ARTICLE

Chronic Fatigue Syndrome in Adolescents

A Follow-up Study

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Objectives: To compare the frequency of persistent symptoms up to 8 years after illness onset in adolescents diagnosed as having chronic fatigue syndrome, idiopathic chronic fatigue, and unexplained fatigue for less than 6 months, and to determine if hospital admission is associated with outcome.

Design: A cohort study using questionnaire follow-up.

Setting: A tertiary referral hospital.

Patients: Consecutive adolescents referred for assessment of persistent fatigue were identified and retrospectively divided into 3 groups according to the diagnostic criteria for chronic fatigue syndrome and idiopathic chronic fatigue.

Intervention: A questionnaire was designed and administered by telephone at a mean of 4.57 years after the initial examination.

Main Outcome Measure: The persistence of self-reported symptoms was compared with respect to patient group and admission.

Results: Outcome data were obtained for 34 (69%) of the 49 eligible subjects. Twenty-five percent of the chronic fatigue syndrome group showed near to complete improvement, 31% showed partial improvement, and 44% showed no improvement. The idiopathic chronic fatigue group had near to complete recovery in 50%, partial in 10%, and no improvement in 40%. Those with unexplained fatigue for less than 6 months had all recovered. There was no difference between the outcome of the subjects admitted to the hospital and those managed as outpatients.

Conclusions: Adolescents with less than 6 months of fatigue have a good outcome. Unexplained fatigue lasting more than 6 months has a similar outcome regardless of the presence of minor criteria for chronic fatigue syndrome.

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CHRONIC FATIGUE SYNdrome (CFS) is a clinical diagnosis defined on the basis of inclusion and exclusion criteria established in adult patients. It is characterized by severe, debilitating fatigue in association with physical symptoms such as sore throat, headache, lymphadenopathy, arthralgia, and myalgia.[1] In 1988, the term *chronic fatigue syndrome* was defined by the Centers for Disease Control and Prevention (CDC). This definition required 2 major criteria describing the type of fatigue and the exclusion of various medical and psychological diagnoses, as well as 8 minor symptoms or 6 minor symptoms with 2 physical criteria.[2] In 1994, the definition was revised to include the major criteria and 4 minor symptoms.[3] This definition has been shown to distinguish adults with CFS from healthy controls and from those with other diseases.[4] *Idiopathic chronic fatigue* (ICF) is a term used for those with fatigue lasting more than 6 months, for which no other medical or psychological explanation is found but with fewer than 4 of the additional minor symptoms required by the CDC definition of CFS.

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There are no CFS diagnostic criteria specific for children and adolescents, and thus, the adult criteria developed by the CDC are usually used.[1] It has been suggested that 3 months of persistent unexplained fatigue are sufficient for diagnosis in children and adolescents rather than the 6 months required by the adult definition[5]; however, this is not universally accepted.

The prevalence of CFS in the Australian pediatric population has been es

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Table 1. Characteristics of the Total Cohort at Diagnosis*

Characteristic	Total (N = 49)	Contacted (n = 34)	Noncontactable (n = 15)	*P* Value
Age at diagnosis mean ± SD, y	14.13 ± 2.09	14.28 ± 2.22	13.8 ± 1.8	.67
Male	16 (33)	12 (35)	4 (27)	.94
Reside in rural area	20 (41)	13 (38)	7 (47)	.96
Admitted to hospital	35 (71)	24 (71)	11 (73)	.99
Group 1 (CFS)	22 (45)	16 (47)	6 (40)	
Group 2 (ICF)	17 (35)	10 (29)	7 (47)	.91
Group 3 (<6 mo)	10 (20)	8 (24)	2 (13)	

Abbreviations: CFS, chronic fatigue syndrome; ICF, idiopathic chronic fatigue.
*Data are given as number (percentage) unless otherwise indicated.

timated at 37.1 per 100 000; 5.5 per 100 000 in ages 0 through 9 years; and 47.9 per 100 000 in ages 10 through 19 years.[6] These figures are based on Australian criteria, which are less stringent than the CDC criteria but still require a minimum of 6 months of fatigue and exclusion of other possible diagnoses.

Most outcome studies of CFS have been performed in adults; those in children and adolescents have shown variable results. The subjective nature of the condition makes documentation of improvement difficult. In the published studies, younger patients appear to have a more favorable outcome; in most series, more than 50% improve or recover.[1] There is, however, a significant minority of patients who have ongoing fatigue and resultant disability.

At our institution, adolescents referred with symptoms suggestive of CFS attend the infectious diseases/immunology clinic for assessment, investigation, and treatment. If other medical illnesses are identified, patients are appropriately referred. The remainder are managed with a combination of education, exercise, counseling, and in some cases, admission to the hospital for 1 to 4 weeks. Once management has been instituted, most return to their local pediatrician or general practitioner for ongoing care; therefore, information on their long-term progress is not always obtained.

This study was designed to assess long-term outcome in this patient group. We were interested to compare the outcome of those who met CDC criteria for CFS at the outset with those who did not (ICF and unexplained fatigue of less than 6 months) to help determine the most appropriate symptom duration to use for diagnosis of this syndrome in adolescents. A secondary objective was to compare the outcome of those admitted to the hospital with those treated wholly as outpatients.

METHODS

Consecutive patients referred between October 1993 and August 2001 with a possible diagnosis of CFS were identified from the databases of the pediatric and adult infectious diseases/immunology clinics in our institution and confirmed by a search of the medical records by diagnosis. The files were retrospectively reviewed using the case definition of the CDC, revised in 1994 by the International Chronic Fatigue Syndrome study group.[6] Subjects were divided into those with CFS, those with ICF, and those with prominent unexplained fatigue of less than 6 months. Anxiety disorders and less severe depression were not considered exclusions to a diagnosis of CFS. Patients with other medical illnesses, including fatigue secondary to chronic pain states such as allodynia and fibromyalgia, were excluded. Baseline age, sex, home location, and admission status were obtained from the medical records.

Admission to the hospital involved 1 to 4 weeks on the adolescent ward, daily physiotherapy to institute a graded exercise regime, attendance at the hospital school, and involvement of the adolescent counselors of the psychiatry team. The subjects' agreement to return to their own school at discharge was a condition of entering the program. Subjects managed as outpatients were educated about the course and management of CFS and encouraged to return to school and engage in a graded exercise program.

A questionnaire was designed to address self-reported symptoms, attendance at school or work, and ongoing health concerns. It was based on a validated screening questionnaire used to identify adult patients with CFS.[7] The study was approved by the hospital ethics committee. An explanatory letter was sent to the eligible subjects and contact was made by telephone. The objective and methods of the study were explained, and subjects were offered the opportunity to decline or agree to participate. All questionnaires were administered by the same investigator (A.C.G.).

The primary outcome measure was the proportion of patients in each group with significant ongoing symptoms. Information was collected and compared for possible confounding factors. The responses to each survey question were compared across the subject groups. A qualitative assessment of each subject's responses by a single investigator enabled allocation to one of the following groups: complete or near complete recovery, improvement but with ongoing symptoms , or no improvement or worse and likely to still meet the CDC definition for CFS. The χ^2 and *t* tests were used as appropriate for statistical analysis. A *P* value of $<.05$ was considered significant.

RESULTS

Forty-nine subjects were identified. Twenty-two (45%) met the diagnostic criteria for CFS (group 1), and 17 (35%) were classified as ICF (group 2). Ten subjects had symptoms consistent with CFS but failed to meet the definition, as symptom duration was less than 6 months (mean ± SD, 3.21 ± 1.15 months). These 10 subjects constituted group 3.

Follow-up data were obtained in 34 (69%) of the 49 subjects. No outcome information was obtained in 15 patients; 5 were contacted but declined to participate, and 10 could not be contacted by telephone or mail. Most had moved from their last known address. Baseline characteristics of the contacted and noncontacted subjects were not significantly different (**Table 1**). One subject in the cohort was diagnosed as having ulcerative colitis 2 years after resolution of the CFS.

The groups of subjects were compared with respect to potential confounding factors at baseline, age at the time of the survey, and interval from diagnosis to survey (**Table 2**). There were no statistically significant differences between the groups in these measures. The mean duration of symptoms prior to assessment in the clinic was not significantly different between groups 1 and 2 ($P = .80$).

Table 3 presents the outcome results of the 3 groups of subjects. All of the subjects in group 3 experienced near to complete recovery, with little fatigue and fewer

Table 2. Baseline Characteristics by Group for the Contacted Subjects*

Characteristic	Group 1, CFS (n = 16)	Group 2, ICF (n = 10)	Group 3, Fatigue <6 mo (n = 8)	*P* Value
Age at diagnosis, mean ± SD, y	14.85 ± 2.43	13.71 ± 1.94	13.84 ± 2.07	.22†
Male	4 (25)	4 (40)	4 (50)	.90
Reside in rural area	5 (31)	4 (40)	4 (50)	.98
Admitted to hospital	12 (75)	7 (70)	5 (63)	.99
Age at survey, mean ± SD, y	18.97 ± 3.19	17.94 ± 2.38	19.68 ± 1.65	.10†
Interval from diagnosis to survey, mean ± SD, y	4.12 ± 2.06	4.23 ± 2.38	5.84 ± 2.07	.07†
No. of minor criteria at diagnosis, mean ± SD	4.32 ± 0.58	2.1 ± 0.57	1.73 ± 1.56	<.001†
Symptom duration at initial assessment, mo	18.2 (18.7)	16.6 (14.1)	3.29 (1.52)	.80

Abbreviations: CFS, chronic fatigue syndrome; ICF, idiopathic chronic fatigue.
*Data are given as number (percentage) unless otherwise indicated.
†Tests of significance used the 2 most different of the 3 means.

Table 3. Outcome According to Group*

Outcome Measure	Group 1, CFS (n = 16)	Group 2, ICF (n = 10)	Group 3, Fatigue <6 mo (n = 8)	*P* Value
No. (%) who have "resumed normal activities"	9 (56)	9 (90)	8 (100)	.20
No. (%) with "current fatigue"	12 (75)	7 (70)	3 (38)	.63
No. (%) who have "fatigue when enjoying an activity"	12 (75)	5 (50)	1 (13)	.13
No. (%) still exercising regularly	11 (69)	5 (50)	6 (60)	.92
No. (%) receiving counseling	0	2 (20)	1 (13)	.22
No. (%) who attended school or work part-time for >2 years from diagnosis	3 (19)	2 (20)	0	.47
Estimate of "current best level of activity out of 10"	7.33 ± 1.67	8.26 ± 1.52	9.55 ± 0.66	.09† <.001‡
Days tired per week	4.22 ± 2.75	4.15 ± 2.79	1.62 ± 1.03	.48† .009‡
Symptoms over the last month	4 ± 1.72	3.1 ± 2.18	1.12 ± 0.95	.13† <.001‡
Mean (SD) time from diagnosis to return to school, mo	4.39 (8.9)	7.77 (18.56)	2.40 (3.97)	.27†
Median (range)	1 (0-36)	1.25 (0.60)	1 (0-12)	.28‡
Mean (SD) days missed in the last month	8.12 (10.81)	2.7 (4.55)	0	.07†
Median (range)	3 (0-29)	0.5 (0-14)		.02‡
Mean (SD) days missed in the last year	63.56 (93.9)	35.6 (53.0)	3.5 (6.48)	.20†
Median (range)	22.5 (0.328)	10.5 (1-140)	0 (0-14)	.04‡
Qualitative outcome, No. (%)				
Near or complete improvement	4 (25)	5 (50)	8 (100)	
Some symptoms but improved	5 (31)	1 (10)	0	
No improvement or worsening and meet CFS definition	7 (44)	4 (40)	0	.69† .03‡

Abbreviations: CFS, chronic fatigue syndrome; ICF, idiopathic chronic fatigue.
*Data are given as mean ± SD unless otherwise indicated.
†Significance of the difference between groups 1 and 2.
‡Significance of the difference between groups 1 and 3.

than 1 symptom. All but 1 estimated their current best level of activity at over 9.5 of 10. They missed very few days from school or work and had resumed their normal activities. Many of the 16 group 1 subjects continued to have significant symptoms, with 12 [75%] complaining of current fatigue and fatigue when they were enjoying an activity. Nine (56%) reported that they had resumed normal activities; however, several had attended work or school part-time for more than 2 years (range, 2-5 years) or returned to school up to 60 months after diagnosis. The outcome measures in group 2 were similar to those in group 1. Although more group 2 subjects had resumed normal activities, had better estimates of best level of activity, and had slightly fewer of the minor symptoms, these trends were not statistically significant. Statistically, there was no difference between groups 1 and 2. Group 3 was significantly different from groups 1 and 2 with respect to several of the individual measures.

Qualitatively, group 1 had the highest proportion with a poor outcome. Seven (44%) of 16 were unimproved or worse; 5 (31%) had improved but not completely; and 4 (25%) were nearly or completely resolved. Group 2 was less severely affected but 4 (40%) showed no improvement or declined, and only 5 (50%) had nearly or completely resolved. Group 3 had a uniformly good outcome. Forty-four percent (10) of group 1 and 40% (7) of group 2 subjects were likely to meet the definition of CFS at follow-up. Overall, only 3 subjects were receiving counseling, while 22 (65%) still engaged in regular physical exercise. The proportion that exercised was similar across all groups.

What This Study Adds

Many younger patients do not meet the formal definition of having CFS as defined in adults but have significant physical and social impairment as a result of their symptoms. This study of adolescents with fatigue (those who met the adult definition and those with fewer symptoms or shorter duration of fatigue at the outset) compared the outcomes of those admitted with those treated as outpatients only. Outcome was best in those whose fatigue onset was less than 6 months before the initial examination. In those with more than 6 months of fatigue, the patients meeting the formal definition of CFS had a similar outcome to those with ICF. A symptom duration of more than 6 months was associated with an increased risk of poor outcome. The distinction between CFS and ICF may not be clinically relevant, as the patients require similar management and have similar outcomes. Admission to the hospital did not correlate with improved outcome in this cohort.

As the outcomes for groups 1 and 2 were similar, these groups were combined to address the association of outcome with admission to the hospital. Although the numbers are small, there was no significant difference in outcome between those admitted and those managed wholly as outpatients. Patients from rural areas are more likely to be admitted for purely logistical reasons; however, in this cohort, the proportion of these patients in each category was the same. The outpatients were surveyed at a significantly longer interval from diagnosis (mean, 5.8 years) than the admitted subjects (mean, 3.5 years) ($P = .04$).

COMMENT

This study found that a significant proportion of children and adolescents diagnosed as having CFS using the adult definition have ongoing symptoms for up to 8 years from diagnosis. Those with ICF as a group may have a slightly better outcome, although in this cohort, the difference was not statistically significant. Several of the ICF subjects had ongoing symptoms, and 40% (7) met the CFS definition at follow-up. Subjects with less than 6 months of symptoms at the outset had a much better long-term outcome. There was a trend to a longer follow-up interval for these subjects, and this may partly explain the finding. An alternative explanation is that intervention before 6 months have elapsed is associated with a more favorable outcome. It is also possible that this group has a higher resolution rate regardless of any evaluation or intervention.

The results support the use of the 6-month criteria to select patients who are likely to require ongoing intervention, and they suggest that those with fewer than 4 minor criteria also deserve additional attention if the duration of fatigue is more than 6 months. Early intervention before a full 6 months of fatigue may be associated with a better long-term outcome and less need for ongoing intervention. It is not possible in a retrospective study to determine if this group of patients would have improved even without treatment.

In this cohort, brief hospital admission in those with more than 6 months of fatigue was not associated with a significantly different outcome. Those admitted might represent patients with more severe illness who would therefore be expected to have a poorer outcome. The subjects managed wholly as outpatients were surveyed after a longer interval and could be expected to have fewer symptoms as more time had elapsed. Due to the small sample size, this finding is of uncertain significance.

Many of the subjects, even those with ongoing symptoms, still engaged in regular exercise. This may indicate understanding of the need to maintain physical condition despite fatigue. It also suggests that regular exercise alone is not sufficient to prevent ongoing symptoms.

These results are similar to previous case series examining the question of outcome in CFS; however, no published reports directly compare adolescent subjects with CFS with those with ICF and unexplained fatigue of less than 6 months. Studies vary in the definition used, the method of follow-up, and the interval between diagnosis and follow-up; therefore, comparison is difficult. Bell et al[8] reviewed 35 of 46 children and adolescents with CDC-defined CFS 13 years after diagnosis. Of these, 37.1% had resolved, 42.9% were better but not resolved, 11.3% were chronically ill, and 8.6% were worse. The amount of missed school early in the illness was most predictive of poor long-term outcome.

Smith et al[9] performed telephone follow-up of 15 children with CFS as defined by the CDC, after an interval of 13 to 32 months. Only 4 (27%) had recovered, 4 had improved but not fully, and 7 (46%) were worse or the same. An Australian study[10] published recently in abstract form assessed 200 young people with CFS aged 13 to 25 at 1 to 10 years from diagnosis. Thirty percent were well; 60% were in full-time work or study. Most were fatigued for 3 to 4 years, and 20% still received a disability allowance.

Studies with less well-defined inclusion criteria[11-13] had better overall outcomes. A much-cited study by Krilov et al[14] performed 1-hour telephone interviews with 42 of 58 families of children 1 to 3 years after being examined for fatigue. Clinical inclusion criteria and minimum duration of fatigue were not mentioned. Forty-three percent of families felt their children were "cured," 52% thought they had improved, and 5% were unchanged. No clinical or demographic factors were associated with outcome. The definition used must be considered when interpreting results of outcome studies. Adults with CFS have a more guarded prognosis,[15,16] but it is possible that overinclusion of patients with unspecified "fatigue" in the adolescent studies is partly responsible for the difference.

Treatment of CFS is difficult to evaluate, as a proportion of patients improve spontaneously or with no treatment.[17] Most treatment evaluation studies include only the more severely affected patients seen in specialist clinics.[18] Graded exercise programs and cognitive behavior therapy are associated with improved outcome in randomized controlled trials,[18,19] although improvement may be modest and unsustained. The beneficial effect of exercise is sustained for up to a year when compared with controls who received flexibility and relaxation therapy rather than aerobic exercise.[20] Provision of edu-

cation about exercise, frequent discussion of problems, and motivational interviewing to enable patients to manage their own exercise program is also helpful[21] and is claimed to be shorter and to require less therapist skill than cognitive behavioral therapy. Evidence for the efficacy of medications, such as antidepressants, corticosteroids, dietary supplements, and immunotherapy, is scarce.[18] Prolonged rest has not been shown to be helpful and may in fact be harmful.

Hospital admission was specifically addressed in a recently published Australian study.[22] A cohort of 57 adolescents who met diagnostic criteria for CFS and had failed outpatient management was evaluated 3 months to 5 years after a 4-week multidisciplinary inpatient program. The 42 responders retrospectively reported better levels of activity and school attendance after the program in comparison with their time on the waiting list. With respect to activity level, 19% were completely better, 70% were better with some limitation, and 12% were worse or unchanged. Ninety-five percent rated the program as helpful or very helpful. It is possible that the longer admission duration was more effective than the shorter admission assessed in our study. Like ours, this study lacked a prospective assessment of the subjects' symptoms prior to the intervention.

Unfortunately, there were several limitations of our study. The retrospective nature meant that baseline data were dependent on documentation in the clinic notes or medical records. Inadequate documentation may have led to incorrect assignment of subjects to the various clinical groups. Second, the small sample size limited the statistical power. Subjects were referred to a tertiary setting and therefore may not be representative of all patients with CFS. Thirty percent of the original sample could not be contacted or declined to participate, further reducing the sample size, but the contacted group was representative of the total with respect to the baseline data. Third, questionnaire responses were subjective and assessed the symptoms and fatigue at a single point in time, although CFS is a condition known to fluctuate in severity. An additional question addressing qualitative self-assessment of improvement from diagnosis would have provided useful information and enabled comparison of the patients' perception of illness with their overall symptom score. Finally, the exclusion of patients with fibromyalgia from the study may reduce the generalizability of the results to patient groups that include children with fibromyalgia.

Other than hospital admission, this study did not address type or duration of treatment or subjects' adherence to treatment plans. Therefore, no conclusions regarding the effectiveness of treatments can be made. A prospective study design using a similar questionnaire completed at diagnosis, prior to intervention, and then repeated at follow-up would enable a more direct and accurate comparison of symptoms and activity level.

In conclusion, adolescent CFS is a condition with the potential for long-term effects on health and level of activity. The use of a standard definition is important in a research and clinical setting; however, it is an arbitrary division of patients with a spectrum of fatigue states. Brief hospital admission at the outset is not necessarily important in the long term in these 2 groups of patients. Ongoing treatment is probably of greater importance. This should be individualized and include maintenance of academic and recreational activity, sleep hygiene, psychosocial support, education about the condition, pharmacologic and other treatments for specific symptoms, school liaison, and graded return to exercise. Prospective research with a larger sample will be needed to address whether specific interventions are associated with improved outcome in children and adolescents with fatigue.

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