



Chronic fatigue syndrome in children

David W. Beverley*

York Hospital, Wigginton Road, York YO31 8HE, UK

KEYWORDS

Chronic fatigue syndrome;
Children

Summary Chronic fatigue syndrome/myalgic encephalopathy (CFS/ME) is a heterogeneous condition that causes significant morbidity in young people. Its cause is unknown with current evidence suggesting that, in mild and moderate cases, cognitive behaviour therapy and/or graded exercise should be the treatment of choice. The majority of adolescents will improve or get better. Further research is required to determine aetiology and optimum management.

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Practice points

- Chronic fatigue syndrome/myalgic encephalopathy (CFS/ME) is a common condition that causes significant morbidity and time lost from school
- Despite many theories the aetiology of CFS/ME is not understood
- Treatment in children *MUST* be collaborative with the young person and their family
- Data from adult studies suggest that in mild and moderate cases graded exercise and/or cognitive behaviour therapy is the treatment of choice
- Preliminary studies in children would suggest that the data from adults can be extrapolated to children

- The long-term prognosis in children is good with the majority improving or returning to normal

Introduction

Despite the Chief Medical Officer's (CMO) report¹ chronic fatigue syndrome/myalgic encephalopathy (CFS/ME) remains a controversial condition. The Australian Medical Association rightly describes it as an illness that causes significant disability both in adults and children,² but is not a disease such as meningococcal meningitis where aetiology, pathophysiology and treatment are clearly understood. Moreover it is a condition with significant morbidity causing more time to be lost from school than any other childhood condition including malignancies.³

In this article current views on aetiology and management of the syndrome will be reviewed and areas for future research discussed.

*Tel.: +01904725510.

E-mail address: david.w.beverley@york.nhs.uk.

Demography

United Kingdom prevalence studies suggest that approximately 0.05–0.2% of children and adolescents are affected by CFS/ME.⁴ This equates to approximately one or two children in each secondary school in the United Kingdom being affected by the condition at any one time. Similar prevalence figures are given for the United States and Australasia.^{5,6} The condition seems to be more common in girls. In the paper by Haines et al.⁷ the incidence was similar in boys and girls between the ages of 5 and 9, but in the age range 10–15 years 62% of affected individuals were female and in 16–19 year olds 72% were girls. Moreover, in the same study she reports that in boys there was a pronounced peak at 15 years of age with numbers falling rapidly after this age whilst in girls there was a longer peak between 14 and 18 years of age.

It has been said that CFS/ME is more common in white middle class families, but this notion of 'yuppie flu'⁸ has not been borne out as individuals with CFS occur in all socio-economic groups.^{5,8–10}

Diagnosis

There are two frequently used diagnostic criteria for CFS (Boxes 1 and 2).^{11,12} Both state that the fatigue must be debilitating, present for at least 6 months and cause some degree of functional impairment and that there must not be any other clinical condition that could account for the fatigue. The, soon to be published, Royal College of Paediatrics and Child Health (RCPCH) guidelines on the management of CFS/ME suggest that the investigations outlined in Box 3 should be performed as screening tests in children. Most paediatricians working in the field of CFS/ME feel that the 6 month criteria is too long in childhood particularly when the functional impairment involves time off school at a crucial time in a young person's education. For this reason the criteria have been modified in children to reflect these concerns and the fatigue has to be present for 3 months instead.

Symptomology

There have been two studies in the United Kingdom that have specifically looked at the symptoms that occur in young people with CFS/ME. G. Saidi & L. Haines (unpublished results), in a cross-sectional survey in primary care, found that in addition to fatigue, 69% of their study group had sore throats,

Box 1 Revised 1994 CDC diagnostic criteria. Both the Major Criteria A and B and four out of the eight minor criteria should be fulfilled for the diagnosis of chronic fatigue syndrome (CFS)

Major criteria

- (A) Debilitating fatigue reducing activity to less than 50% of the patients premorbid activity for at least 6 months.
- (B) Symptoms not explained by other medical or psychiatric illness.

Minor criteria

- (1) Sore throat
- (2) Painful cervical or axillary lymphadenopathy
- (3) Muscle discomfort and pain
- (4) Prolonged generalised fatigue after usual levels of activity
- (5) Headaches
- (6) Arthralgias (without redness or swelling)
- (7) Neuropsychological disorders such as forgetfulness lack of concentration etc.
- (8) Sleep disturbance

65% headaches, 58% mood disturbance, 57% sleeping difficulties, 44% myalgia, 39% abdominal pain, 37% nausea and vomiting and 32% concentration difficulties. Other symptoms such as joint pain, photophobia, lymph node pain and hyperacusis occurred to a lesser extent. These are very similar to the data of Tucker and Tatum.¹³

Aetiology

Despite extensive research there is no consensus on the cause of CFS/ME: it is likely that in such a heterogeneous condition no one single cause will be found. However, many theories as to its aetiology have been proposed, some of which have a scientific basis (see below):

- (1) *Infection*. Self-reporting of symptoms prior to the onset of CFS/ME has suggested that infections may be an important predisposing factor in the development of CFS/ME. A variety of agents have been implicated including Epstein–Barr virus,¹⁴ enteroviruses,¹⁵ retroviruses,¹⁶ human herpes virus 6,¹⁴ Q fever,

Box 2 Oxford criteria

- (1) A syndrome characterised by fatigue as the principal symptom
- (2) A syndrome of definite onset that is not life long
- (3) The fatigue is severe, disabling and affects physical and mental functioning
- (4) The symptom of fatigue should have been present for more than 50% of the time
- (5) Other symptoms may be present, particularly myalgia, mood and sleep disturbance
- (6) Certain patients should be excluded from the definition. They include:

Patients with established medical conditions known to produce chronic fatigue (e.g. severe anaemia). Such patients should be excluded whether the medical condition is diagnosed at presentation or only subsequently. All patients should have a history and physical examination by a competent physician.

Patients with a current diagnosis of schizophrenia, manic–depressive illness, substance abuse, eating disorder or proven organic brain disease. Other psychiatric disorders (including depressive illness, anxiety disorders). and hyperventilation syndrome are not necessarily reasons for exclusion.

Box 3 Screening investigations for CFS/ME

Full blood count and film ESR/CRP	To exclude anaemia, iron deficiency and leukaemia Unlikely to be elevated in CFS/ME. A high level suggests autoimmune disease such as systemic lupus erythematosus (SLE) or chronic infection e.g. tuberculosis (TB)
Blood glucose	To exclude diabetes
Blood biochemistry (Na, K, urea, creatinine)	To look for renal impairment or endocrine abnormality such as Addison's disease
CPK	For evidence of muscle disease
T ₄ and TSH	For evidence of thyroid disease as early clinical signs may be very subtle
Liver function tests	For hepatitis
Urine analysis (for protein, glucose, blood leucocytes and nitrites)	To exclude renal disease, diabetes and urinary tract infections

(From RCPCH guidelines)

Some authors also suggest antigliadin antibodies to exclude coeliac disease although this did not reach consensus in the RCPCH guidelines.

Lyme disease and listeriosis. These studies have relied on high titres of antibodies against these agents but case-control studies indicate that the 'elevated' antibody titres are also found in healthy individuals many years after the original infection.¹⁷

- (2) *Immune dysfunction*. Numerous studies have been undertaken to examine the role of immunity in CFS/ME. Several have shown reduced lymphocyte proliferation¹⁸ but these

findings are non-specific, other studies have suggested reduced IgG and its sub-classes¹⁹ whilst associations with atopy have been described.²⁰ Very many studies, using different methodologies, have given conflicting evidence for increased cytokines. However, none of the abnormalities described above are sufficiently marked or consistent to make them useful for either routine clinical assessment or diagnostic purposes.²¹

- (3) *Neuro-endocrine abnormalities.* There have been several studies that have shown abnormalities of the hypothalamic–pituitary–adrenal axis,^{22,23} but what is not apparent is whether these abnormalities are primary or secondary to the inactivity associated with the condition. Similarly, the finding that there is hypo-perfusion of the brain in CFS/ME does not exclude excessive rest and inactivity as its cause.²⁴
- (4) *Muscle fatigue and weakness.* The data on muscle function is problematical. Muscle strength, endurance and recovery are normal²⁵ whilst the evidence for mitochondrial dysfunction is conflicting. Lane²⁶ has questioned the notion that the muscle symptoms in CFS/ME are simply due to inactivity and Paul et al.²⁷ have reported evidence for post-exercise fatigue using repetitive quadriceps exercise testing. However, studies show that prolonged rest affects 'virtually every physiological system'.²⁸ A period of rest of as little as 1 week can lead to measurable loss of muscle volume²⁹ and 4–6 weeks of rest can result in up to 40% loss of muscle strength.³⁰
- (5) *Neuro-psychological problems.* Sleep disturbances and disturbances of the circadian rhythms are common in CFS/ME,³¹ as are disturbances in attention, concentration and other measures of cognitive function.³² Psychiatric symptoms can coexist with chronic fatigue in adolescents,³³ particularly depression, although many children and adolescents do not have problems in this area. Some patients have other family members with CFS/ME.³³ Clusters may be related to infection, or to the psychological response to the illness within the family or in communities.³³

Management

Unfortunately, all the therapies reported in adults have been based on small studies, which have been poorly designed and have given contradictory results. There have been very few studies undertaken in children and adolescents, which makes the extrapolation from the adult data very difficult. What is very clear is that whatever treatment plan is embarked upon there must be a collaborative approach involving closely the parent and the child in the decisions about treatment options. This is particularly the case when psychological interventions are considered as the young person and their families may have belief systems that negate such interventions. It is crucial that the treatment team

fully engages with the family to ensure that there is not a breakdown in the professional relationship leaving the young person in a therapeutic vacuum. The following treatments have been considered:

- (1) *Pharmacological agents.* A variety of different drugs have been used without evidence of any beneficial effects. Two studies evaluating interferon have given contradictory results.³⁴ Antiviral agents such as aciclovir and ganciclovir have been used without any major benefits.³⁴ Two trials³⁴ have evaluated hydrocortisone reporting beneficial effects and two further trials fludrocortisone without.³⁴ Use of anticholinergic drugs, growth hormone and nicotinamide have given equivocal results.³⁴ With many of the above therapies patients withdrew from the treatment arm because of adverse side effects.
- (2) *Immunoglobulin treatment.* There have been five randomised controlled trials³⁴ using immunoglobulin, one of which was conducted in children and adolescents.³⁵ It gave a positive benefit in four of the trials including the one with children, however, the largest of the five trials, which enrolled 99 patients, found no effect of treatment.³⁴
- (3) *Antidepressants.* Two studies (totalling 131 adult patients)³⁴ have evaluated antidepressants as having no benefit to CFS/ME patients. Similar results have been found with fluoxetine and moclobemide.³⁴
- (4) *Behavioural treatments.* Two different forms of behavioural therapies have been evaluated in the management of CFS/ME. Cognitive behavioural therapy (CBT) is a therapeutic approach that has been used to promote active patient participation with self-monitoring and it takes into account previous experiences, both beneficial and adverse. CBT encourages the patient to adopt a wider view of the range of medical and psychological approaches and through an understanding of these the patient is enabled to break the vicious cycles that help perpetuate their illness.³⁶ The other form of therapy commonly used is graded exercise (GET), which is a form of structured supervised activity that aims to gradually and progressively increase aerobic activities such as climbing stairs or walking. Both these therapies have been found to significantly improve outcome in adults compared to pacing.³⁴ Our group has recently completed a small randomised controlled trial in children comparing the effects of family based CBT and pacing in 13 children with CFS/ME.^{37,38} In those children receiving CBT there

was a significant improvement in outcome in terms of activity and school attendance 1 year after the start of therapy (73% attendance versus 28%) and this was sustained 18 months after the start of treatment (85% versus 28%). Viner et al.³⁹ has reported similar results: in an open study, families receiving supportive care with GET and family sessions had a better outcome than those receiving supportive care alone.

Some authors have suggested that CBT and GET are harmful to patients^{40,41} and have advocated total rest until recovery is complete. This view is not generally upheld and the deleterious effects of total rest have been well described.⁴²

- (5) *Symptom control*. It is important that symptoms of pain, sleep disturbance, mood disturbance, headache, dizziness and gastrointestinal symptoms are actively managed.⁴³ Symptom control not only improves quality of life but also enables the teenager to participate in treatment programmes. Young people with CFS/ME are often relatively intolerant of medication and may need much lower doses than usually prescribed. Simple non-steroidal anti-inflammatory drugs are useful for pain relief and if not effective then low dose tricyclics or anticonvulsants may be of help. Good sleep hygiene is very important and anecdotal evidence suggests that Melatonin or low dose tricyclics are preferable to hypnotics.
- (6) *Alternative therapies*. Many patients find that alternative therapies are of help and certainly two trials of homeopathy have given some early promising results.³⁴ Many alternative treatments have been advocated, and the review by the Royal Australasian College of Physicians² lists over 20 for which scientific evidence is lacking. In my own personal practice, I do not actively discourage alternative therapies which the patient has found of benefit, as long as the therapy does not have any deleterious effect or side effect such as St. John's Wort interacting with other medication.
- (7) *Education*. CFS/ME often affects young people at a crucial time in their education. It is important to recognise that a child's education is not only the academic part of the curriculum but also the social networking and interaction with peers and loss of these interactions leads to a child becoming socially isolated. There are statutory duties placed on paediatricians by the School Attendance Act. The revised joint report of the Royal Colleges of Physicians, Psychiatrists and General Practitioners⁸ states 'tuition at home should be reserved for the most severely

affected and should be for as short a time as possible, and always in close liaison with the school. In the largest series to date if the children were no longer in school immediate return to school was encouraged'.

- (8) *Child protection*. There have been occasions when children with CFS/ME have been subject to child protection procedures; this usually occurs when the relationship between the clinician and the family has broken down. The CMO's working party noted that 'neither the fact that the child having unexplained symptoms nor the exercising of selective choice about treatment or education in itself constituted abuse'.¹ However, the report goes on to say that children with CFS/ME may suffer harm and this is part of the differential diagnosis. In cases where this is suspected then evidence clearly suggestive of harm should be obtained before invoking child protection procedures.
- (9) *Severely affected patients*. A small proportion of children are so severely affected that they are either wheelchair or bed bound. They are often the most challenging patients to help and may need intensive support from many health professionals. The majority of these families receive their care in a primary care setting. There are few specialised inpatient services for these children and a busy acute inpatient paediatric ward is not an appropriate environment in which to look after these teenagers. The principles of management are set out above, recognising that treatment may take many months or even years.

Outcome

In a tertiary setting, Rangel et al. described the mean duration of symptoms to be just over 3 years⁴⁴ and others have suggested a longer duration of symptoms of up to 4½ years.⁴⁵ In the more severely affected children, up to 30% have symptoms resistant to treatment that lasted for years.⁴⁶ However, most children have a better prognosis. One sample of paediatric outpatients had a good overall outcome in nearly 95% of cases.⁴⁷ Carter et al.'s⁴⁸ case series reported that in children with fatigue of more than 4 months' duration, 77% had returned to normality or had improved, with occasional relapses, after a median of 17 months. A more recent study reported that 29 out of 36 subjects had returned to normal health or had significant improvement.⁴⁹

Future research

It is quite apparent that the quality of current research in CFS/ME is poor; with most papers either being observational, case series, or very small randomised controlled trials. The RCPCH clinical guidelines will confirm the paucity of research work in that only seven out of the 45 recommendations to be published are based on good or at least reasonable quality evidence. Larger trials are necessary to have the necessary power to answer many of the outstanding questions in relation to aetiology and optimum management. Currently the Medical Research Council is conducting a randomised controlled trial, in adults, looking at four different treatment options. The research unit of the RCPCH is also exploring the feasibility of a large multi-centred study in the United Kingdom. This latter study will investigate possible aetiologies and treatment options in children with CFS/ME.

Conclusions

Chronic fatigue syndrome is an illness that causes significant morbidity at a crucial time in a young person's growth and development. Its treatment remains a challenge to paediatricians. With good management, many teenagers will improve or make a complete recovery. There is an urgency for further research work to determine aetiology and optimum treatment of this condition in young people.

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