

A JOINT INITIATIVE OF

DOCTOR



The Royal College
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COMMON SENSE PATHOLOGY

Chronic Fatigue Syndrome

Contents

- Diagnostic criteria
- Laboratory investigations
- Differential diagnoses

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REBETRON COMBINATION THERAPY Indications:

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Contraindications: Hypersensitivity to ribavirin/alfa interferon/any components of Rebetron; pregnancy, pregnancy in partner; lactation; severe cardiac disease; haemoglobinopathies; renal impairment; epilepsy, compromised CNS function; decompensated hepatic cirrhosis; concomitant immunosuppressives (excluding short-term corticosteroids); autoimmune disease (especially hepatitis); immunosuppressed transplant recipients; uncontrolled thyroid disease; severe psychiatric disorder (or history), especially if severe depressed/suicidal.

Precautions: Rebetol not to be used alone; *ribavirin teratogenic risk: Extreme care must be taken to avoid pregnancy in female patients and in partners of male patients on Rebetron therapy. Do not initiate therapy until a report of a negative pregnancy test has been obtained. Women of childbearing potential and men must use two forms of effective contraception during treatment and for six months post-treatment. Routine monthly pregnancy tests must be performed during this time.*

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*If pregnancy does occur during treatment/six months post-treatment, the patient must be advised of the significant teratogenic risk of ribavirin to the foetus. Haemolysis; debilitating medical conditions (pulmonary disease, diabetes); coagulation disorders, severe myelosuppression; m-cresol (preservative); liver function abnormalities; hypotension; fever (flu-like syndrome); pulmonary function impairment (concomitant use with Shosaikoto – Chinese herb); ocular changes; CNS effects (depression); cardiovascular disorders; psoriasis, auto-antibodies; thyroid abnormalities; regular blood tests (FBC, blood chemistry, pregnancy tests, etc) prior to and during therapy; children; elderly. **Drug Interactions:** NRTIs (zidovudine, stavudine, didanosine, abacavir); narcotics, hypnotics or sedatives; xanthine derivatives (theophylline). **Adverse Reactions:** Flu-like syndrome (include fatigue, fever, headache, malaise, myalgia/ arthralgia); asthenia; rigors; weight loss; dizziness; GI effects (abdominal pain, anorexia, diarrhoea, dyspepsia, nausea); musculo-skeletal pain; CNS/psychiatric effects (anxiety, impaired concentration, depression, insomnia, irritability); anaemia, other haematological changes; dyspnoea; Dermatological effects (alopecia, pruritus/rash, dry skin), others – see Product Information.*

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Dear Reader

It is with great pleasure that the Royal College of Pathologists of Australasia and *Australian Doctor* present a new series of *Common Sense Pathology*.

The first series was very well received and lauded as providing clear, concise information that is useful and necessary for GPs; indeed, back copies are still eagerly sought. *Common Sense Pathology* has been sorely missed since its demise in 1999 due to the cessation of a Federal Government funding initiative.

The college and *Australian Doctor* are delighted to have reached an agreement to produce a new series. Suitable topics to present on the appropriate use of pathology in the clinical setting abound, and we look forward to a productive association. We thank Dr Peter Clyne for reviewing each article.

The 2002 series will consist of six articles, each of which will be published as a separate booklet and delivered with your *Australian Doctor*. In addition, the articles will be posted on the college web site, www.rcpa.edu.au. It is hoped you will find this fourth article on chronic fatigue syndrome to be a valuable education and reference tool.

Both the college and *Australian Doctor* are pleased to be able to provide this resource to the medical fraternity.

Yours sincerely

Dr Matthew Meerkin
Editor
Common Sense Pathology

Dr Kerri Parnell
Medical Editor
Australian Doctor

Common Sense Pathology is a joint initiative of *Australian Doctor* and The Royal College of Pathologists of Australasia.

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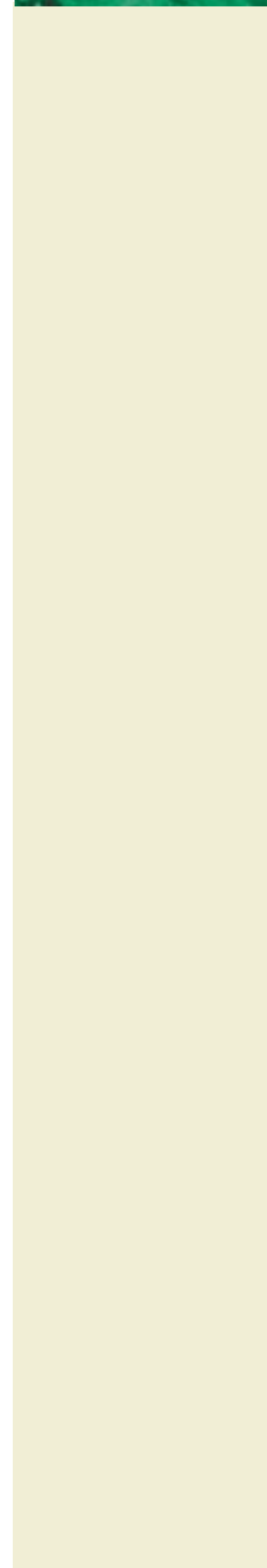
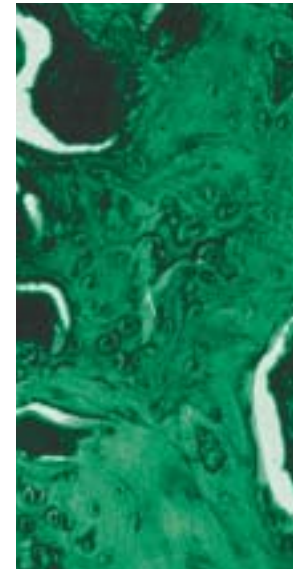
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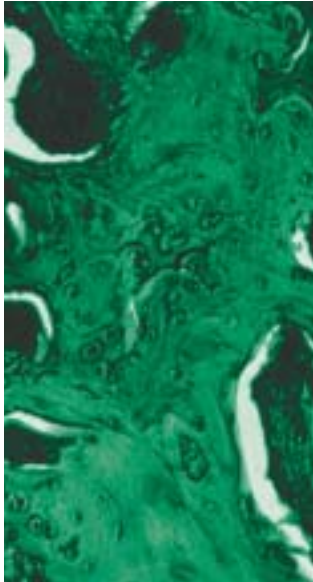
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Chronic Fatigue Syndrome

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Chronic fatigue syndrome (CFS) is diagnosed on clinical grounds. It is based on the presence of characteristic features (next page), and the exclusion of alternative diagnoses. The symptoms of CFS may overlap with other common syndromes such as fibromyalgia and sleep disorders. The primary diagnosis depends on which symptoms are most dominant and disabling. People with CFS often have concurrent depression and sleep disorders and these need not exclude the primary diagnosis of CFS.

Symptoms similar to those of CFS may occur in a range of other disorders like diabetes, thyroid disease, anaemia, major depression and Cushing's syndrome. The first priority in clinical assessment is to exclude alternative explanations for the patient's fatigue. A careful history, physical examination and a restricted set of laboratory investigations can achieve this.

It is important to note the characteristic features of the fatigue in patients with CFS. In patients with CFS, fatigue is typically exacerbated by relatively minor physical activities and is associated with a protracted recovery period which can last for hours or days. The fatigue should be differentiated from muscle weakness (neuromuscular disease), dyspnoea (cardiac or respiratory disease), somnolence (primary sleep disorders) and loss of motivation and anhedonia (major depression).

Additional clues which could point to alternative diagnoses may include any of the following: unexplained weight loss (occult infection, malignancy, thyrotoxicosis, inflammatory bowel disease), cold intolerance (hypothyroidism), snoring and daytime sleepiness (sleep apnoea), infections (HIV, hepatitis C), depression or anxiety, autoimmune diseases and drug misuse. A history of altered bowel habit may indicate an underlying gastrointestinal disease (coeliac disease, inflammatory bowel disease) or thyroid disease.

Characteristically, there are no abnormal physical findings in people with CFS. The physical examination and mental state examination are primarily directed towards excluding other disorders. A careful assessment for neurological deficits or signs of anaemia, cardiac failure, respiratory disease, infection, autoimmune diseases or malignancy should be performed. The presence of persistent fever, lymphadenopathy and hepatosplenomegaly are not features of CFS and where present would always warrant further investigation.

It should be clearly understood that there are no laboratory tests to confirm the diagnosis of CFS. The purpose of employing laboratory investigation is to help

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exclude other disorders.

Recommended first-line investigations include the following:

- Full blood count and erythrocyte sedimentation rate.
- Serum electrolyte, glucose, calcium and creatinine levels.
- Liver function tests.
- Thyroid function tests (TSH).
- Urinalysis for blood, protein and glucose.

Additional investigations should be ordered only if the history or examination plausibly suggests other diagnoses (eg, autoimmune disease, coeliac disease), or if abnormalities are found in the initial investigations. Routine analysis of immune function (lymphocyte subsets, immunoglobulin and immunoglobulin subclass levels), infectious disease serology or environmental toxins is not recommended.

Diagnostic criteria for chronic fatigue syndrome

1. *Fatigue*

Clinically evaluated, unexplained, persistent or relapsing fatigue persistent for six months or more that is:

- Of new or definite onset;
- Not the result of ongoing exertion;
- Not substantially alleviated by rest;

and results in substantial reduction in previous levels of occupational, educational, social or personal activities;

and

2. *Other symptoms*

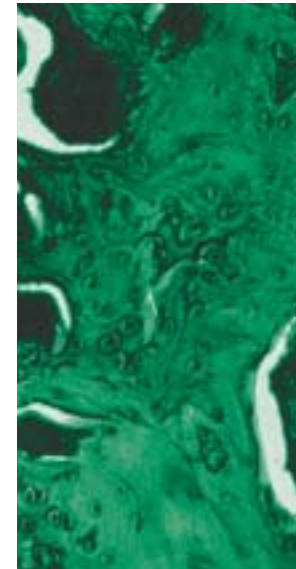
Four or more of the following symptoms that are concurrent, persistent for six months or more, and which did not predate the fatigue:


- Impaired short-term memory or concentration.
- Sore throat.
- Tender cervical or axillary lymph nodes.
- Muscle pain.
- Multi-joint pain without arthritis.
- Headaches of a new type, pattern or severity.
- Unrefreshing sleep.
- Post-exertional malaise lasting more than 24 hours.

Case 1

A 37-year-old woman presents with an eight-month history of fatigue and lethargy. The symptoms were insidious in onset and associated with impairment of memory and concentration, as well as diffuse arthralgia and myalgia. There has been no weight loss or GI symptoms. She denies symptoms related to depression or other psychological problems. Her sleep has been unchanged in pattern but has become unrefreshing in quality. The fatigue and other symptoms were substantially disrupting her ability to keep up with her work as an administrative assistant.

Physical examination revealed a thin woman who was afebrile. Blood pressure was 120/80mmHg, heart sounds were dual, and her chest was clear. There were no abnormal findings on abdominal examination. There were no neurological abnormalities and there was no evidence of myopathy.





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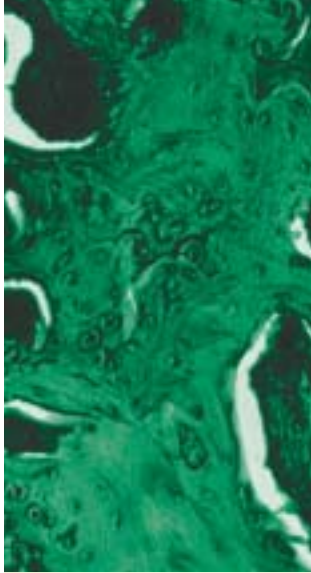
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is 300 mg once daily. References: 1. Karvea (irbesartan) TGA Approved Product Information, July 2002. 2. Parving HH, et al. *N Engl J Med* 2001; 345: 870-878. 3. Lewis EJ, et al. *N Engl J Med* 2001; 345: 861-860. © Registered Trademark. 07/02 SASKA0622. **Because health matters**



Question 1: What are the possible causes of this woman's fatigue?

There are a large number of causes of chronic fatigue. The aetiology is often evident from a careful history and physical examination. Attention should be given to features that suggest an inflammatory or infective illness, neurological deficits, symptoms which are suggestive of metabolic disturbance, as well as sleep and psychological disorders, and, in particular, depression. In the absence of such findings, a diagnosis of CFS could be entertained. The diagnosis should be based on the criteria as laid down by the International Consensus Definition (Fukuda et al, 1994). The systematic approach to the diagnosis of CFS is outlined in the clinical practice guidelines recently published in the *Medical Journal of Australia*. The diagnosis of CFS requires that a patient has a new onset of fatigue which has been present for more than six months and that it be disabling. There may be associated arthralgia and myalgia present. The diagnosis remains one of exclusion of other common causes of fatigue by appropriate history, physical examination and investigations.

Question 2: What investigations would be appropriate in this case?

In the absence of any historical or physical signs suggestive of an underlying disorder, a limited number of investigations are required, notably a full blood count and differential white cell count; renal, liver and thyroid function tests; as well as a urinalysis for blood, glucose and protein. These tests are aimed at excluding common causes of chronic fatigue such as anaemia, diabetes and thyroid disease.

Case 2

A 52-year-old man complains of severe fatigue and daytime tiredness which have been present for 12 months. He sleeps for eight hours a night, but wakes non-refreshed. He complains of daytime somnolence. His alcohol intake is 100g each day (ie, 10 standard drinks).

Physical examination reveals an obese man with a thick neck. Pharyngeal injection is present. His blood pressure is 150/100mmHg, and his pulse rate is 70 and regular. There are no stigmata of chronic liver disease. No other abnormalities are detected.

Question 1: What are the possible causes of this man's fatigue?

The clinical features are suggestive of obstructive sleep apnoea. Further history related to the presence of snoring or obstruction during sleep, waking with a sore throat and early morning headaches would also help confirm such a diagnosis. The presence of a narrow pharynx, with pharyngeal erythema, and hypertension is also suggestive of obstructive sleep apnoea. This is now recognised to be a common cause of fatigue associated with daytime somnolence. Other diagnoses to be considered in this case would include secondary causes of hypertension (including renal disease and Cushing's syndrome) and hypothyroidism. In addition, alcohol-related liver disease and its complications should be considered.

Question 2: What further investigations would be warranted in this case?

In addition to the shortlist of investigations outlined for Case 1, the most informative test would be an overnight sleep study demonstrating presence of apnoeas and hypopnoeas with

oxygen desaturation during rapid eye movement sleep. If the LFTs are abnormal, further investigations to evaluate liver synthetic function, such as prothrombin time may be indicated. In addition, tests for causes of secondary hypertension, including a 24-hour urinary free cortisol estimation, may be pertinent in such a case.

Question 3: The results of investigations indicated a normal 24-hour urinary free cortisol. However, the LFTs were abnormal, with a GGT of 659, SAP of 175, AST 566, ALT 275, and a normal bilirubin with an albumin of 28g/L. What is the likely cause of these abnormalities and what further investigations are indicated?

These abnormalities most likely indicate alcohol-related liver disease. Relevant further investigations include viral serology (hepatitis C, hepatitis B), serum ferritin, INR, serum protein, EPG and IEPG. Following this, a liver ultrasound and possible liver biopsy may be indicated, depending on the results of these studies.

Case 3

A 45-year-old abattoir worker presents with a 12-month history of tiredness, lethargy and intermittent night sweats. He dates the onset of his symptoms from a febrile illness 12 months earlier which he was told was a bad bout of “the flu”. His fatigue is such that he is no longer able to work. He has short-term memory and concentration impairment and recurrent headaches, but no fevers. Physical examination is unremarkable.

Question 1: What are the possible causes of fatigue in this situation?

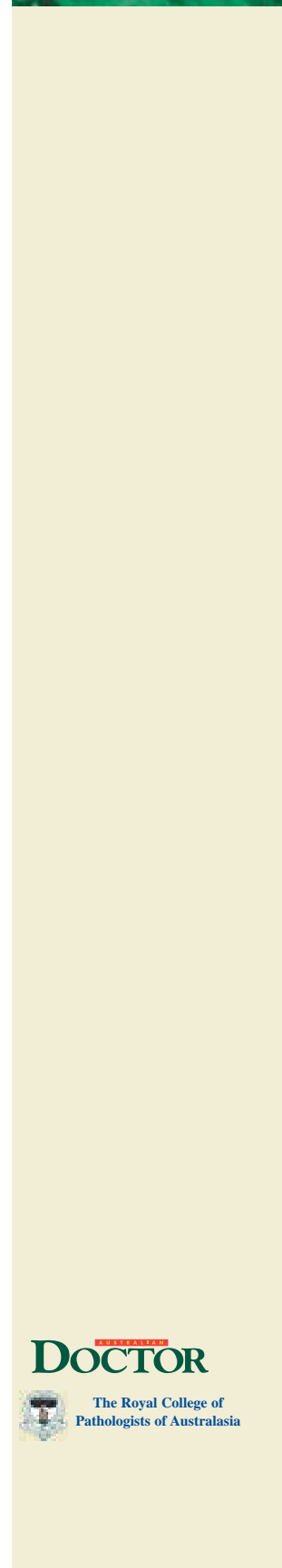
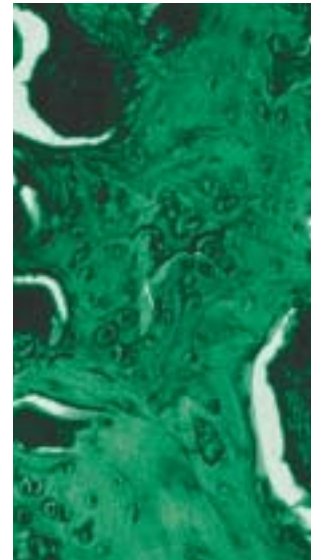
The presence of significant fatigue associated with night sweats and fevers in an abattoir worker are suggestive of an occupationally acquired zoonotic infection, such as Q fever or leptospirosis. Other considerations would include the presence of a chronic infection (TB, endocarditis) or neoplasm (lymphoma). Other chronic inflammatory diseases including sarcoidosis should be considered.

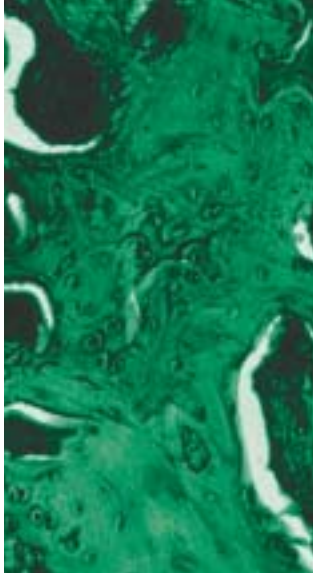
Question 2: Results of investigations indicate the presence of positive Q fever serology with a complement fixation antibody titre of 128 and a positive IgM antibody. What is the significance of these results?

These results are consistent with an infection with *Coxiella burnetii* (the causative agent of Q fever) in the last 12-18 months. These results do not indicate whether this person has chronic, localised infection in the form of endocarditis, granulomatous hepatitis or osteomyelitis.

Question 3: What further investigations would indicate the presence of chronic Q fever infection?

A rising titre of IgA and IgG antibodies against the phase I *C burnetii* antigen is indicative of such an ongoing infection. A trans-oesophageal cardiogram was reported as normal. The patient had persistently abnormal LFTs with elevated alkaline phosphatase and GGT, suggesting cholestasis, possibly due to a space-occupying lesion. Liver biopsy confirmed the presence of non-caseating granulomata consistent with Q fever. Subsequent prolonged treatment with doxycycline, rifampicin and hydroxychloroquine brought about slow resolution in the cholestatic liver damage and the fatigue syndrome.





Case 4

A 20-year-old woman presents with a six-year history of fatigue. She developed anorexia nervosa at 15, with associated depression. She has been under treatment for this for four years and reports that she has now overcome her anorexia nervosa and no longer feels depressed. However, despite this she continues to have persistent fatigue and malaise. Her menstrual periods have returned and she has increased her weight by 5kg in the past 12 months. Apart from a relatively aesthenic body habitus and mild glossitis, the physical examination is normal. Investigation of her nutritional status reveals a low serum iron, a low serum ferritin level and a low transferrin saturation. She also has a reduced 25-hydroxy vitamin D level.

Question 1: Based on the results of these investigations, what is the most likely cause of this ongoing fatigue?

Vitamin deficiency and associated iron deficiency: The iron deficiency may be due to poor intake or to excess loss in the form of menstrual or GI blood loss. The vitamin D deficiency may be due to dietary factors or to lack of sunlight exposure. These results may also be indicative of an underlying malabsorption syndrome such as coeliac disease.

Question 2: What further investigations would be relevant in this case?

Although the iron deficiency may be related to previous dietary problems or heavy menses, the history does not substantiate this and thus the patient should be assessed for possible bleeding from the GI tract. The presence of vitamin D deficiency should be further assessed and the presence of malabsorption also needs to be excluded. Tests for other fat-soluble vitamin deficiencies (such as vitamin K) should be performed by measurement of the prothrombin time. She should also have anti-endomysial and transglutaminase antibodies assayed to test for coeliac disease.

Reference: *MJA* 6 May 2002; vol 176 suppl.

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1. Alcohol Pharmacotherapy Forum (2001) *Diagnosis and Management of Alcohol Misuse - A Guide for General Practice in Australia*. 2. Sass H, Sokya M, Mann K, Zieglansberger W (1996) Relapse prevention by acamprosate. *Arch Gen Psychiatry* 53: 673-680. **Indication:** CAMPRAL is indicated as therapy to maintain abstinence in alcohol dependent patients. It should be combined with counselling. **Dosage:** 2 x 333mg tablets tds (for patients <60kg the dose is 2 x 333mg in the morning, 1 x 333mg at midday and 1 x 333mg in the evening). Treatment should be initiated as soon as possible after withdrawal period and be maintained if the patient relapses. The recommended period of treatment is 1 year. **Contraindications:** Patients with known hypersensitivity to the drug; pregnant or breastfeeding women; renal insufficiency (serum creatinine > 120micromol/L); severe hepatic failure (Childs-Pugh Classification C). **Precautions:** CAMPRAL does not constitute treatment for the withdrawal period. **Side effects:** Adverse events associated with CAMPRAL tend to be mild and transient in nature. The most frequently observed side effect is diarrhoea which has been reported in 10% of patients at the initiation of treatment. **Please review Product Information before prescribing. Full disclosure Product Information is available on request from Alphapharm Pty Ltd, Chase Building 2, Wentworth Park Road, Glebe NSW 2037.**



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