ARTICLE

Adolescent Chronic Fatigue Syndrome

A Follow-up Study

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Objective: To describe the symptomatic and educational long-term outcomes, health care use, and risk factors of nonrecovery in adolescent chronic fatigue syndrome (CFS).

Design: Follow-up study.

Setting: Academic pediatric hospital.

Participants: Sixty adolescents with CFS.

Interventions: Regular care.

Outcome Measures: The Checklist Individual Strength, Child Health Questionnaire, and a general questionnaire regarding further symptoms, school attendance, work attendance, and treatment.

Results: Complete measurements were returned for 54 adolescents (90%). At initial assessment, their mean (SD) age was 16.0 (1.5) years and 20.4% were male. The mean follow-up duration was 2.2 years. At follow-up, the mean (SD) age was 18.2 (1.5) years; 28 adolescents (51.9%) had nearly complete improvement of symptoms but 26 (48.1%) did not experience improvement. Adolescents who attended school (n=41) had missed an average of 33% of classes during the last month. The rest (n=13) had worked an average of 38.7% of a full-time job during the last month. A total of 66.7% of subjects were treated by a physiotherapist, 38.9% were clinically treated in rehabilitation, 48.1% had received psychological support, and 53.7% had used alternative treatment.

Conclusions: About half of the adolescents had recovered from CFS at follow-up. The other half was still severely fatigued and physically impaired. Health care use had been high, and school and work attendance were low. Older age at inclusion was a risk factor, and pain, poor mental health, self-esteem, and general health perception at outcome were associated with an unfavorable outcome. Future research should focus on customizing existing treatment and studying additional treatment options.

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Chronic fatigue syndrome (CFS) in adolescence is a heterogeneous and medically unexplained condition.[1] No laboratory tests for adolescent CFS are available.[2] Its main symptom is functionally disabling fatigue, severely affecting young patients' lives.[3] Like in adult CFS, the most commonly used criteria in adolescent CFS are the English Oxford[4] and the US Centers for Disease Control and Prevention (CDC)[5] criteria. The Oxford criteria are considered somewhat less restrictive.[6] The prevalence of adolescent CFS has been estimated to be 1.3% to 4.4% in British and US populations.[7,8] Estimations of the prevalence of adolescent CFS in other populations are sometimes lower.[9] The incidence of adolescent CFS is estimated at 0.5%,[10] and the female to male ratio is estimated at 4:1.[11] Randomized controlled treatment trials for adolescent CFS have been rare but there is growing support for a positive effect of cognitive behavioral therapy.[12,13]

See also pages 803, and 817

There have only been a few follow-up studies that described the outcome of adolescent CFS after regular care, applying either Oxford or CDC criteria for CFS. In **Table 1**, the main studies of the prognosis of adolescent CFS are presented. About one-third to one-half of the patients in the studies described still experienced severe fatigue, physical impairment, and little improvement at follow-up. At present, the largest cohort described in a follow-up study of pediatric CFS included 35 patients. Most studies so far have used the Oxford criteria for CFS, and there is only 1 follow-up study that has used the 1994 CDC criteria for CFS. However, all diagnoses in these studies were made retrospectively. Furthermore, most studies had a disproportionately high percentage of male participants and a wide age range. In this study, the outcomes of 54 ado-

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Table 1. Follow-up Studies of Adolescent Chronic Fatigue Syndrome[a]

Study	Participants, No. (Response Rate, %)	Age, Mean (SD) [Range]	Male, %	Duration of Follow-up, Mean (Range)	Diagnostic Criteria	Outcome
Smith et al, 1991[14]	15 (100)[b]	14.5 (1.7)	40	(1.1-2.7)	1998 CDC[c]	26.7% Recovered; 26.7% marked improvement; 46.7% unimproved or worse
Rangel et al, 2000[15]	25 (78.1)	11.7 (2.2)	40	3.8	Oxford[c]	36% Recovered; 32% mildly fatigued and impaired; 32% unimproved or worse
Bell et al, 2001[16]	35 (76)[d]	12.1 [5-18]	31.4	13.0	Patients diagnosed before 1988[c]	37.1% Recovered; 42.9% better but not resolved; 11.4% chronically ill; 8.6% more ill
Gill et al, 2004[17]	16 (72)	14.9 (2.4)	25	4.1	CDC[c]	25% Nearly complete improvement; 31% partial improvement; 44% unimproved or worse
Sankey et al, 2006[18]	28 (60)	13.3 [7-17]	54	3.0	Oxford[c]	66.7% Improved; 33.3% unimproved or worse

Abbreviations: CDC, Centers for Disease Control and Prevention; CFS, chronic fatigue syndrome.

[a] The table might not include all research on outcome in adolescent CFS (according to the Oxford or CDC criteria) but to the authors' best knowledge represents the main studies in the field.

[b] Five subjects also had major depression (including some who were also diagnosed with CFS), the respondent was either the adolescent or the adolescent's parent, and eventually, only 6 patients fulfilled 1998 CDC criteria for CFS.[19]

[c] Diagnosis established retrospectively.

[d] Patients were part of a cluster outbreak of CFS, and authors' own CFS criteria were used.[20]

lescents who fulfilled the 1994 CDC criteria for CFS are described.

METHOD

PARTICIPANTS

All participating adolescents had first visited a general practitioner before being referred to a general pediatrician in a nonacademic setting. Subsequently, they were referred to the academic pediatric hospital. Seventy-four adolescents who had previously participated in a number of research studies of adolescent CFS[21,22] were considered for inclusion. At initial examination, these adolescents were assessed for CFS, and the diagnosis, in accordance with the 1994 CDC criteria, was either made or confirmed by a specialized academic pediatrician. Although they had been clinically diagnosed with CFS, 14 of the 74 adolescents (18.9%) were not eligible for participation in this follow-up study because their initial scores on the subjective fatigue subscale of the Checklist Individual Strength (CIS-20) were below cutoff (see "Primary Outcome Measures" section). Questionnaires were sent to the remaining 60 adolescents. All questionnaires were filled out at home. The duration of the follow-up was defined as the time between the initial research examinations at the academic pediatric hospital and the present study's assessments. The study was approved by the ethical committee of the hospital, and informed consent was obtained from all participating adolescents and their parents.

PRIMARY OUTCOME MEASURES

Fatigue was assessed using the subjective fatigue subscale of the CIS-20.[23] This scale measures experience of fatigue and consists of 8 items; scores range from 8, no fatigue, to 56, extremely fatigued. It is a reliable, validated assessment measure with good internal consistency (Cronbach $\alpha = .93$[12]). The CIS-20 has previously been used in research into adolescent CFS.[22] Various cutoff scores (range, 35.7-40) for recovery on this measure have been used.[12,24] In this study, the cutoff on the subscale was set at 40 (mean plus 2 SD of the subjective fatigue distribution in healthy adolescents[24]) to dichotomize the outcomes as improved (score <40) or not improved (score ≥ 40).

Functional impairment was measured using the physical role functioning subscale of the Child Health Questionnaire–Child Form (CHQ-CF87).[25] This scale measures limitations in school work and daily activities as a result of physical health and consists of 3 items; scores range from 0, severe limitations due to physical problems, to 100, no limitations due to physical problems. It is a reliable, validated assessment measure with good internal consistency (Cronbach $\alpha = .86$[26]). The CHQ-CF87 has previously been used in research regarding adolescent CFS.[23] Cutoff scores for recovery on the physical role functioning subscale of the CHQ-CF87 have not yet been set for adolescent CFS. However, on the physical functioning subscale of the Short-Form General Health Survey[27] (also ranging from 0, maximal physical limitation, to 100, ability to do all activities, and previously used in adolescent CFS), a cutoff of 65 has been used.[12] In this study, the cutoff for the physical role functioning subscale of the CHQ-CF87 was correspondingly set at 65 to dichotomize outcomes as improved (score >65) or not improved (score ≤ 65). A classification of nearly complete improvement required a score of less than 40 on the subjective fatigue subscale of the CIS-20 combined with a score greater than 65 on the physical role functioning subscale of the CHQ-CF87.

SECONDARY OUTCOME MEASURES

In addition to the physical role functioning subscale of the CHQ-CF87, we used the emotional role functioning subscale, which measures limitations in school work and daily activities as a result of emotional problems such as worry or sorrow (Cronbach $\alpha = .90$[26]); the behavioral role functioning subscale, which measures limitations in school work and daily activities as a result of behavioral problems (Cronbach $\alpha = .71$[26]); the bodily pain subscale, which measures the severity and frequency of bodily pain (Cronbach $\alpha = .85$[26]); the general behavior subscale, which measures the exhibition of aggressive, delinquent, and immature behavior (Cronbach $\alpha = .79$[26]); the mental health subscale, which measures a diversity of positive and negative feelings (Cronbach $\alpha = .86$[26]); the self-esteem subscale, which measures satisfaction with abilities, looks, family/peer relations, and life overall (Cronbach $\alpha = .89$[26]); and the gen-

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Table 2. Primary Outcome Measures

Outcome Measure	Mean (SD)	Patients Below CIS-20 or Above CHQ-CF87 Cutoff, No. (%)[a]
CIS-20[b]		
Subjective fatigue	34.3 (14.1)	30 (55.6)
CHQ-CF87[c]		
Role functioning: physical, 3 items	71.9 (28.3)	38 (70.4)
Nearly complete improvement, No. (%)[d]		28 (51.9)[e]

Abbreviations: CHQ-CF87, Child Health Questionnaire; CIS-20, Checklist Individual Strength.
[a] Score lower than 40 on the CIS-20 and 65 or greater on the CHQ-CF87.
[b] Score ranges from 8-56; a high score indicates a high level of fatigue.
[c] Three items; score ranges from 0 to 100; a high score indicates better physical functioning.
[d] Primary outcome measure.
[e] Subjective fatigue subscale of CIS-20 score lower than 40 and physical role functioning subscale of CHQ-87 score greater than 65.

Table 3. Secondary Outcome Measures

Outcome Measure	Mean (SD)	Patients Above CHQ-CF87 or Below CDC Criteria Cutoff, No. (%)[a]
CHQ-CF87[b]		
Role functioning: emotional, 3 items	84.9 (25.2)	46 (85.1)
Role functioning: behavioral, 3 items	95.8 (10.5)	52 (96.3)
Bodily pain, 2 items	56.1 (27.9)	22 (40.7)
General behavior, 16 items	82.0 (10.7)	49 (90.7)
Mental health, 16 items	68.8 (14.9)	34 (63.0)
Self-esteem, 14 items	66.2 (14.6)	28 (51.9)
General health perceptions, 13 items	46.8 (18.7)	10 (18.5)
CDC criteria[c]		
Additional symptoms	3.8 (2.3)	20 (37)

Abbreviations: CDC, Centers for Disease Control and Prevention; CHQ-CF87, Child Health Questionnaire.
[a] Score of 65 or greater for CHQ-CF87 and lower than 40 for CDC criteria.
[b] Scores range from 0 to 100; higher scores indicate greater well-being.
[c] Score ranges from 0 to 8; a high score indicates more symptoms in accordance with 1994 CDC criteria.

eral health perceptions subscale, which measures beliefs concerning health (Cronbach $\alpha = .77$[26]). This was done to cover additional physical and psychosocial domains at outcome.

In a further general questionnaire, the participants were asked to indicate (yes/no) the regular presence during the last month of 8 symptoms according to the 1994 CDC criteria (self-reported impairment in memory or concentration, sore throat, tender cervical or lymph nodes, muscle pain, multijoint pain, headache, unrefreshing sleep, postexertional malaise lasting 24 hours or more). School attendance was measured as the percentage of classes the adolescent had attended at school during the last month compared with the school schedule of classmates. If the participants no longer attended school, work attendance was calculated as the percentage of a fulltime job (38 hours) the adolescent had worked during the last month. Finally, participants were asked to estimate the total number of therapeutic visits they had (if any) with physiotherapists, psychologists, and alternative health care suppliers in the follow-up period and (if applicable) to estimate the months they had spent in clinical rehabilitation.

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS version 16.0 (SPSS Inc, Chicago, Illinois). On the outcome variables, group means and standard deviations were calculated. Potential risk factors (eg, sex, age, severity of fatigue at inclusion, duration of follow-up) were quantified with odds ratios using logistic regression with outcome (recovered vs not recovered) as the dependent variable. The significance level was set at $P < .05$ (2-tailed tests).

RESULTS

Complete data for 54 (90%) adolescents were returned. At first inclusion, their mean (SD) age was 16.0 (1.5) years, all were white, 20.4% were male, and their mean (SD) score on the subjective fatigue subscale of the CIS-20 was 49.4 (5.1). Onset had been gradual in 27 (50%) cases, following "flulike illness" in 22 cases (40.7%) and acute (ie, sudden onset without preceding flulike symptoms) in 5 cases (9.3%). At follow-up, the mean (SD) age was 18.2 (1.5) years. There were no significant differences between responders and nonresponders in sex, age, or fatigue severity. The mean (SD) follow-up duration was 2.2 (1.6) years but the symptoms in most cases had existed substantially in the years prior to initial assessment. During this time, 43 adolescents (79.6%) had not received any other diagnosis, 3 (5.6%) were diagnosed with celiac disease, 3 (5.6%) had lactose intolerance, 2 (3.7%) had metabolic disorder, 1 (1.9%) had hypermobility syndrome, 1 (1.9%) had major depressive disorder, and 1 (1.9%) had anxiety disorder.

Table 2 shows the scores on the primary outcome measures of the 54 adolescents for whom complete measurements were returned. At follow-up, 28 adolescents (51.9%) had a score of less than 40 on the subjective fatigue subscale of the CIS-20 and a score greater than 65 on the physical role functioning subscale of the CHQ-CF87, indicating that they had a nearly complete improvement of CFS at follow-up.

Table 3 shows the scores on the secondary outcome measures. The mean scores on the behavioral role functioning, emotional role functioning, and general behavior subscales of the CHQ-CF87 were generally good. However, the mean scores on the mental health and self-esteem subscales of the CHQ-CF87 were unfavorable (approximately 1 SD below the mean scores in a healthy young population[26]); the mean scores on the bodily pain and general health perceptions subscales of the CHQ-CF87 were particularly low (respectively, about 1.5 and 2 SD below the mean scores in a healthy young population[26]).

Table 4 shows school attendance, work attendance, and therapeutic contacts for the 54 adolescents for whom complete measurements were returned. At follow-up, the participants who still attended school had, on average, missed approximately one-third of regular classes during the last month. For a previously described cohort of 167 healthy adolescents, this percentage was only 12.5%.[21] In the Netherlands, it is common to start a full-time job

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after finishing school. However, participants who no longer attended school had worked only an average of approximately one-third of a full-time job during the last month. The variety and frequency of therapeutic health care use had been considerable between initial assessment and follow-up.

Only a higher age at initial inclusion was found to be a risk factor for nonrecovery of CFS at follow-up (odds ratio [OR], 1.59; 95% confidence interval [CI], 1.06-2.39; $P=.03$). Sex, severity of fatigue at inclusion, type of onset, other diagnoses, health care use (psychological treatment, physiotherapy, rehabilitation, or alternative treatment), and length of time between inclusion and follow-up were not associated with outcome. At follow-up, a high amount of reported CDC CFS symptoms (OR, 1.62; 95% CI, 1.19-2.22; $P=.002$) and a low score on the mental health (OR, 0.95; 95% CI, 0.90-0.99; $P=.01$), self esteem (OR, 0.94; 95% CI, 0.90-0.99; $P=.01$), bodily pain (OR, 0.93; 95% CI, 0.93-0.99; $P=.002$), and general health perceptions (OR, 0.92; 95% CI, 0.84-0.96; $P<.001$) subscales of the CHQ-CF87 were associated with nonrecovery.

Table 4. School Attendance, Work Attendance, and Health Care Use at Follow-up

Variable	
School Attendance and Work	
Adolescents attending school, No. (%)	41 (75.9)
Classes followed, % (SD)	67.0 (34.2)
Adolescents working, No. (%)[a]	13 (24.1)
Percentage of full-time job worked, % (SD)[b]	38.7 (35.0)
Health Care Use	
Physiotherapy, No. (%)	36 (66.7)
Contacts, mean (SD), No.	45.9 (46.6)
Alternative treatment, No. (%)	29 (53.7)
Contacts, mean (SD), No.	16.8 (15.5)
Psychological support, No. (%)[c]	26 (48.1)
Contacts, mean (SD), No.	32.6 (32.6)
Clinical treatment in rehabilitation, No. (%)	21 (38.9)
Duration of treatment, mean (SD), mo	3.6 (2.2)

[a] Only adolescents who no longer attended school.
[b] Full-time job considered 38 h/wk.
[c] General cognitive behavioral therapy not specific for chronic fatigue syndrome was common in routine psychological support.

COMMENT

The outcome of unexplained pediatric chronic fatigue (ie, not diagnosed as CFS) is mostly positive.[28,29] It is generally thought that the prognosis for adolescent CFS is also relatively good.[1,2] In this study it was found that, although about half of the participating adolescents had nearly complete improvement, the other half were still severely fatigued, had impaired physical functioning, and would probably still fulfill 1994 CDC criteria for CFS at follow-up.

The cohort of adolescents who participated in this study is the largest described in any follow-up after regular care. The diagnosis of CFS was established according to the 1994 CDC criteria at initial examination, the female to male ratio was in accordance with research findings, the mean age of participants did not have a wide range, and a strict cut-off score on a validated measure of adolescent CFS was used to qualify subjects for inclusion. However, the CHQ-CF87 was not used at inclusion. Therefore, potential predictors of outcome were limited. Furthermore, while all questionnaires were validated for this age group and no adolescents indicated that they had difficulty with completion, the answering of questionnaires at home might not ensure complete confidentiality without parental influence.

In previous studies, few risk factors for adolescent CFS have been identified.[30] As in our study, older age at diagnosis has been found to imply an increased risk of prolonged adolescent CFS.[3,10] The high levels of school nonattendance are in concordance with the literature.[1-3] The use of health care services in adolescent CFS was high and comparable with recent studies.[32,33] While no specific form of health care was associated with a better outcome, almost all adolescents had received some kind of treatment, and it is difficult to estimate what the outcome would have been had this not been the case. Although some of the participating adolescents had received cognitive behavioral therapy as part of routine psychological support, this also did not result in a superior outcome. This is consistent with findings that the results of cognitive behavioral therapy for CFS are generally superior within, rather than outside, the confines of randomized controlled trials.[34] The percentage of adolescents who had not recovered from CFS at follow-up in this study was somewhat higher than in previous studies and more like the outcome rates in adult CFS.[35] This might be owing to the strict use of 1994 CDC criteria for CFS, the use of a cutoff score for eligibility, and a higher age of participants at inclusion. In addition, the diagnosis of CFS in the adolescents who participated in this study was established (or confirmed) in a tertiary academic hospital setting and might represent a particularly impaired cohort.

Despite intensive health care use, a substantial proportion of adolescent patients with CFS remain severely fatigued and physically impaired. This is associated with considerable pain and poor mental health, self-esteem, and general health, and greatly affects school and work attendance. Therefore, future research into adolescent CFS should not only focus on recognizing patient characteristics for a favorable outcome but should also be directed toward further customizing existing treatment and studying additional interventions for patients who do not benefit from established treatment options.[36,37]

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