Investigating lethargy

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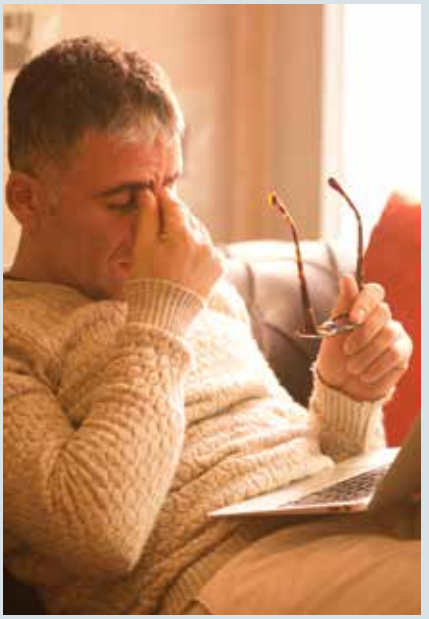
Case scenarios are used in this section to educate doctors on the best approach to the diagnosis and management of patients with different endocrine problems. The appropriate selection of tests and correct interpretation of test results are discussed.



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Generalised lethargy or fatigue is a common presenting symptom in general practice, reported in 1 to 7% of general practice encounters and it is often a diagnostic dilemma.[1,2] Lethargy may be defined as extreme fatigue or drowsiness in the absence of increased physical activity, unrelieved by rest. Although the most common causes tend to be psychosocial or lifestyle related, serious pathology may underpin such presentations. The prevalence of actual underlying pathology ranges from less than 10% to up to 50% of patients presenting with lethargy.[2] This large range most likely reflects a wide variation in study methodology.[2] Patients are sometimes extensively investigated and may be referred to multiple specialists, including endocrinologists, in an attempt to assuage patient concern and rule out underlying pathophysiology (Box 1). It is therefore essential that GPs are confident in their approach to managing such cases as extensive blanket investigation can lead to significant false-positive results and unwarranted healthcare costs, exacerbate patient anxiety and expose patients to unnecessary risk.[2,3] As such it is important to take a thorough history, perform a physical examination and order appropriate targeted investigations to rule out significant reversible pathologies. In the absence of identifiable medical pathologies, diagnoses such as chronic fatigue syndrome, psychosocial stressors or affective issues should be considered.[4]

Chronic fatigue syndrome should be considered as a diagnosis of exclusion in patients presenting with persistent fatigue for over six months with associated severe impairment in occupational, educational, social and personal activities in the absence of other identifiable pathology.[5] Although a diagnosis of exclusion, acute physical or psychological stress may precipitate chronic fatigue syndrome, whereas psychological and social factors including illness perception and the patient and caregivers' behaviour may perpetuate the symptoms.[5] An assessment of the patient's psychosocial state and current stressors is vital and management often requires ongoing lifestyle advice and counselling with regular follow up. Cognitive behavioural therapy and graded exercise therapy are the only forms of therapy that have shown benefit in patients with chronic fatigue syndrome.[5,6] A recent systematic review noted benefits from exercise therapy similar to cognitive behavioural therapy in levels of fatigue, physical functioning and sleep; however, no evidence for improvements in chronic pain, anxiety, depression and quality of life were shown. The optimal type and intensity of exercise remains unclear.[7]

Guidelines on the approach to fatigue have been published but vary in different countries.[4,8] A diagnostic approach for fatigue was outlined in the Australian Therapeutic Guidelines, which considered pretest probability based on patient demographics and potential associated red flags, weighing the costs and benefits of investigations.[8] These red flags include recent onset of fatigue in a previously well older patient, abnormal bleeding, unintentional weight loss, fevers, clinically significant lymphadenopathy, focal neurological signs, or signs or symptoms of cardiorespiratory, inflammatory or rheumatological disease. In the absence of red flags, it is reasonable that patients should be monitored for a four-week period before initiating investigations.[2,8] Screening questionnaires for depression and obstructive sleep apnoea, such as the K10 checklist and the Epworth Sleepiness Scale, should be used to assess potential psychosocial and lifestyle factors. On examination, in particular, the patient's weight, body habitus and mental state should be monitored and pallor, signs of cardiac or respiratory disease, focal neurological signs, organomegaly and lymphadenopathy should be assessed. Appropriate initial investigations should be targeted based on the clinical assessment (Box 2).

1. Causes of lethargy

Physical

- Anaemia
- Infections (Epstein–Barr virus, HIV, cytomegalovirus, hepatitis B and C, malaria, tuberculosis, various tropical infections)
- Endocrine and metabolic conditions (diabetes, hypo/hyperthyroidism, electrolyte abnormalities, Addison's disease, hypopituitarism, renal failure, liver disease, haemochromatosis, coeliac disease, vitamin deficiencies)
- Malignancy
- Inflammatory conditions (rheumatoid arthritis, systemic lupus erythematosus, polymyalgia rheumatica, chronic fatigue syndrome, fibromyalgia)
- Cardiac or respiratory conditions (heart failure, arrhythmias, coronary heart disease, respiratory failure, asthma, sleep apnoea)
- Neurological and neuromuscular conditions (multiple sclerosis, myasthenia gravis, Parkinson's disease)
- Chronic pain
- Medication or treatment (e.g. chemotherapy, radiotherapy, statins, beta blockers)
- Fatigue syndromes (diagnoses of exclusion – chronic fatigue syndrome, fibromyalgia, post-viral syndrome)

Psychosocial

- Anxiety
- Depression
- Stress
- Bereavement
- Bullying
- Interpersonal difficulties
- Insurance claims
- Domestic abuse

Lifestyle

- Diet
- Drug and alcohol abuse
- Occupation or study
- Significant life events
- Sleep disorders
- Sedentary lifestyle

The following three vignettes outline the history, examination, investigations and management of three patients with differing presentations of lethargy.

Case 1

A 48-year-old man presents with a six-month history of nonspecific lethargy and cold intolerance on a background of type 1 diabetes and a strong family history of Hashimoto's thyroiditis. Diet and mood are normal, he does not drink alcohol or smoke. Sleep is good without snoring or daytime somnolence and his weight is stable (body mass index [BMI] 26 kg/m^2). On examination, his pulse is regular at 54 beats per minute. No goitre or palpable cervical lymphadenopathy are present. Cardiovascular, respiratory, gastrointestinal and neurological examinations are all normal.

What initial investigations should be ordered?

Full blood count (FBC), urea, electrolytes and creatinine (UEC) levels, blood glucose levels, and calcium, magnesium and phosphate (CMP) levels should be measured. Liver function tests (LFTs) should also be performed. Screening for thyroid dysfunction should also be carried out by measuring levels of thyroid-stimulating hormone (TSH) because of his strong family history of Hashimoto's thyroiditis. His TSH level was elevated at 12.6 mIU/L (normal range, 0.4 to 4.0 mIU/L).

Given the strong history of autoimmune disease, testing for other relevant autoimmune conditions, including coeliac disease and pernicious anaemia, may also be appropriate for this case.

What further investigations should be ordered?

The elevated TSH level warrants further testing with measurement of free T4 levels and a thyroid peroxidase antibody test. A thyroid ultrasound is not required, unless significant goitre or nodularity are detected on examination, as most patients with autoimmune thyroid disease will have normal sized or atrophic glands and ultrasonography is not diagnostic in itself. If there is evidence of vena caval or tracheal obstruction, a noncontrast CT scan should be performed.

What is the diagnosis?

A repeat TSH level was again elevated at 13.2 mIU/L (normal range, 0.4 to 4.0 mIU/L); free T4 level was low-normal at 10.6 pmol/L (normal range, 10 to 20 pmol/L) with a strongly positive thyroid peroxidase antibody test (>1000 IU/mL). This man was diagnosed with subclinical hypothyroidism with positive thyroid antibodies consistent with underlying Hashimoto's thyroiditis.

2. Basic investigations for lethargy

- Blood tests
  - full blood count
  - fasting blood glucose level
  - electrolytes and renal function
  - calcium, magnesium and phosphate level
  - liver function tests
  - thyroid-stimulating hormone level
  - iron studies
  - erythrocyte sedimentation rate or C-reactive protein
- Urinalysis

How should this patient be managed?

Given the lethargy, TSH level and associated autoimmunity, this man should be commenced on thyroxine replacement therapy (approximately 50 µg/day).[9] Repeat thyroid function tests and clinical review would be recommended in three months to monitor his progress and symptoms with dose titration aimed at normalising TSH levels. Repeat testing of serum TSH levels should be performed at least four to six weeks following dose adjustment.

Case 2

A 35-year-old woman presents with a two-year history of worsening fatigue on the background of menorrhagia. She has three children aged between 2 and 10 years. She previously worked as a cleaner but because of her symptoms she has been unable to return to work following her third pregnancy two years ago. She also reports increased hair loss. She has gained weight (10 kg) since her last pregnancy (BMI is now 31 kg/m^2). Menstruation recommenced 12 months ago but her periods have been irregular with four- to eight-week cycles and bleeding lasting for up to seven days with painful clotting at times. She sleeps well, has good appetite and a well-balanced diet and denies any mood disturbance. She does not smoke and only drinks alcohol occasionally. There is no family history of bowel cancer. She reports some dizziness on standing and occasional palpitations, but there are no other cardiorespiratory

symptoms. Her bowels motions are regular with no change in colour or consistency. Blood pressure is 110/60 mmHg (supine) with no postural drop on standing. Gastrointestinal and haematological examinations are unremarkable.

What initial investigations should be ordered?

This woman's symptoms and history suggest possible iron deficiency and/or anaemia caused by menstrual blood loss. FBC and UEC, CMP and fasting blood glucose levels should be measured. LFTs and iron studies should also be performed. Measurement of TSH levels and erythrocyte sedimentation rate or C-reactive protein may also be part of an initial screen. Investigations reveal a microcytic anaemia with a haemoglobin level of 106 g/L (normal range, 110 to 145 g/L) and mean cell volume of 78 fL (normal range, 80 to 96 fL). Iron studies show low iron, low ferritin, low iron saturation and high transferrin consistent with iron deficiency.

What further investigations should be ordered?

Although menstrual blood loss is the most likely explanation, coeliac serology (including immunoglobulin A transglutaminase antibodies) may be carried out because they may be positive in the absence of any symptoms and are recommended by some bodies as part of a lethargy screen. These were found to be negative in this case.

What is the diagnosis?

This woman was diagnosed with iron deficiency anaemia due to menstrual blood loss.

How should this patient be managed?

Oral iron replacement, with repeat FBC and iron studies in three months, should be first-line therapy. The recommended dose in adults is 100 to 200 mg of elemental iron daily (in two to three divided doses).[10] Gastrointestinal disturbance is the main adverse effect, which can be minimised with either lowered doses or taking with food or at night. Patients with menstrual iron loss who do not respond to oral replacement can be considered for parenteral replacement. Ferric carboxymaltose is listed on the PBS, and is safe and relatively easy to administer as a 1000 mg dose intravenous infusion over 15 minutes. Intramuscular iron therapy is painful and may cause permanent skin staining so is not recommended.[10] Emergence of underlying bowel symptoms and/or failure to respond to either oral or parental iron replacement should prompt referral of the patient to exclude other sources of iron deficiency or loss.

Case 3

A 27-year-old single mother presents with lethargy on a background of longstanding mild asthma. She denies any recent exacerbations, and has no respiratory or other system specific symptoms. She has a 4-year-old daughter and currently works part-time in office administration. She had recently separated from her partner following a volatile and abusive relationship and reports ongoing low mood with periods of crying, poor appetite, poor sleep and general anhedonia. She reports a period of previous intravenous drug use but denies any use since the birth of her daughter. She is unaware of any previous serological screening for blood-borne infections. She denies current thoughts of self-harm. She previously trialled duloxetine; however, she stopped this, believing it was causing weight gain. Bowels motions are regular. She reports regular although heavy menses. She is overweight with a BMI of 29 kg/m^2 but there are no significant abnormalities noted on examination.

What investigations should be ordered?

For initial screening, FBC and UEC, CMP, TSH and fasting blood glucose levels should be measured. LFTs should also be carried out. If not previously tested, serological screening for blood-borne infections including hepatitis B and C and HIV should be performed given the risk factor of previous intravenous drug use. An erythrocyte sedimentation rate or C-reactive protein and iron studies may also be considered.

What further investigations should be ordered?

Results of all investigations were normal. In the absence of any other symptoms or new complaints, no further pathology testing or imaging is warranted at this stage. Although there are no physical red flags, there are risk factors for psychological disease that should be considered.

What is the diagnosis?

This woman was diagnosed with lethargy due to reactive depression/anxiety.

How should this patient be managed?

This patient's lethargy in the absence of any red flags or abnormalities on pathology testing is most likely due to ongoing depression and anxiety in the context of multiple life stressors. The mainstay of management would be ongoing cognitive behavioural therapy to identify her life stresses and focus on strategies to manage them. Ongoing reassurance is often necessary when explaining the interaction of psychosocial factors to patients and should be combined with lifestyle advice on a well-balanced diet, good sleep hygiene, regular physical activity and relaxation techniques.[11] If symptoms persist and an antidepressant is deemed appropriate, a selective serotonin reuptake inhibitor may be trialled. Side effects including insomnia, agitation, weight changes and, ironically in the context of this case, lethargy should be monitored for. Selective serotonin reuptake inhibitors have been shown to be either weight neutral or produce slight weight loss in some studies (although weight gain has also been reported and there is potential variation in responses between individual agents).[12]

Summary

Lethargy is a common presenting complaint in general practice. Although a few cases will have underlying reversible pathology, a careful history, examination and judicious use of investigation are paramount to identify potential red flags that may indicate serious underlying medical or psychological pathology, and to allow reassurance of the remaining majority of patients in whom lethargy may be a manifestation of nonpathological work-life pressures and stresses.[13] As such it is important that GPs are familiar with the wide variety of potential presenting features and underlying causes of lethargy, appropriate use of initial investigations and subsequent investigation, as well as the referral pathways. **ET**

References

A list of references is included in the website version of this article (www.endocrinologytoday.com.au).

COMPETING INTERESTS: None.

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