

# Thirteen-Year Follow-Up of Children and Adolescents With Chronic Fatigue Syndrome

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**ABSTRACT.** *Objective.* To describe the educational, social, and symptomatic outcome of children and adolescents with chronic fatigue syndrome 13 years after illness onset.

*Methods.* Between January 1984 and December 1987, 46 children and adolescents developed an illness suggestive of chronic fatigue syndrome. Follow-up questionnaires were obtained from 35 participants an average of 13 years after illness onset. Data were obtained concerning subsequent medical diagnoses, amount of school missed, presence and severity of current symptoms, and subjective assessment of degree of illness resolution.

*Results.* Of the 35 participants, 24 were female (68.6%) and 11 were male (31.4%). Average age at illness onset was 12.1 years. Eight participants (22.9%) had an acute onset of symptoms, 27 (77.1%) had a gradual onset. No participant received an alternative medical diagnosis that could have explained the symptom complex between illness onset and follow-up. Thirteen participants (37.1%) considered themselves resolved of illness at follow-up; 15 participants (42.9%) considered themselves well but not resolved; 4 (11.4%) considered themselves chronically ill; and 3 (8.6%) considered themselves more ill than during the early years of illness. Correlation with the Medical Outcomes Study Short Form Health Survey was good for current level of symptoms and degree of recovery. Eight participants (22.9%) missed >2 years of school, and 5 of these were still ill at follow-up. Amount of school missed correlated with both illness severity at follow-up and perceived social impact of the illness.

*Conclusions.* These data demonstrate the presence of an illness consistent with the current definition of chronic fatigue syndrome. Eighty percent of children and adolescents affected had a satisfactory outcome from their fatiguing illness, although the majority of these participants had mild to moderate persisting symptoms. Twenty percent of participants remain ill with significant symptoms and activity limitation 13 years after illness onset. Chronic fatigue syndrome in children and adolescents may result in persistent somatic symptoms and disability in a minority of those affected. *Pediatrics* 2001;107:994-998; *chronic fatigue syndrome, pediatric chronic fatigue syndrome.*

ABBREVIATIONS. CFS, chronic fatigue syndrome; SF-36, Medical Outcomes Study Short Form Health Survey; CDC, Centers for Disease Control and Prevention; VAS, visual analog scale.

Chronic fatigue syndrome (CFS) is an illness of unknown cause characterized by unexplained, debilitating fatigue usually worsened by exertion and not resolving with rest, occurring in both children and adults. In addition to fatigue, patients experience an associated symptom pattern that includes headache, sore throat, lymph node tenderness, muscle pain and subjective weakness, joint pain, sleep disturbance, cognitive dysfunction, and neurologic symptoms.<sup>1-6</sup> Although diagnostic criteria are available for adults,<sup>7</sup> criteria specific for children have not been developed.

Hypotheses concerning the cause of CFS have ranged from persistent infection with viral or other agents to a primary psychiatric disturbance. However, no specific infectious agents have been consistently linked to the illness, and many adolescents with CFS have no demonstrable emotional illness. More recent studies point toward abnormalities in autonomic nervous system function.<sup>8-10</sup> Issues concerning epidemiology, immunology, and the role of infectious disease have been hampered by lack of a diagnostic marker and reliance on subjective symptoms. Because current adult diagnostic criteria are relatively recent, few studies of the natural history of CFS have been conducted.

Between January 1984 and December 1987, 214 persons experienced an illness suggestive of CFS in an isolated rural community in upstate New York. Of these persons, 46 (21.5%) were under age 18 years at illness onset. Some of these children were reported earlier in a study showing no correlation with Epstein-Barr virus antibody levels<sup>11</sup> and in a case-control, risk factor study.<sup>12</sup> Because this apparent illness cluster occurred before the publication of present diagnostic criteria for CFS,<sup>7</sup> criteria for diagnosis of these patients were developed.<sup>13</sup>

For the pediatrician, the difficulty is more acute because of lack of specific diagnostic criteria. Yet the pediatrician is often faced with the clinical management of children and adolescents with numerous, medically unexplained, somatic symptoms and activity-limiting fatigue. The present study seeks to address the prognosis of CFS in a defined group of children and adolescents over a 13-year span.

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## Participants

Forty-six children and adolescents who became ill between January 1984 and December 1987 had been interviewed and examined by one of us (D.S.B.), often within days or months of symptom onset, although the diagnosis of CFS was not made until at least 6 months of persisting symptoms. All participants had unexplained, activity-limiting fatigue and numerous somatic complaints. This study was conducted in a rural private practice setting, and verbal consent was obtained from participants.

## METHODS

The records of participants were reviewed for symptom pattern and type of illness onset an average of 13 years after illness onset by the diagnosing clinician and compared with the present adult criteria for CFS.<sup>7</sup> A questionnaire was mailed to all participants inquiring about present health status. The questionnaire included the following:

1. Current health assessment with 4 answer options: "I have recovered completely and feel entirely well," "I have never recovered completely but feel pretty well," "I recovered somewhat but remain ill," and "I am more ill than I was 10 years ago."
2. Subsequent medical and emotional diagnoses.
3. Subjective effect of the illness on social and educational life.
4. Amount of time out of school because of illness.
5. Subjective assessment of illness severity during worst month of illness.
6. Visual analog score (0 = none; 10 = very severe) indicating present severity of 12 symptoms seen in CFS (fatigue, sore throat, lymph node tenderness, eye pain and/or light sensitivity, abdominal discomfort, headache, depression, muscle pain, memory and/or attention problems, sleep disturbance, dizziness and/or lightheadedness, and joint pain).
7. Medical Outcomes Study Short Form Health Survey (SF-36). This 36-item instrument is self-administered and is designed to assess functional status and quality of life. The 8 subscales in the SF-36 are physical, emotional, social, role functioning, body pain, mental health, vitality, and general health. Higher scores indicate better health and less discomfort. This instrument has been documented to have high reliability and validity in numerous patient populations<sup>14,15</sup> and has been used in the assessment of CFS.<sup>16,17</sup>

## RESULTS

Of the 46 participants, 35 (76.1%) completed and returned questionnaires. Of the remaining 11 participants, present location was unknown for 5, and the questionnaires were not returned by the remaining 6. Telephone discussion with these latter 6 participants suggested a similar overall pattern of response to those participants returning questionnaire, but their data were not included in study results.

Twenty-four participants were female (68.6%), 11 were male (31.4%). The average age of illness onset was 12.1 years (male: 11.1 years; female: 12.8 years). All participants retrospectively met current Centers for Disease Control and Prevention (CDC) diagnostic criteria for CFS defined as a new onset of unexplained, activity-limiting fatigue, not relieved by rest, not caused by excessive exertion, and lasting at least 6 months. All participants had at least 4 of the 8 symptoms of the CDC criteria (cognitive dysfunction, sore throat, tender lymph nodes, muscle pain, multijoint pain, headaches, unrefreshing sleep, and postexertional malaise).<sup>7</sup> Eight participants (22.9%) had an acute flu-like onset with symptom pattern

occurring suddenly within a 1-week period. The remaining 27 participants (77.1%) had a gradual onset of symptom pattern over weeks to months. The majority of participants were adolescents, and only 8 (22.9%) were <10 years old at illness onset. No participant had illness onset below age 5 years. See Table 1 for demographic data.

As part of the entry criteria, no participant was clinically believed to have a primary psychiatric disorder, substance abuse, or eating disorder to account for the symptom complex. In addition to fatigue, the symptoms documented at illness onset included sore throat (91.4%), myalgia (91.4%), headache (85.7%), lymph node tenderness (82.9%), memory and attention difficulties (77.1%), and joint pain (74.3%). Post-exertional malaise and sleep disturbance were not systematically inquired about at illness onset. There was a high frequency of abdominal pain, photophobia, sensation of fever, and flushing, symptoms not presently included in adult diagnostic criteria.

At follow-up, no participant reported an alternative or subsequent medical diagnosis that could have retrospectively explained the symptom complex. Fibromyalgia was listed but not included in this analysis because of its overlap with CFS.<sup>18</sup> Other diagnoses listed included endometriosis (2), depression (2), posttraumatic stress disorder (1), migraine (1), in situ cancer of the cervix (1), and mitral valve prolapse (1). No psychiatric hospitalizations were recorded.

In terms of outcome, 13 (37.1%) reported, "recovered completely and feel entirely well." Fifteen participants (42.9%) listed, "I have never recovered completely but feel pretty well." Four participants (11.4%) listed, "I recovered somewhat but remain ill," and 3 participants (8.6%) listed, "I am more ill than I was 10 years ago." Thus, an overall favorable outcome was reported by 80% of participants an average of 13 years after illness onset (Table 2).

Of the 13 participants "completely recovered," only 9 could date the length of time from illness onset to recovery. In these participants, none recovered within 1 year, 2 between 1 and 2 years, 1 between 2 and 3 years, 3 between 3 and 4 years, and 3

**TABLE 1.** Demographic Data of Children and Adolescents With Unexplained Chronic Fatigue With Illness Onset Between January 1984 and December 1987

Sex ( <i>n</i> = 35)	
Male, 11 (31.4%)	
Female, 24 (68.6%)	
Type of onset ( <i>n</i> = 35)	
Acute, 8 (22.9%; 2 male, 6 female)	
Gradual, 27 (77.1%; 9 male, 18 female)	
Age at illness onset ( <i>n</i> = 35)	
5-9 y 8 (22.9%)	
10-14 y 16 (45.7%)	
15-18 y 11 (31.4%)	
Onset symptoms	
Unexplained fatigue	35 (100%)
Recurrent sore throat	32 (91.4%)
Myalgia	32 (91.4%)
Headache	30 (85.7%)
Lymph node tenderness	29 (82.9%)
Cognitive difficulties	27 (77.1%)
Multijoint pain	26 (74.3%)

**TABLE 2.** Subjective Assessment of Health at Follow-Up

Chosen Assessment	
"I have recovered completely and feel entirely well."	13 (37.1%)
"I have never recovered completely but feel pretty well."	15 (42.9%)
"I have recovered somewhat, but remain ill."	4 (11.4%)
"I am more ill than I was 10 years ago."	3 (8.6%)

recovered after 4 years of illness. The longest recovery occurred 9½ years after onset. There was no correlation between degree of recovery and the age at illness onset, gender, type of onset, or family clustering. An attempt was made to assess severity during the "worst month of illness" by estimating average daily activity, and no correlation was found to outcome.

The educational impact of the illness most closely correlated with illness outcome. Fourteen participants (40%) missed "little or no school," 8 (22.9%) missed from 1 to 6 months, 3 (8.6%) missed 6 to 12 months, 2 (5.7%) missed 1 to 2 years of school, and 8 (22.9%) missed >2 years of school. Of these latter 8 participants, none reported complete recovery, 3 were "never recovered completely but feel pretty well," 3 were "recovered somewhat but remain ill," and 2 were "more ill." Of 14 participants who missed "little or no school," 10 (71.4%) "recovered completely," and the remaining 4 (28.6%) were "never recovered completely but feel pretty well."

Correlation of illness outcome by questionnaire and SF-36 was good because participants reporting better recovery had higher scores in all 8 domains. Symptom analysis did not show correlation between specific symptoms most prominent at onset and symptoms most prominent at follow-up with exception of photophobia (data not shown). However, it should be noted that visual analog scales (VASs) for symptom severity were not used at illness onset.

The VAS scores used in data analysis were the sum of 12 symptom-specific scores graded from 0 (no symptom) to 10 (very severe symptom). In general the VAS sums correlated to degree of recovery in those participants who had "completely recovered," and those who were "more ill than at onset," with average scores being 15.4 for the former group and 74.7 for the latter. The 2 middle groups displayed considerable overlap with scores for "never recovered completely but feel pretty well" ranging from 17 to 87, and "recovered somewhat but remain ill," ranging from 45 to 93.

Twelve participants (34.3%) believed that their illness did not have an overall social effect on their life, 10 of whom reported they had recovered completely. Sixteen participants (45.7%) believed that their illness affected their life to a mild degree, 3 (8.6%) believed that there was a moderate social effect, and 4 (11.4%) believed that their illness had a severe effect on their life. In general, the social effect paralleled the perceived illness outcome.

#### DISCUSSION

In this study, 35 children and adolescents were diagnosed with unexplained chronic fatigue between

1984 and 1987 and followed for an average of 13 years. The criteria used in diagnosing this group of patients was described previously,<sup>13</sup> and all participants would retrospectively fit CDC criteria for CFS. Clinically, none had prominent emotional or behavioral symptoms or were believed to have a primary emotional disorder.

The existence of cluster outbreaks of CFS has been one of the central questions in current research. Although the medical literature describes over 50 CFS-like outbreaks,<sup>19</sup> the publication of these reports before 1988 has left uncertainty that these illnesses would have met current criteria for CFS. The children described in this study were part of a larger group of 213 patients, adults and children, in an isolated rural area containing no cities of >15 000 population, thus implying a cluster outbreak. As described in this study, there have been no subsequent medical explanations for the original symptom complex or the persisting illness present in 20% of the sample. Moreover, the clinical similarity of patients meeting CFS criteria diagnosed after 1988 leave the authors with the conclusion that the participants of this study had, and some continue to have, CFS. Whether symptom resolution or persistence would be the same in sporadic cases of CFS, as opposed to cluster cases, was not addressed in this study.

The adult literature on prognosis of CFS has been contradictory because of differing diagnostic criteria before 1988 and variations in the definition of improvement. Because CFS has no objective markers to validate symptom severity, subjective impressions are relied on to assess outcome and are subject to both exaggeration and denial, dependent on the coping style of participants. The pediatric literature concerning the natural history of unexplained chronic fatigue has been even more scant.

In a recent article, Krilov et al<sup>4</sup> conducted a follow-up telephone survey of the families of 42 children with chronic fatigue from 1 to 4 years after medical evaluation. At follow-up, 43% considered their child "cured," 52% considered their child "improved," and 5% considered their child unchanged. Smith et al<sup>5</sup> described 15 adolescents followed for 13 to 32 months with 4 well (26.7%), 4 improved (26.7%), and 8 unchanged or worse (53.3%). Marshall et al<sup>6</sup> followed 17 children and adolescents over 16 months with 76% demonstrating improvement, although 38% had occasional symptoms. A minority were "persistently and severely affected." In a case-control study, Carter et al<sup>3</sup> compared 31 children with chronic fatigue to both healthy children and those with depression. Half of the participants with chronic fatigue were reevaluated at 17 months with 3 being cured and the remainder improved.

In the present study, an overall good functional outcome was reported in 80% of participants an average of 13 years after onset. Many of the participants of this study have been followed by the same clinician for the entire length of illness, and our observations are in keeping with those of Krilov et al<sup>4</sup> that as improvement occurs, periods of severe debility become shorter and less frequent. However, we also notice that in those who do not improve, coping

skills develop so that moderate symptoms are modified by a lifestyle that includes activity restriction, flexibility of daily schedule, and avoidance of sustained activity.

The lifestyle variation is the most difficult factor to analyze in studies attempting to address the natural history of unexplained chronic fatigue. We compared perceived illness outcome (by questionnaire and SF-36) with specific symptom severity (VAS scores). CFS is characterized by somatic symptoms that may vary in severity but persist over time. Nine participants reported complete resolution of illness and had VAS scores below 25 as would be expected in complete recovery. Four participants reporting illness resolution had VAS sums ranging from 28 to 48, indicating mild symptomatology. Of those participants considering themselves "never recovered completely but pretty well," 2 had low VAS sums between 10 and 19, 6 had moderate VAS sums between 25 and 49, and 5 had high VAS sums between 50 and 87. Two participants did not record VAS scores with 1 expressing health identity confusion by writing in the margin of the questionnaire, "The survey is hard to answer because. . . I was so young when I became ill, I do not know if I am a well person, or a person who thinks he is well but doesn't know what well really is." Thus, perception of complete illness resolution and low VAS scores suggesting minimal, if any, symptoms were reported in only 25.7% of the entire group. This wide variation in somatic discomfort has been the cause of the difficulty in assessing overall outcome in CFS and needs additional clarification.

The best predictor of eventual outcome was the amount of school missed during the first years of illness. All participants in this study were managed during the early years of their illness by one clinician (D.S.B.) and all were encouraged to attend school as much as possible, with home tutoring provided when school attendance was not possible. Thus, differences in clinical approach and management is unlikely responsible for clinical outcome. Because increasing time missed from school correlated with a poorer outcome, it can be argued that illness severity during the first years of illness was a predictor of outcome. It can also be argued that school absenteeism is a psychosocial marker reflecting illness behavior, but this trend was not observed by the treating clinician. However, this possibility needs to be more fully explored.

In the present study, no participant was diagnosed with another medical illness that could have retrospectively explained the chronic fatigue. Thus, unexplained chronic fatigue is unlikely to be a precursor to another medical illness. Although this study was not designed to explore psychiatric illness, no participant experienced psychiatric hospitalization or listed significant psychiatric illness, substance abuse, or eating disorders as a diagnosis in the years following illness onset.

It has been suggested that children with CFS not be given the diagnosis because it would encourage illness behavior.<sup>20</sup> In our opinion, this would have created severe difficulties in clinical management.

The use of the diagnostic term CFS, while not implying cause, was helpful in reducing both patient anxiety and unnecessary laboratory evaluations and in attempting symptom control. It has also been suggested that persistence of symptoms in illnesses without clear cause is related to encouragement by "sympathetic physicians."<sup>21</sup> Ten participants in this study (28.6%) maintained contact and/or were clinically managed for >10 years by the diagnosing physician who would be considered sympathetic to the diagnosis of CFS, whereas 25 participants (71.4%) were not followed clinically after the early years of illness. Results from questionnaire showed no differences in clinical outcome between these 2 groups, implying that clinician empathy was not a prognostic factor.

This study has several limitations. Diagnostic criteria for unexplained chronic fatigue were not available in 1984 and the criteria developed, although similar to the present CDC criteria, were designed for this specific group of patients. At present, diagnostic criteria for CFS have not been developed for children, and developing specific pediatric criteria would be helpful for the pediatrician. VASs were not obtained for the 12 symptoms at illness onset that would have allowed a more accurate assessment of specific symptom persistence. Finally, the natural history seen in this study sheds little light on the current controversies surrounding the role of emotions in unexplained chronic fatigue, although it remains the clinical opinion of the authors that emotions had little to do with either illness onset or illness persistence.

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## ANNOUNCEMENT

The Fifth World Congress of Perinatal Medicine, under the auspices of the World Association of Perinatal Medicine, will be held in Barcelona, Spain, from September 23–27, 2001.

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