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REVIEW

Clinical Practice: Chronic fatigue syndrome

Charlotte L. Werker · Sanne L. Nijhof · Elise M. van de Putte

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Abstract The diagnosis chronic fatigue syndrome (CFS) was conceptualized in the mid-1980s. It is a clinically defined condition characterized by severe and disabling new onset fatigue with at least four additional symptoms: impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, new headaches, unrefreshing sleep or post-exertion malaise. Chronic fatigue syndrome in adolescents is a rare condition compared to symptomatic fatigue. The estimated prevalence of adolescent CFS ranges between 0.11 and 1.29 % in Dutch, British, and US populations. Diagnosis of the chronic fatigue syndrome is established through exclusion of other medical and psychiatric causes of chronic fatiguing illness. Taking a full clinical history and a full physical examination are therefore vital. In adolescence, CFS is associated with considerable school absence with long-term detrimental effects on academic and social development. One of the most successful potential treatments for adolescents with CFS is cognitive behavioural therapy, which has been shown to be effective after 6 months in two thirds of the adolescents with CFS. This treatment effect sustains at 2–3-year follow-up. In conclusion, the diagnosis CFS should be considered in any adolescent patient with severe disabling long-lasting fatigue. Cognitive behavioural therapy is effective in 60–70 % of the patients. Prompt diagnosis favours the prognosis.

Keywords Chronic fatigue syndrome · Chronic fatigue · Adolescents · Cognitive behavioural therapy · Prevalence

Abbreviations

CBT	Cognitive behavioural therapy
CDC	Centre for Disease Control and Prevention
CFS	Chronic fatigue syndrome
UMC Utrecht	University Medical Centre Utrecht

Introduction and historical overview

Fatigue is a universally experienced symptom defined as 'Lassitude or weariness resulting from either bodily or mental exertion' [13]. It is described as a 'condition of muscles, organs or cells characterized by a temporary reduction in power or sensitivity following a period of prolonged activity or stimulation' [40]. Acute fatigue and exhaustion are normal reactions to exercise. These physiological phenomena are protective and transient, decreasing by rest, drinking and eating [2]. Fatigue is thus a very common symptom. However, fatigue can also be a symptom of disorders such as infections, organ diseases, metabolic diseases, deficiencies, malignancies and major depression. If fatigue persists for more than 6 months, without evidence of a specific fatiguing disease, it is called chronic fatigue [36], which is typically not relieved by rest or nourishment. In the presence of additional symptoms and fatigue-related disabilities, this chronic fatigue may constitute chronic fatigue syndrome.

It was not until the middle of the nineteenth century that fatigue was recognized as a medical problem with the introduction of neurasthenia, a diagnostic entity with fatigue as the principal symptom. In the UK, the term 'myalgic encephalomyelitis' (ME) was first mentioned in a leading article in 1956 [3]. The term ME was applied as a descriptive diagnosis for a series of outbreaks of a contagious condition, causing symptoms referable to the central nervous system, such as extreme fatigue, weakness, muscle pain, dizziness and neurocognitive

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C. L. Werker · S. L. Nijhof · E. M. van de Putte
Department of Pediatrics, Wilhelmina Children's Hospital,
University Medical Centre Utrecht, Utrecht, The Netherlands

C. L. Werker
e-mail: c.l.werker@students.uu.nl

S. L. Nijhof
e-mail: s.l.nijhof@umcutrecht.nl

E. M. van de Putte (✉)
Department of Pediatrics, University Medical Centre Utrecht,
Office KE 04.133.1, Postbox 85090,
3508 AB Utrecht, The Netherlands
e-mail: e.vandeputte@umcutrecht.nl

problems [3]. The conceptualization of chronic fatigue syndrome (CFS) began in the mid-1980s. Although little convincing evidence was provided on the existence of a discrete syndrome, CFS was accepted as a new, well-defined, syndrome [47]. The first publication of CFS in children was in 1989 in the BMJ ‘Myalgic encephalomyelitis by proxy’, a diagnosis pushed forward by malingering parents [19].

CFS, also known as myalgic encephalomyelitis, myalgic encephalopathy or ME, is characterized by disabling persistent (>6 months) or relapsing severe unexplained fatigue that is not the result of ongoing exertion and is not alleviated by rest. In CFS, fatigue is accompanied by other symptoms, such as muscle pain and concentration problems [16]. In adolescents, CFS may lead to considerable school absence with long-term consequences for educational and social development [12, 25, 29].

Etiology

The etiology of adolescent CFS remains largely unknown, though many potential mechanisms have been proposed. No single triggering factor, deviant laboratory test or infectious vector could be assigned as the primary causative agent of CFS [1]. Neuroendocrine studies, however, have consistently found mild hypocortisolism with enhanced negative feedback with increased sensitivity of the glucocorticoid receptor and impaired response to activation by the hypothalamic–pituitary–adrenal (HPA) axis [38]. This change to the HPA axis, though, is not specific or uniform for CFS, and prospective studies have suggested that the changes are the consequences, rather than the cause, of CFS [38]. Several studies have reported a high prevalence of psychopathology in patients with CFS, predominantly depression, somatization disorder, anxiety and hypochondria [17, 18]. Other studies have focused on personality disorders or personality traits [43], reporting among others higher levels of neuroticism and alexithymia for adolescents with CFS [37, 42]. Up till now, there is insufficient support for either a purely somatic or psychic cause. It is more likely that we need to apply a multifactorial model to understand CFS such as proposed by Engel in 1977 as the biopsychosocial model [14]. Previous research has shown that it is also useful to distinguish between predisposing, precipitating and perpetuating factors at a biological and psychosocial level [23, 45]. Examples of these factors in adolescents are shown in detail in Table 1.

Prevalence/incidence

Symptomatic fatigue in 5–18-year olds is common, but chronic fatigue and chronic fatigue syndrome are relatively rare [9, 39]. Adolescent girls are more susceptible to fatigue and comorbidity than boys [39, 41].

The prevalence of adolescent CFS has been estimated to range between 0.11 and 1.29 % in Dutch, British, and US populations, with a female-to-male ratio ranging from 2:1 to 5:1 [7, 15, 21, 29, 32]. Most of these estimates were primarily established by questionnaires and telephone interviews reflecting self-reported symptoms. Most recent estimations of incidence and prevalence based on physicians' diagnosis are lower than estimations in population surveys (0.11 %) [29].

Clinical presentation and criteria

Several diagnostic criteria for CFS exist, such as the Oxford criteria, the Canadian criteria and the Centre for Disease Control and Prevention criteria (CDC-1994). The CDC-1994 criteria are commonly used in paediatric studies [16, 28, 35]. According to these criteria, CFS is characterized by severe and disabling new onset fatigue lasting for at least 6 months, concurrently accompanied by four or more of the following signs and symptoms: impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain, new onset headaches, unrefreshing sleep and post-exertion malaise. Somatic and psychiatric illnesses should be excluded [16]. The CDC criteria are based on signs and symptoms and do not refer to an underlying pathophysiological mechanism.

The importance of early diagnosis and effective and prompt advice on managing CFS is vital because early intervention can improve patient outcomes [8]. However, starting an intervention too early in children and adolescents with unexplained fatigue not yet complying with CFS criteria can have an adverse effect. It reduces motivation and increases incidence of persistent fatigue with significant school absence [6]. Moreover, half of the adolescents with severe disabling fatigue shorter than 6 months will recover spontaneously within 6 months without intervention [5]. Nevertheless, physicians in the UK adhere to the NICE guidelines which have incorporated the Royal College of Paediatrics and Child Health guidelines wherein at least 3 months of severe disabling fatigue suffice for the diagnosis of CFS/ME [34].

Diagnostic workup

Taking a full clinical history is the most crucial diagnostic tool for CFS, primarily to complete the differential diagnosis and secondarily to recognize key features out of the histories of the child and parents [20]. Comprehensive physical examination is vital, if only to help exclude other conditions. A

Table 1 Factors involved in chronic fatigue syndrome in adolescents, adapted from [4]

	Biological	Psychological	Social
Predisposing	1. Genetic vulnerability	1. Parent's excessive attention to physical complaints of their children	1. Family members with physical or mental diseases
	2. Physical vulnerability	2. Disease or somatic trauma	2. Family's attitude in dealing with illnesses
	3. Physical diseases	3. Neglect	
	4. Early physical and/or sexual trauma	4. Insecure attachment	
	5. Genetic vulnerability to stress	5. Anxiety, depression	
Precipitating	1. Physical overload	1. Stress	1. Life events inside or outside the family
	2. Physical stress (infections, operations, trauma)	2. Psychotrauma	
Perpetuating	1. Disturbed sleep–wake cycle	1. Loss of concentration	1. Isolation
	2. Disordered food intake	2. Severe emotions	2. Excessive medical consumption
	3. Condition loss	3. Increased concern	
	4. Exhaustion	4. Anxiety, depression	
	5. Overactive or underactive life style	5. Reinforcement of unhelpful beliefs	
	6. Increased muscle tension	6. Fearful avoidance of activity	

positive diagnosis can usually be made from clinical history and examination alone [8]. There is no definitive test for CFS because there are no confirmatory physical signs or characteristic abnormalities on laboratory testing. Therefore, routine screening tests in the diagnosis of CFS are performed only to rule out any alternative diagnoses and not to diagnose CFS [8]. The basic tests to assist in differential diagnosis are listed in Table 2.

Differential diagnosis

Accurately diagnosing CFS requires exclusion of other illnesses (both physical and psychiatric) that could cause similar complaints, but require different treatment. Red flags are signs and symptoms that refer to other (treatable) conditions; they should not be attributed to CFS without careful consideration of alternative diagnoses or comorbidities. The following features warrant further investigation [27]:

Table 2 Basic tests to assist in differential diagnosis in children (NICE 2007) [27]

- Full blood count
- Urea and electrolytes
- Liver function
- Thyroid function
- Random blood glucose
- Erythrocyte sedimentation rate
- C-reactive protein
- Serum creatinine
- Screening bloods for gluten sensitivity
- Serum calcium
- Creatine kinase
- Urinalysis for protein, blood and glucose
- Assessment of serum ferritin levels

- Localizing/focal neurological signs
- Signs and symptoms of inflammatory arthritis or connective tissue disease
- Signs and symptoms of cardiorespiratory disease
- Significant weight loss
- Sleep apnea
- Clinically significant lymphadenopathy

Additional red flags in the history and physical examination of children are:

- Deviant height growth
- Deviant pubertal development (in children)

The following psychiatric differential diagnoses should be ruled out (in children and adolescents):

- Eating disorders
- Bipolar disorders
- Depression
- Anxiety disorders (post-traumatic stress disorder)

Dialogue with adolescent and parent

Shared decision-making between the child with CFS and the parents and healthcare professionals should take place during all phases of care. The dialogue starts with a full history of the main complaints and the related disabilities, completed with the cognitions about the perceived cause by parents and child. It is important to acknowledge the reality and impact of the condition and the symptoms, to provide information on the possible causes, nature and course of CFS. Furthermore, it is important to take the person's age into account, the severity of CFS, his or her preferences and experiences and the outcome of previous treatment.

It is essential to speak to the adolescent alone, to reveal factors that are important or have been important in the development of chronic fatigue, for example intoxications or negative life events (sexual assault, child abuse, neglect). After exclusion of primary somatic and psychiatric causes, chronic fatigue can be explained within the biopsychosocial model with predisposing, precipitating and perpetuating factors for this particular patient (Table 1).

Management

General management strategy after diagnosis

Evidence for treatment effect of children and adolescents with CFS is only present for cognitive behavioural therapy (CBT) and to a lesser extent physiotherapist-guided graded exercise therapy (GET). There is no known pharmacological treatment or cure for CFS. Treatment with intravenous gamma globulin has been proposed, but the benefit is equivocal [33]. Although there is sufficient evidence for a mild hypocortisolism accompanying symptoms of CFS, treatment with hydrocortisone has been evaluated in a few studies, but was not effective [11, 26].

An important step in the management of adolescent CFS is to treat the most disruptive symptom first and to encourage an appropriate balance between rest and activity. Sleep management is an important factor in the treatment of CFS. Patients with CFS should avoid excessive sleep, because this may further disrupt their circadian rhythm. Another emphasis should be on eating habits; a regular eating pattern is essential, including breakfast [27]. Accompanying symptoms such as pain, memory and concentration problems, depression or anxiety should be addressed if prioritized by the patient. Many treatment programmes offer a combination of strategies to promote fatigue resolution, including a psycho-educational part [10].

Cognitive behavioural therapy

CBT is an intensive face-to-face psychological treatment, consisting of multiple treatment steps, and takes half a year on average to complete. CBT covers a range of subjects, from psycho-education to restoration of the circadian rhythm, to normalising physical activities. The specialized psychotherapists should tailor their interventions to the patient's individual needs. CBT aims on changing patient cognitions regarding disease and behaviour. Several randomized controlled trials (RCTs) in adolescents have been published on treatment effects and sustainability, with clinical significant improvement ranging 60–70 % directly after treatment [24, 30, 35]. Long-term treatment effects appear to be sustainable [22, 31].

CBT for adolescent CFS requires specialized therapists, not always available at an acceptable travelling distance of the patient with CFS. An alternative way to enhance the availability of CBT is the recently developed web-based CBT for adolescents with CFS (FITNET). This internet therapy has shown treatment effects comparable to face-to-face therapy [30]. The FITNET trial compared web-based CBT with ‘usual care’, defined as the care available in the patients proximity. The 6-month-lasting FITNET treatment resulted in an eight times higher chance of recovery than usual care with a number needed to treat of 1.8. Treatment effects sustained through 12 months. FITNET is available in the Netherlands for adolescents with CFS (www.umcutrecht.nl/cvs and https://mijn.nkcv.nl) and hopefully will be translated soon in English in collaboration with colleagues from the UK.

Graded exercise therapy

GET aims at gradually increasing physical activity, guided by a physiotherapist or rehabilitation specialist. Currently, no RCTs have been published regarding graded exercise for CFS in adolescents. Efficacy has been studied in adult CFS, and treatment effects are comparable with CBT [48]. In adolescents, improvement in quality of life and school attendance has been described in an open study [46]. Long-term effects and sustainability are currently not well studied.

Prognosis

Adolescents diagnosed with unexplained chronic fatigue, not diagnosed as CFS, generally have a good prognosis. The natural course for adolescent CFS is not well known. One publication showed a reasonably good prognosis in a 13-year follow-up study, with a satisfactory outcome in 80 % of the adolescents [7]. In contrast, a 2–3-year follow-up study in adolescents with severe CFS who were all intensively treated has shown that only half of the participating CFS adolescents had nearly complete improvement and described by the authors as not being severely fatigued and physically dysfunctional anymore [44]. The other half were still severely fatigued, suffered from impaired physical functioning and would probably still meet the criteria for CFS. CBT shows recovery in 60–70 % of the adolescents after 6 months of treatment with comparable results at 2–3-year follow-up [22, 31]. During the course of disease, school attendance is diminished, with serious consequences for intellectual and social development. This emphasizes the need for proper and rapid diagnosis and treatment.

Future directions

CBT has shown to be effective in 60–70 % of the adolescents with CFS. The efficacy of CBT is partly determined by pretreatment disease duration and by the focus on bodily symptoms by the mother [31]. Immediately recognizing adolescent CFS and prompt initiation of treatment might further reduce morbidity rate with subsequent positive effects on educational and social development. Availability of CBT per internet (e.g. FITNET) might favour this prompt initiation.

Although the parents are involved in CBT, this seems to be insufficient, whereas focusing on bodily symptoms by the mother is a predictor of treatment effect. More attention to the role of the family and especially the mother in the perpetuation of adolescent CFS might attribute to a higher recovery rate.

Revelation of the neurobiological basis of CFS might offer more therapeutic possibilities in the future. MRI studies interlinked with deficits in specific (neuropsychological) tasks might help to reveal the neurobiological basis.

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Conflict of interest The authors declare that they have no competing interests.

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