



# Fatigue and endocrine disorders

## *Causes and comorbidities*

**BACKGROUND** Most causes of fatigue are ill defined, self limiting or elude diagnosis. Many endocrine disorders present with nonspecific features including fatigue, so are difficult to differentiate on clinical grounds. However, avoiding diagnostic delay is vital to prevent significant morbidity and mortality. Thus, a high index of suspicion and knowledge of appropriate investigations is important. Endocrine disorders predispose the individual to developing related disorders; fatigue may be one sign of associated comorbidity.

**OBJECTIVE** This article discusses the endocrine disorders that commonly present with or develop fatigue as a prominent feature, with emphasis on particular challenges for diagnosis, investigation or management. Screening recommendations for comorbid disease was generated by an extensive review of current evidence.

**DISCUSSION** The identification of endocrine disorders can be both challenging - due to patterns of presentation - and rewarding for doctors and patients alike, due to importance and effectiveness of treatment.

Fatigue describes reduced power output or muscular force, reduced capacity to perform multiple tasks over time, or the subjective experience of feeling exhausted, tired, weak or having lack of energy.<sup>1</sup> This can be summarised as physical, affective or cognitive fatigue, although this distinction is not always helpful in practice as many physical causes may also present with affective or cognitive fatigue.

Fatigue is subjectively experienced and described, and some community surveys have found up to 20–25% of normal controls reporting fatigue.<sup>1</sup> Fatigue accounts for 1–3% of encounters in primary care<sup>2</sup> with a physical disease found in less than 10% of patients presenting with fatigue.<sup>3</sup> Nonetheless, fatigue is a prominent symptom of several endocrine disorders which are common in our community (Table 1). In addition, many endocrine conditions are associated with an increased prevalence of other disease processes where fatigue is a common complaint (Table 2).

In some cases a thorough history and examina-

tion may suggest the likely cause of fatigue. Where the diagnosis remains elusive, suggested initial investigations should include blood glucose, calcium and liver function tests, full blood count and sedimentation rate, creatine kinase, thyroid stimulating hormone and HIV testing. Excluding cortisol defi-

Adam Morton,  
David King



Adam Morton,  
MBBS, FRACP,  
is a physician,  
Mater Adult  
Hospital,  
South Brisbane,  
Queensland.

David King,  
MBBS, MPH,  
FRACGP, is Lecturer,  
Centre for General  
Practice,  
The University of  
Queensland, and  
Medical Officer,  
University Health  
Service,  
The University of  
Queensland.

**Table 1. Endocrine disorders associated with fatigue**

### Common

Diabetes mellitus  
Hypothyroidism  
Hypogonadism  
Hyperparathyroidism

### Uncommon

Hypoadrenalism  
Apathetic hyperthyroidism  
Growth hormone deficiency  
Glucocorticoid resistance

**Table 2. Fatigue associated disorders with increased prevalence in endocrine diseases**

|  | Prevalence | Suggested frequency screening                 |
|--|------------|---|
| <b>Type 1 diabetes mellitus</b>                                |            |   |
| Coeliac disease  | 4.5%       | At diagnosis, then at 3–5 years <sup>37</sup> |
| Hypothyroidism   | 13%        | Annual <sup>38, 39</sup>                      |
| Pernicious anaemia   | 6.3%*      | If anaemic <sup>40</sup>                      |
| Addison disease  | 0.8%       | If symptomatic <sup>38</sup>                  |
| * Patients with type 1 diabetes and autoimmune thyroid disease |            |   |
| <b>Type 2 diabetes mellitus</b>                                |            |   |
| Haemochromatosis   | 1–1.3%     | At diagnosis <sup>5,41–43</sup>               |
| Obstructive sleep apnoea                                       | 20%        | If symptomatic <sup>7</sup>                   |
| Vitamin B12 deficiency   | 10–30%     | After 10 years metformin <sup>9</sup>         |
| <b>Hashimotos thyroiditis</b>                                  |            |   |
| Coeliac disease  | 3.3%       | At diagnosis <sup>44</sup>                    |
| Addison disease  | Rare       | If symptomatic                                |
| Pernicious anaemia   | Rare       | If anaemic                                    |
| <b>Addison disease</b>   |            |   |
| Hypothyroidism   | 20.5%      | Annually <sup>45</sup>                        |
| Coeliac disease  | 1.2–12.2%  | At diagnosis <sup>45,46</sup>                 |
| Premature menopause  | 7.3%       | If symptomatic <sup>45</sup>                  |
| Pernicious anaemia   | 4.8%       | If symptomatic <sup>45</sup>                  |
| Type 1 diabetes mellitus                                       | 1.2%       | If symptomatic <sup>45</sup>                  |
| <b>Hypogonadism</b>  |            |   |
| Other anterior pituitary deficiencies                          |            | At diagnosis                                  |
| Obstructive sleep apnoea                                       | Common     | If symptomatic                                |
| Haemochromatosis   | Rare       | At diagnosis                                  |
| Anaemia  | 46%        |   |

ciency, although rare, should be considered given the possible lethal consequences of missing this diagnosis. Knowledge of disease presentation and relative frequency is important in developing a comprehensive yet realistic differential diagnosis and the judicious ordering of appropriate investigations.

**Diabetes mellitus**

Diabetes mellitus (DM) is a common disorder, with 85–90% of diagnosed cases due to type 2 disease. An estimated 3% of the Australian population has diagnosed diabetes, with a similar proportion having undiagnosed diabetes. Diabetes mellitus is associated with an increased prevalence of a number of medical disorders that have fatigue as a common symptom (Table 2). Fibromyalgia (FM) was shown to affect 17% of patients with diabetes compared with 2% of healthy controls.<sup>4</sup> Those patients with FM had sig-

nificantly higher levels of HbA1c than those without. Depression is three times more prevalent in diabetics than in nondiabetics, and higher HbA1c levels are significantly correlated with worse depression, tension and fatigue and poorer general wellbeing.<sup>5,6</sup>

It is controversial whether all type 2 diabetics should be screened for haemochromatosis at diagnosis. Several studies have found the prevalence of haemochromatosis in DM 2–6 times the rate of the general population, while other studies have found no difference.<sup>7,8</sup>

Moderate or severe obstructive sleep apnoea (OSA) was demonstrated in 70% of obese type 2 diabetics who complained of heavy snoring or excessive sleepiness, and 18.6% of randomly selected type 2 diabetics.<sup>9,10</sup> Sleep disordered breathing was also demonstrated in five of 12 lean type 1 diabetics, with a close association with the

presence of neuropathy.<sup>11</sup>

Vitamin B12 deficiency is seen in 10–30% of patients taking metformin for greater than 10 years, although these cases are not all symptomatic.<sup>13</sup> Vitamin B12 deficiency may also occur in type 1 diabetics due to coexistent coeliac disease or pernicious anaemia.<sup>12,13</sup> Type 1 diabetes is also associated with other autoimmune disorders including coeliac disease, primary hypothyroidism due to Hashimoto disease, and Addison disease. Postpartum thyroiditis occurs in 25% of type 1 diabetic women with thyroid antibodies; fatigue and depression being prominent symptoms.<sup>14,15</sup> In addition, complications of diabetes mellitus such as renal failure, cardiac failure and autonomic neuropathy may cause fatigue.

### Thyroid disorders

Community studies in the United States and the United Kingdom have found the prevalence of overt hypothyroidism to range between 1–3% (Figure 1); subclinical hypothyroidism in the over 55 years of age between 8–17%, with 3–7% having thyrotropin (TSH) levels greater than 10 mIU/L.<sup>16–20</sup> Women are affected 10 times more often than men and the rate increases with advancing age. Studies have presented contrary results on the benefits of treating individuals with subclinical hypothyroidism (normal free T<sub>4</sub>, TSH 4–10 mIU/L). A recent six month double blind placebo controlled study found no symptomatic benefit. Instead patients treated with thyroxine became more anxious than those on placebo.<sup>21</sup> Women of child bearing age not using contraception should always be treated given the association of elevated TSH and reduced intellectual performance in offspring.<sup>22</sup> A recent review on the cardiovascular effects of subclinical hypothyroidism noted its association with impaired left ventricular function, enhanced risk for atherosclerosis and myocardial infarction.<sup>23</sup> Of the 14 studies included in the review, nine had mean TSH concentrations greater than 10 mIU/L, making the results less generalisable to mild subclinical hypothyroidism. Thus, the treatment of subclinical hypothyroidism needs to be individualised.

Like type 1 DM, hypothyroidism due to Hashimoto disease is associated with other autoimmune endocrinopathies which should be excluded if symptoms persist despite adequate biochemical replacement (Table 2). It is particularly important

to exclude coeliac disease in women of child bearing age given adverse outcomes in pregnancy associated with this disorder. Addison disease should be considered particularly if individuals deteriorate after commencing thyroxine (T<sub>4</sub>) replacement. Thyroxine should be taken fasting as a number of substances can interfere with absorption, particularly iron, calcium and cholestyramine. As the half life of T<sub>4</sub> is approximately seven days, one should wait approximately six weeks before checking thyroid function after dosage changes.

Hyperthyroidism and anxiety/depression have overlapping features that may cause misdiagnosis during initial presentation, and comorbidity is common. Persisting symptoms following specific thyroid treatment warrant psychiatric review. The number of classic signs of hyperthyroidism is significantly less in the elderly compared with younger patients. The nonspecific features of fatigue, weight loss and tachycardia were found in over 50% of elderly first presenting with hyperthyroidism.<sup>24</sup>

### Hyperparathyroidism

Primary hyperparathyroidism affects approximately 1% of the adult population, particularly elderly women. Many individuals with mild hypercalcaemia are asymptomatic of classic symptoms but report vague psychological symptoms including fatigue, irritability, confusion, insomnia and depression. These symptoms have been shown to improve within 7–10 days of surgery, with patients reporting a 60% increase in their health one year after successful parathyroidectomy.<sup>25–27</sup> Therefore, even mild hypercalcaemia due to hyperparathyroidism should be considered a potentially curable cause of fatigue. It is important to check ionised or free calcium levels in individuals with corrected calcium at the upper end of normal, otherwise hyperparathyroidism may be missed.

### Hypoadrenalism

Hypoadrenalism is rare, with chronic primary adrenal insufficiency having an prevalence of 93–140 per million in white populations, and secondary adrenal insufficiency a prevalence of 150–280 per million.<sup>28</sup> In developed countries autoimmune adrenalitis accounts for 80–90% of



Figure 1. Hypothyroidism



Figure 2. Addison disease (affected sister on left)

cases of primary hypoadrenalism (Figure 2). The most common cause of secondary adrenal insufficiency is administration of exogenous glucocorticoids (Case 1). Other causes include pituitary and hypothalamic tumours, and lymphocytic hypophysitis. Symptoms common to both primary and secondary hypoadrenalism include fatigue, anorexia, nausea, weight loss,

epigastric pain, myalgias and arthralgias due to glucocorticoid deficiency, and women may complain of loss of libido and reduced body hair due to loss of adrenal androgens. Those with primary hypoadrenalism may also complain of salt craving and postural dizziness due to mineralocorticoid deficiency and hyperpigmentation. Those with secondary insufficiency may have mass effect symptoms related to pituitary expansion, or symptoms related to other anterior pituitary hormone

excess or deficiency.

Initial testing should be an early morning serum cortisol and ACTH level. A random cortisol greater than 500 nmol/L effectively rules out hypothalamic-pituitary-adrenal axis insufficiency, and a level less than 100 nmol/L confirms deficiency, with plasma ACTH then indicating a primary or secondary disorder. For values between 100 and 500 nmol/L a short synacthen, metyrapone or insulin hypoglycaemia test should be performed. It is important that affected individuals wear a medical alert bracelet, know to double their glucocorticoid dose with even minor intercurrent illness, and the need for urgent parenteral treatment in the event of vomiting. Dehydroepiandrosterone (25–50 mg per day) has been shown to improve wellbeing, mood and libido in women, and should be considered in all patients with adrenal insufficiency.<sup>29–31</sup>

## Hypogonadism

Symptoms of male hypogonadism include fatigue, loss of libido, cognitive dysfunction, and reduced muscle strength (Case 2). It is critical to make a firm diagnosis of testosterone deficiency before commencing androgen therapy as most double blind trials demonstrate a 30–40% placebo response. Testosterone is secreted in a diurnal rhythm so levels must be taken early in the morning, and three separate tests of total testosterone should be consistently low before diagnosing hypogonadism. Luteinising hormone levels will then establish whether the deficiency is primary (elevated LH) or secondary to hypothalamic/pituitary disease (inappropriately normal or low LH). In the setting of secondary hypogonadism, serum prolactin and other tests of anterior pituitary function should be performed including imaging with magnetic resonance imaging. Significant pituitary or hypothalamic abnormalities are demonstrated in only 5.0–6.7% of men with secondary hypogonadism.<sup>32,33</sup> Other causes of secondary hypogonadism include haemochromatosis, cardiac, renal, respiratory or hepatic failure, glucocorticoid therapy, low body weight and OSA. The latter is particularly important to exclude as it is a common cause of hypogonadism in clinical practice, androgen deficiency may be reversible with continuous positive airways pressure, and OSA may be precipitated or aggravated by androgen replacement.<sup>34–36</sup> Baseline bone mineral densitometry, haemoglobin, bladder outlet obstructive symptoms and prostate

### Case 1

A 32 year old engineer was referred by her gynaecologist because of androgenic symptoms and high testosterone levels due to danazol treatment for endometriosis. She also complained of marked fatigue, weight loss of 5 kg, myalgias and arthralgias, and symptoms suggestive of hypoglycaemia. She had previously been diagnosed with asthma, currently inadequately controlled despite salmeterol and fluticasone 500 µg twice per day. On examination she appeared cushingoid with thin skin, easy bruising and proximal muscle weakness. Investigations revealed undetectable morning cortisol and serum ACTH of 8 nmol/L (normal 10–50). Thyroid function tests were normal. A diagnosis of hypothalamic-pituitary-adrenal axis suppression due to fluticasone was made, and she was commenced on replacement doses of cortisone acetate. After discussion with her respiratory physician her fluticasone was changed to budesonide, and her adrenal function recovered after a period of six months. Her bone density was normal.

### Case 2

A 63 year old man was referred regarding hypogonadism. Investigations performed because of impotence, fatigue and poor muscle strength revealed three morning testosterone levels to be consistently around 5 nmol/L (normal 10–33) with inappropriately low luteinising hormone (LH) of 6 U/L (normal 3–20). His past history was significant for ischaemic cardiomyopathy with an ejection fraction of 40%. Serum prolactin, LH, follicle stimulating hormone (FSH) and pituitary imaging were normal. Transferrin saturation and ferritin were normal, excluding haemochromatosis. On further questioning his wife gave a history of heavy snoring, apnoeas and severe periodic leg movements (PLMS), and he described day time somnolence, poor memory and concentration. A sleep study confirmed severe sleep apnoea. He was commenced on cabergoline for his PLMS, and awaits a trial of continuous positive airways pressure for the possible benefits to his symptoms, androgen deficiency and cardiac function.

serum antigen should be assessed before commencing androgen replacement.

## Conclusion

Endocrine disorders may present with nonspecific symptoms including fatigue. Consideration of the possibility of endocrine disease in this setting is important. In addition, in patients with known endocrine disease the development of fatigue may be an indication that a related disorder or complication is developing.

### SUMMARY OF IMPORTANT POINTS

- Fatigue is a prominent symptom of several endocrine disorders.
- Diabetes, thyroid disorders, hyperparathyroidism, hypoadrenalism, and hypogonadism should all be considered.
- Cortisol deficiency, although rare, should also be considered.

Conflict of interest: none.

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AFP

## CORRESPONDENCE

Email: amorton@mater.org.au