome as a separate diagnostic entity. There are no diagnostic tests available.

Some patients find the diagnostic label useful and it gives them an explanation for their condition and allows them to get on with lifestyle-based interventions without pursuing further medical investigations.
- International diagnostic criteria for chronic fatigue syndrome (Morriss, 1998).

1. Persistent tiredness or fatigability, which persists or shows a relapsing course for six months or more.

2. Four or more of the following symptoms have been present for six months or more:
   - Impaired memory or concentration
   - Sore throat
   - Tender cervical or axillary lymph nodes
   - Muscle pain
   - Multi-joint pain
   - New headaches
   - Unrefreshing sleep
   - Malaise after exertion lasting >24 hours

3. Fatigue that cannot be fully explained by any active medical condition - for example, untreated hypothyroidism, sleep apnoea, iatrogenic causes (drug side effects), unresolved medical condition (hepatitis B), alcohol or substance misuse within two years before or at any time after the onset of fatigue, severe obesity (body mass index > 45), and severe mental illness (major depressive disorder with psychotic or melancholic and somatic features, bipolar affective disorder, schizophrenia, delusional disorder, dementia, anorexia nervosa, bulimia nervosa).
References


