



# Chronic fatigue syndrome

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Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME) is a complex physical illness characterised by debilitating fatigue, post-exertional malaise and many other symptoms. Microglial activity in the brain is accompanied by chronic immune activation, changes in energy metabolism and abnormalities in the metabolome and microbiome.

The illness was first described in the 18th century BC by Hammurabi, a Babylonian philosopher. Its history has been somewhat stormy. Charles Darwin and Florence Nightingale probably suffered from CFS/ME. Over the last century, outbreaks of viral illnesses have resulted in cohorts of people with serious ongoing health problems, which we now call CFS/ME. One of these cluster outbreaks occurred among medical staff at the Royal Free Hospital in London in 1955. Many remained very ill long-term. The name, 'Royal Free Disease' was coined. It was considered a serious physical illness, although in 1970 was re-labelled as 'mass hysteria'.<sup>1</sup> Patients' symptoms were not adequately investigated and much damage was done. Many still consider CFS/ME to be a psychiatric illness, despite research evidence to the contrary. In 1978, the Royal Society of Medicine concluded the illness had a clear organic basis. The World Health Organization's International Classification of Diseases (ICD-10) now classifies CFS/ME as a neurological illness (G93.3).

In 2015, the US Institute of Medicine proposed replacing CFS/ME with a new name: Systemic Exertion Intolerance Disease (SEID). The rationale for this name change is that SEID focuses on the core symptom of post-exertional malaise, involving the entire body, emphasising the physical aspect of the condition. However, the term SEID has not yet been universally embraced.<sup>2</sup>

Epidemiological studies cite CFS/ME incidence as 3–4 per 1000,<sup>3</sup> equating to ~20,000 sufferers in

New Zealand. The illness affects people of all ages, ethnic, socio-economic and educational groups. Genes have been identified that become altered during the illness for people with inherited vulnerability.<sup>4</sup> Many patients experience physical or mental stress in the weeks before onset, increasing vulnerability.<sup>5</sup>

Most patients describe acute onset with associated viral infection but other types of onset have been described.<sup>6</sup> The immune system responds to infection by producing cytokines, increasing white blood cells, etc. This is accompanied by typical symptoms: fever, aching and fatigue, coupled with more specific symptoms depending on the particular infection. During this acute phase, there is cerebral microglial activity and patients feel ill and want to rest.<sup>7</sup> Most patients recover.

However, a sub-group of patients remains unwell with ongoing symptoms, suffering from 'Post-Viral Syndrome'. If this continues beyond 6 months, a diagnosis of CFS/ME is appropriate. The immune system of these patients has remained in an abnormal mode. Altered expression occurs in genes involved in immune modulation, oxidative stress and apoptosis (cell death). A range of specific immune abnormalities is responsible for the ongoing symptoms.<sup>8</sup> Over time natural killer cell function diminishes.

Some patients experience a gradual onset or onset after an event such as an accident, toxicity or surgery.<sup>6</sup> Any virus can trigger the illness and ongoing symptoms are similar to symptoms experienced with the initial infection. Patients often describe flu-like symptoms, or feel they still have the original illness, such as infectious mononucleosis. The illness may wax and wane, worsen or slowly improve. The most prominent symptoms are post-exertional malaise and cognitive difficulties. Duration and severity are variable. Some patients recover within a year while others suffer lifelong serious

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illness needing full-time care. Patients diagnosed early and managed correctly, and young people, have a better chance of recovery.<sup>9</sup>

Diagnosis is difficult, based on history and examination, coupled with blood tests and investigations to eliminate other diseases. There is no specific diagnostic test for CFS/ME. To fulfill diagnostic criteria, specific symptoms must be present. As well as malaise, other frequent symptoms include: orthostatic intolerance, gastrointestinal upsets, sleep disturbances and neurological sensitivities. Concurrent psychological diagnoses have a confounding effect, and should be treated before a diagnosis of CFS/ME is considered.<sup>10</sup>

Several diagnostic criteria have been proposed over 30 years, but the simplest are the Fukuda criteria.<sup>11</sup> Canadian criteria have been established which are more encompassing and accurate, but can be time consuming to assess.<sup>12</sup> Having established a diagnosis, other conditions may also co-exist or develop. Ongoing surveillance is vital, particularly if symptoms change or new symptoms develop.

### **CFS/ME should be managed in general practice**

Diagnosis, acknowledgment and education are major steps in helping patients cope with this serious illness. Much can be achieved with support, understanding and a personalized management plan. Practicing relaxation strategies with good breathing technique should be encouraged, as stress is an aggravating factor in any illness. These patients are able to exercise only minimally but do not lack motivation. Exercise intolerance is a core symptom associated with the altered gene expression<sup>13</sup> and mitochondrial dysfunction.<sup>14</sup> The ill effects are often delayed, with prolonged recovery or relapse.<sup>15</sup> Some patients are bedridden, others can cope with low-key regular exercise. Sports people find it particularly hard to slow down to allow recovery. As symptoms of orthostatic intolerance are prominent, exercise lying down, such as swimming, may be the best type of exercise.

Gastro-intestinal symptoms are common, with sluggish movement of food through the gut and bloating discomfort.<sup>16</sup> Many patients will have tried different diets but unless there is an identified food allergy or intolerance, such as gluten or lactose,<sup>17</sup> the aim is for

varied, balanced nutrition. Fad diets rarely have benefit, and may compromise nutrition.

Small frequent meals should be encouraged. Caffeine and alcohol can exacerbate symptoms. Minerals and vitamins are best absorbed from food, but patients will often have tried many supplements, despite little evidence of benefit.<sup>18</sup> Supplements that have been shown to be useful include Vitamin D (because of lack of daylight exposure), magnesium at bedtime to relieve pain, CoEnzyme Q10 (levels have been shown to be lower in patients than controls, inversely related to symptom severity<sup>19</sup>), Zinc (inadequate zinc intake contributes to decreased NK cell function<sup>20</sup>) and Vitamin B12 (cerebrospinal fluid levels of B12 may be depleted<sup>21</sup>). Mega-doses of Vitamin C should be avoided as this will aggravate bowel symptoms.

Most CFS/ME patients are hypotensive, with orthostatic intolerance, possibly due to lowered blood volume and dysautonomia.<sup>22</sup> Having plenty of salt (5–10 g) regularly spaced through the day can improve these symptoms. Fludrocortisone may be useful.

Women with CFS/ME outnumber men 4:1 so hormonal issues maybe involved.<sup>23</sup> Many experience cyclical illness fluctuations or problems at menopause. Oestrogen has potentially positive effects in improving cerebral circulation, cognition, muscle and joint elasticity, relieving flushes and insomnia and can decrease immune overactivity.<sup>24</sup> Hormonal management with contraception or hormone replacement alleviates cyclical symptoms.

Pregnancy is not contra-indicated but should be planned when health improves.<sup>25</sup> Most CFS/ME patients do well in pregnancy. B12 use should probably be stopped in pregnancy as it may be associated with increased risk of autism.<sup>26</sup>

For teenagers with acne, local skin preparations, antibiotics or oral contraceptives are suitable. Isotretinoin has been anecdotally associated with CFS/ME onset or relapse.

Non-restorative sleep is a feature of CFS/ME.<sup>27</sup> Hypersomnia is common early in the illness. Other sleep disorders can co-exist. Sleep hygiene and maintaining a normal sleep/wake cycle is vital. A

light snack at bedtime is helpful because the orexin system is faulty. Increasing glucose levels will lower orexin thereby improving sleep.<sup>28</sup> Bedtime stimulation with electronic devices should be avoided.<sup>29</sup> Some patients try natural approaches to sleep management, including 5HTP, tart cherry or chamomile. Prescribed medication is often needed.

Benzodiazepines should usually be avoided<sup>30</sup> but clonazepam helps anxiety, spasms and pain. Habituation in CFS/ME is rare.<sup>9</sup> Low dose tricyclics (eg 5 mg nortriptyline 5 h before bedtime) for sleep and pain relief are usually tolerated well. Melatonin is useful for patients who have difficulty getting asleep. Quetiapine may also be helpful. Sleep disturbances may relate to blocked nose, snoring or allergy. In this case a low dose sedating antihistamine such as promethazine 10 mg is useful. Restless legs syndrome is common and should prompt consideration of ropinarole.

Pain is common in this illness. Headaches, particularly in teenagers, can be seriously disabling.<sup>31</sup> A pain management plan should be established, with further investigation if pain changes. Simple measures are useful to help manage pain, such as warmth, massage, relaxation with correct breathing, stretching, self-hypnosis, and meditation. Acupuncture and physiotherapy may help.

If pain is mild, simple analgesics, can be tried. Stronger analgesics should be reserved for occasional use for more severe pain, with warnings of addictive potential. Non-steroidal anti-inflammatory drugs such as diclofenac and naproxen may help if pain has an inflammatory character. Orphenadrine is useful for spasm or cramps. Opioids are best managed by a pain specialist.

Anti-epileptic drugs have a place but may not be well tolerated. However, gabapentin or pregabalin can help, titrating up cautiously and encouraging perseverance.

CFS/ME patients often become depressed, particularly if they are severely ill long-term.<sup>32</sup> Patients recently diagnosed or who have mild illness are also at risk of depression. So much is 'lost' by people with CFS/ME, such as relationships, money, jobs, and health. This should be acknowledged and discussed. Counselling may be needed.

Depression must be treated. These patients are often scared that their illness may be labelled psychological. Explanation of how anti-depressants work, safety, and freedom from addiction needs discussion. Reassurance should be given that very small doses will be used and increased gradually, depending on response, over several weeks. SSRIs and SNRIs may improve energy and cognition and this aspect can be emphasised. With many drugs used for sleep, depression and pain relief it is important to discuss serotonin syndrome.

### Other issues that may come up in discussion

Patients may ask whether immunizations are safe for them. There are some reported uncommon instances of illness onset or relapse following an immunization.<sup>33</sup>

Lyme disease and other chronic infections may be misdiagnosed as CFS/ME, and should be treated appropriately. Recurrences of herpes infections can contribute to relapse and should be treated. Anti-viral treatment for several months alleviates this risk. Overall symptoms may improve, indicating that underlying viral load was an aggravation. However, recent studies report finding fewer viruses in severely ill patients than in healthy controls.<sup>34</sup>

Some CFS/ME patients may need surgical procedures for other reasons. Guidelines on managing this are outlined in the Primer for Clinical practitioners (appendix E).<sup>9</sup>

Low dose naltrexone shows some success in treating concurrent fibromyalgia.<sup>35</sup>

There is no evidence that removal of mercury dental amalgam will be beneficial.

It is possible there is an increased risk of some cancers for people with CFS/ME.<sup>36</sup>

There is evidence for premature telomere attrition that is associated with accelerated ageing.<sup>37</sup>

### Recovery

Recovery figures are very variable. The patients most likely to recover are younger, diagnosed

early and correctly managed, people with mild illness and those who have good support networks. Over-exercise and major stress can delay recovery and risk relapse.

Figures from a specialised paediatric centre indicate up to 88% recovery for young people with the illness.<sup>38</sup> As few as 5% of adults may fully recover but up to 40% may be able to return to work.<sup>39</sup> The main reason cited for inability to work is cognitive difficulty.

Everyone with this illness needs ongoing surveillance to ensure nothing new is missed. They need encouragement to seek advice to alleviate concerns, and address the possibility of a new or different diagnosis with treatment potential. All CFS/ME patients can experience a better quality of life with compassionate care and a multidisciplinary approach. They need to feel in control of health rather than being controlled by the disease.

### Conflicts of interest

The author declares no conflicts of interest.

### Further reading (all include well referenced material):

Chronic Fatigue Syndrome/Myalgic Encephalomyelitis – Primer for Clinical Practitioners (2014). [http://iacfsme.org/portals/0/pdf/Primer\\_Post\\_2014\\_conference.pdf](http://iacfsme.org/portals/0/pdf/Primer_Post_2014_conference.pdf) – includes information about Canadian and International diagnostic criteria.

ME/CFS – Diagnosis and management in young people – A Primer: (2017). <https://www.frontiersin.org/articles/10.3389/fped.2017.00121/full>

British ME Association ME/CFS/PVFS Clinical and Research Guide. <https://www.meassociation.org.uk/2018/09/me-association-me-cfs-pvfs-clinical-and-research-guide-28-september-2018>

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