Comparative Study of Anxiety, Depression, Somatization, Functional Disability, and Illness Attribution in Adolescents With Chronic Fatigue or Migraine

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ABSTRACT. *Objective.* **To compare adolescents with migraine, unexplained profound chronic fatigue of >6 months duration, and normal school controls on measures of anxiety, depression, somatization, functional disability, and illness attribution.**

Methods. **Adolescents referred to Children's Hospital and Regional Medical Center for behavioral treatment of migraine (n = 179) or evaluation of chronic fatigue (n = 97) were compared with a group of healthy controls of similar age and sex from a middle school (n = 32). Subjects completed the Spielberger State-Trait Anxiety Inventory-Trait Form, the Children's Depression Inventory, the Childhood Somatization Inventory, and estimated the number of school days missed in the past 6 months because of illness. Migraine and fatigued subjects completed an illness attribution questionnaire.**

Results. **Subjects in the 3 groups were 56% to 70% female and ranged from 11 years old to 18 years old with a mean age of 14.0 ± 2.0. Forty-six of the 97 chronically fatigued adolescents met 1994 Centers for Disease Control and Prevention (CDC) criteria for chronic fatigue syndrome (CDC-CFS), while 51 had idiopathic chronic fatigue syndrome (I-CFS) that did not meet full CDC criteria. Adolescents with migraine had significantly higher anxiety scores than those with I-CFS or controls and higher somatization scores than controls. Adolescents with CDC-CFS had significantly higher anxiety scores than those with I-CFS or controls, and higher depression and somatization scores than all other groups. There were significant differences between all groups for school days missed with CDC-CFS more than I-CFS more than migraine more than controls. Parents of adolescents with unexplained I-CFS had significantly lower attribution scores relating illness to possible psychological or stress factors than parents of adolescents with CDC-CFS or migraine.**

Conclusions. **Adolescents referred to an academic center for evaluation of unexplained chronic fatigue had greater rates of school absenteeism than adolescents with migraine or healthy controls. Those meeting CDC-CFS criteria had higher anxiety scores than controls and higher depression and somatization scores than migraineurs or controls. Parents of adolescents with I-CFS were less likely to endorse psychological factors as possibly contributing to their symptoms than parents of adolescents with CDC-CFS or migraine.** *Pediatrics* **2003;111:e376–e381. URL: http://www.pediatrics.org/cgi/content/full/111/4/e376;** ***anxiety, chronic fatigue, depression, functional disability, illness attribution, migraine, somatization.***

ABBREVIATIONS. CFS, chronic fatigue syndrome; CDC, Centers for Disease Control and Prevention; CDC-CFS, Centers for Disease Control and Prevention criteria for chronic fatigue syndrome; I-CFS, idiopathic chronic fatigue syndrome; STAI, Spielberger State-Trait Anxiety Inventory; CDI, Children's Depression Inventory.

Unexplained chronic disabling fatigue, a predominantly adult disorder that appears to be relatively uncommon in adolescence and rare in childhood, is a perplexing problem for the pediatrician. Scant pediatric data estimate a prevalence ranging from 23 to 116 per 100 000 with an approximate 2.5:1 female to male ratio.[1] To qualify for the diagnosis of chronic fatigue syndrome (CFS), profound persistent or intermittent fatigue must be present for >6 months, cause significant functional disability, and be unexplained after a comprehensive medical and psychological evaluation. Various diagnostic criteria have been proposed, but most researchers utilize the 1994 Centers for Disease Control and Prevention (CDC) CFS criteria (CDC-CFS),[2] which emphasize the presence of additional physical symptoms and allow some comorbid psychiatric conditions.

In most systematic reports, the onset of CFS in children and adolescents follows an acute febrile illness in approximately two thirds of cases while one-third may develop symptoms insidiously.[3–5] One report suggests that the clinical course is persistent in approximately two thirds of adolescent cases and intermittent with remissions and relapses of several months' duration in the other third.[3] In addition to profound, disabling fatigue, other common symptoms include: headache, exercise intolerance, sore throat, difficulty with memory or concentration, myalgia, arthralgia, and dizziness.[3–6] Functional disability usually impairs all spheres of activity, and decreased school performance and marked absenteeism are often dramatic.[3–6]

A review of the current evidence suggests that

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pediatric CFS may not be a homogenous disorder and that a single causative factor is unlikely to be found.[1,7,8] It is probable that multiple factors with variable expression are involved in any individual case. Although controversial and unproven, factors of importance might include a genetic predisposition to fatiguing illness[9] or physiologic perturbations[10–12]; precipitating factors such as infectious agents, antigens, or stress[13]; and sustaining factors such as illness attribution that rejects the contribution of psychological factors,[14] maladaptive coping style,[15] and reinforcement of illness behavior.[16]

Because there is a well-established relationship between anxiety, depression, and fatigue,[17] it is reasonable to consider psychological factors as contributing to either the cause or maintenance of adolescent CFS. In addition, it is important to note that of adolescents who meet CFS criteria, more than one-third may have concurrent psychiatric diagnoses (predominantly depression and anxiety disorders).[3,4,18] Several adolescent studies have found CFS patients have more internalizing symptoms,[16,19–21] somatic complaints,[20] or functional disability[22] than comparison groups of adolescents with arthritis, cancer, or cystic fibrosis. Adolescents with CFS who do not have concurrent psychiatric diagnoses often endorse symptoms such as decreased energy, difficulty with concentration and memory, and sleep problems, but they do not often endorse depressed or anxious mood, self-deprecating thoughts, anhedonia, or suicidal ideation.[3] Thus, psychological factors seem to be of major importance in at least one third of adolescents with CFS, but their etiologic role remains primarily undetermined.

Both CFS and migraine are disorders that may be associated with marked distress and functional disability during adolescence. Other similarities between the 2 disorders include the presence of pain and somatic symptoms in the absence of demonstrable organic abnormality. Although the pathophysiology of neither disorder has been elucidated fully, it appears likely that multiple factors are involved in both conditions.[1,22] Headache is a frequently reported symptom in adolescent CFS,[3–6] and headache patients often report fatigue.[23] Preliminary evidence suggests the existence of autonomic nervous system dysfunction in both CFS[10] and migraine.[24] Genetic susceptibility is strongly suggested in migraine,[25] and some evidence suggests that this may be important in CFS as well.[9] Stress is a common precipitant of migraine,[26] but this association has not been studied systematically in adolescent CFS.

For more than a decade, adolescents with CFS and migraine have been evaluated systematically in the Adolescent Medicine Clinic and the Headache and Stress Management Clinic at Children's Hospital and Regional Medical Center (Seattle, WA). Like CFS, adolescent migraine has no obvious organic manifestations and may be associated with marked functional disability. Psychological stress is clearly a potential precipitating factor in migraine and appears to be associated with many cases of adolescent CFS. In an effort to contrast the relationship of psychological factors which might represent primary or secondary phenomena in these disorders, this study compares adolescent migraine and chronic fatigue populations on measures of anxiety, depression, somatization, functional disability, and illness attribution.

METHODS

Study Sample

Patient data for this report are derived from 276 consecutive new referrals (from March 1987 to March 2001) of adolescents 11 years old to 18 years old with either migraine (n = 179) or profound disabling chronic fatigue that was unexplained after medical evaluation (n = 97). All subjects had a duration of illness of >6 months. Patients were referred to either the Adolescent Clinic or the Headache and Stress Management Clinic at Children's Hospital and Regional Medical Center in Seattle and seen by one of the authors (M.S.S. or W.M.W.). Matching the most frequent postal codes of headache clinic patients, a healthy control group (n = 32) balanced to match the age and gender composition of clinic patients, was selected from a junior high school in 1995 as part of a previous study.[27]

Because individual questionnaires used in this report were introduced sequentially and some requested forms were not completed, not all subjects completed all questionnaires. In 1987, as part of the standard intake procedure for all migraine and chronic fatigue patients, adolescents and their parents were asked to complete questionnaires regarding depression and school absenteeism. Anxiety and somatization questionnaires were added in 1990 and an illness attribution questionnaire was introduced into the assessment process in 1992. After removal of identifying information, patient data were maintained for further analysis. In 1995, with hospital and school district institutional review board approval, a comparison sample of healthy junior high school students completed anxiety, depression, somatization, and school absenteeism questionnaires.

Self-Report Measures

Anxiety was measured using the Trait form of the Spielberger State-Trait Anxiety Inventory (STAI) Form X2.[28] The STAI consists of 20 statements on 4-point Likert-type scales that assess the level of anxiety a person reports as generally characteristic of himself or herself. The STAI has been found to have acceptable validity, internal reliability, and test-retest reliability.[29]

Depressive symptoms over the previous 2 weeks were evaluated using the Children's Depression Inventory (CDI),[30] which consists of 27 items rated on a 3-point scale. An item related to suicidal ideation was removed from questionnaires distributed to school subjects because of concerns of the school counseling staff and research administration. Student scores were extrapolated to the 27-item total by adding each student's mean score for the remaining 26 items to their own total score. The CDI has been found to have adequate reliability and validity.[31]

Somatic complaints were evaluated with the Children's Somatization Inventory.[32] This measure rates 35 symptoms based on whether they have been experienced in the previous 2 weeks. Adequate test-retest reliability has been demonstrated for both healthy populations and those with chronic pain syndromes.[32]

Functional disability was measured by averaging parent and patient estimation of the number of school days missed because of illness within the previous 6 months that school was in session.

The illness attribution scale was derived before the onset of this study through principal component analyses of 25 items, which resulted in 13 items subdivided into 2 primary scales characterized for analysis as a constitutional/environmental scale and a psychological/stress scale. Patients and parents rated the 13 questions on 6-point Likert-type scales (strongly disagree to strongly agree) in response to the statement: "I really feel that my/my child's problem comes from. . . ".

The possible constitutional/environmental illness attributions were related to dietary deficiency, functional defect, past injury, imbalance, overreactivity, immune dysfunction, and infection. The possible psychological/stress illness attributions were related to past emotional experience, excessive worry, rumination, oversensitivity, excessive stress, and excessive pressure or expectation.

Analysis of α coefficients for 115 completed questionnaires

revealed acceptable α of .81 for the Constitutional/Environmental scale and .87 for the Psychological/Stress scale. Patterns of intercorrelations with subscales of the CDI and the Illness Behavior Questionnaire suggest promising discriminant validity.

Statistical Analysis

Differences in the distribution of sex and race across migraine, chronic fatigue, and healthy control groups were evaluated with χ^2 analysis. One-way analysis of variance with Student-Neuman-Keuls posthoc multiple comparisons was used to evaluate mean values of age, illness duration, anxiety (STAI) scores, depression (CDI) scores, somatization (Children's Somatization Inventory) scores, and illness attribution scores. Because of non-normal data distribution, group differences in the estimated number of school days missed because of illness were evaluated with the Kruskal-Wallis test.

RESULTS

Table 1 indicates that subjects ranged from 11 years old to 18 years old with a mean age of 14.0 ± 2.0 years and a female to male ratio of 1.3 to 2.3:1. All migraine subjects met International Headache Society criteria for migraine with or without aura or migrainous disorder not fulfilling all criteria.[32] Although all subjects can be characterized as middle adolescent, chronically fatigued adolescents were significantly older than migraineurs and controls ($F = 21.75$; $P < .001$). Chronically fatigued adolescents also had significantly shorter illness duration than migraineurs (t = 10.25; $P < .001$). Forty-six chronically fatigued adolescents met 1994 CDC-CFS and 51 with idiopathic CFS (I-CFS) did not meet criteria. All study groups were >95% white with a female predominance that did not vary significantly across groups.

Table 2 displays the results of comparison analyses of anxiety, depression, somatization, and school absenteeism scores across all 4 groups. These results can be summarized as follows:

- Anxiety. Migraineurs had significantly higher anxiety scores than adolescents with I-CFS or healthy controls but did not differ significantly from those with CDC-CFS. Adolescents with CDC-CFS had significantly higher anxiety scores than those with I-CFS or controls ($F = 7.766$; $P < .001$).
- Depression. Depression scores for adolescents with CDC-CFS were significantly higher than those for all other groups. Adolescents with migraine, I-CFS, and healthy controls did not differ significantly ($F = 3.206$; $P < .01$).
- Somatization. Somatization scores for adolescents with CDC-CFS were significantly higher than those of all other groups. Adolescents with migraine and I-CFS did not differ, although both had significantly higher scores than healthy controls ($F = 11.606$; $P < .001$).
- School absenteeism. Adolescents with both I-CFS and CDC-CFS missed significantly more days of school because of illness than migraineurs or healthy controls. Adolescents with I-CFS missed more school days than migraineurs who missed more than healthy controls (Kruskal-Wallis, $\chi^2 = 128.37$; $P < .001$).

Table 3 contains illness attribution scores of adolescents with migraine, I-CFS, and CDC-CFS, and their parents. Parents of adolescents with I-CFS had significantly lower attribution scores relating illness to possible psychological or stress factors than parents of adolescents with migraine ($F = 4.381$; $P < .05$).

DISCUSSION

Professional and lay discussion of the CFS often evokes strong debate regarding etiologic and sustaining factors of this perplexing disorder. Adolescents with CFS and their families are aware of frequent professional skepticism regarding the legitimacy of their complaints and often maintain illness beliefs that minimize any potential role of psychological distress. Despite increasing evidence that predisposing, precipitating, and sustaining factors in CFS appear to be multifactorial,[1,7,8] some physicians assume polarized positions as well. In the extreme, this professional polarization may lead either to overly extensive medical evaluation and subspecialty referral or minimal work-up and rejection of the validity of patient symptoms and purported functional disability.

In an attempt to elucidate the relationship of psychological distress as a primary or secondary factor in adolescent CFS, several studies have used comparison groups of adolescents with chronic medical conditions including cancer, cystic fibrosis, and juvenile arthritis.[19–21] The present study represents an attempt to modulate this view by comparing CFS with another chronic adolescent disorder without organic manifestation that nevertheless may be associated with marked functional disability and often can be precipitated by psychological stress. Like CFS, the pathophysiology and genetics of pediatric migraine are not fully elucidated, but it is generally held that migraine is a functional disorder of the nervous system with diagnostic validity.[22]

Our results indicate that adolescents with pro-

TABLE 1. Study Population

	N	Duration* (Months)	Age (Years)†	White (%)	Female (%)
Migraine	179	49.8 ± 36.2	13.6 ± 2.0[a]	95	60
Chronic fatigue§	97	18.8 ± 13.2	15.0 ± 1.8[a,b]	99	70
Healthy controls	32	-	13.5 ± 1.0[b]	100	56

* Analysis of variance ($P < .001$).
† Groups with the same letter differ significantly ($P < .05$).
§ Forty-one met CDC-CFS criteria; 51 did not meet criteria.
Student Newman-Keuls test posthoc analysis.

TABLE 2. Comparison of Questionnaire Scores Regarding Anxiety, Depression, and Somatization and School Days Missed Between Adolescents With Migraine Headache, Those With >6 Months of Unexplained Profound Chronic Fatigue, and Normal Controls

	Anxiety (STAIT)	Depression (CDI)	Somatization (CSI)	School Days Missed in Past 6 Months
	ANOVA $F = 7.766$ $P < .001$	ANOVA $F = 3.206$ $P < .05$	ANOVA $F = 11.606$ $P < .001$	Kruskal-Wallis $\chi^2 = 128.187$ $P < .001$
Migraine	44.9 ± 7.2[ac] ($n = 144$)	7.7 ± 7.1[a*] ($n = 179$)	23.0 ± 15.8[a] ($n = 176$)	7.2 ± 12.6[a] ($n = 178$)
Idiopathic profound chronic fatigue >6 mo (I-CFS)	40.35 ± 12.1[ab] ($n = 62$)	10.0 ± 7.8[b] ($n = 85$)	29.0 ± 15.0[b] ($n = 60$)	44.2 ± 37.9[a] ($n = 37$)
CDC 1994 CFS criteria (CDC-CFS)	43.1 ± 13.5[bd] ($n = 28$)	11.1 ± 7.9[abc] ($n = 43$)	35.0 ± 13.1[ab] ($n = 27$)	57.0 ± 37.2[a] ($n = 42$)
Healthy controls	39.1 ± 9.3[cd] ($n = 32$)	6.6 ± 6.8[c] ($n = 32$)	12.3 ± 8.1[ab] ($n = 82$)	0.52 ± 1.7[a] ($n = 82$)

ANOVA indicates analysis of variance.
* Groups with same letter differ significantly ($P < .05$).
Student Newman-Keuls test posthoc analysis.

TABLE 3. Illness Attributions in Adolescents With Migraine or Chronic Fatigue and Their Parents

Illness Attribution (0-6 Point Scale)	Migraine ($n = 161$) ANOVA	Idiopathic Chronic Fatigue >6 Months ($n = 53$) ANOVA	CDC 1994 CFS Criteria ($n = 23$) ANOVA
Psychological/stress			
Patient	3.2 ± 1.2	2.5 ± 1.3	2.7 ± 1.2
$F = .744$			
$P = .478$			
Parent	3.6 ± 1.1[a]	2.7 ± 1.7[a,b*]	3.2 ± 1.9[b]
$F = .4381$			
$P = <.05$			
Constitutional/environmental			
Patient	2.3 ± 1.0	3.2 ± 1.0	3.3 ± 1.0
$F = .846$			
$P = .433$			
Parent	2.7 ± 1.0	3.8 ± 1.0	3.8 ± 1.0
$F = .770$			
$P = .466$			

ANOVA indicates analysis of variance.
* Groups with same letter differ significantly ($P < .05$).
Student Newman-Keuls test posthoc analysis.

found unexplained chronic fatigue seen for evaluation in an academic center report more somatic symptoms and miss many more days of school as a result of their symptoms than adolescents referred for migraine. Additionally, fatigued adolescents who met CDC-CFS had higher depressive symptom scores than those with I-CFS not meeting criteria and migraineurs. Although migraineurs had higher anxiety scores than adolescents with I-CFS and controls, they were not statistically different from scores of those with CDC-CFS.

The significance of multiple somatic symptoms is difficult to interpret since they might reflect an emotional disorder,[34] overinterpretation and amplification of bodily sensations,[35] or an occult medical disorder. Profound fatigue associated with somatic symptoms has been associated with many medical disorders including chronic infection,[36] cytokine therapy,[37] disrupted sleep,[38] autoimmune disease,[39] neurologic disorder,[40] and orthostatic intolerance.[41] In addition, some research suggests that adult medical patients with comorbid anxiety or depressive disorders have significantly more medical symptoms without identified pathology and more functional impairment than those without comorbid psychological conditions.[42]

The level of school absenteeism in adolescents with chronic fatigue is remarkably higher than that reported in other pediatric chronic disease populations[43] and difficult to explain from a purely pathophysiological perspective. Although profound fatigue is a common complaint in many other chronic medical disorders in adolescence, perhaps there is some intrinsic difference in the quality or intensity of fatigue in CFS that promotes more functional disability. However, there is some evidence that adolescents with psychosocial problems miss more school than those with chronic medical conditions,[44] and those with school refusal often have increased levels of anxiety and depression.[45] It is likely that prolonged bed rest and inactivity in CFS contribute significantly to the perception of disabling fatigue and serve to perpetuate the disorder.[46] Additionally, it has been demonstrated that adult CFS patients who fear that exertion will lead to lasting physical damage and subsequently avoid activity have poor outcomes.[47] Although lack of adherence to prescribed rehabilitation programs appears to be a common clinical problem, no systematic data exist regarding the beliefs of adolescents with CFS about the potential effects of activity. Likewise, nothing is known of the sequence of events or specific symptoms that

actually lead to the decision not to attend school or the daily activities of adolescents who remain at home.

Regarding anxiety and depression, it is important to note that the mean scores reported in this study were not in the clinical range. Therefore, significant findings between groups indicate relative differences in symptomatology and not necessarily the presence of specific anxiety or depressive disorders. Nevertheless, similar to several other studies,[16,19–21] adolescents in this study who met CDC criteria for CFS showed increased internalizing symptoms. Whether the anxiety and depression scores reflect primary or secondary conditions in adolescents with chronic fatigue cannot be determined by these data. It is plausible that the presence of a disabling chronic condition could result in internalizing thoughts and emotions. Likewise, the association between primary anxiety and depressive disorders and fatigue is well established.[17]

In this study, parents of adolescents with I-CFS endorsed lower levels of psychological or stress-related illness attributions than parents of adolescents with CDC-CFS or migraine. It is not apparent why parents of adolescents with I-CFS might be more likely than those with CDC-CFS to endorse such a response. Perhaps those with CDC-CFS felt more validated with an "authentic" diagnosis and less guarded about the possibility that psychological stress might contribute to symptoms. Consistent with many current cultural explanations,[48] belief that CFS is caused by a virus or immune system dysfunction was a common response among all CFS patients and their parents. Although some reports have suggested that adult CFS patients reject psychological factors as operative in their illness, other studies have not and the literature is contradictory.[49,50] Thus, the potential role of adolescent or parental illness attributions that deny the impact of psychological factors in sustaining the disability of adolescent CFS remains to be determined.

This study conducted in the clinical setting has several methodological shortcomings. Because all patients were referred to an academic center for evaluation, selection bias may have failed to provide a sample that was representative of either migraine or chronic fatigue in the community. This illustrates the inherent difficulty of any working definition of CFS, since marked functional disability is a sine qua non for diagnosis. Despite the use of well-validated measures, self-report instruments lack validating information and may not allow full and intended description of symptomatology. Although parents and adolescents generally agreed on the number of school days missed because of illness, we averaged their estimates and did not obtain official school absenteeism data. Our attributional scale does not have published validity and may not have been an adequate tool for assessment of this complex dimension. Additionally, although we attempted to evaluate illness attributions, we did not utilize any measures that might have correlated specific attributions with either maladaptive or effective coping styles. Thus, the important question regarding the effects of attributional and coping styles that deny the impact of psychological factors on the disease process remains unanswered by this study.

Acknowledging its limitations, what conclusions might we draw from this study? First, regardless of its cause, a syndrome of profound chronic fatigue exists in adolescence that is associated with multiple somatic symptoms and greater functional disability than that seen in most other chronic medical disorders in this age group. Second, whether primary or secondary, depressive symptoms are more common in adolescents who meet CDC-CFS than in adolescent migraineurs referred for treatment in a tertiary care center.

What then are the implications for the clinician? First, because there are often findings in this curious condition that are atypical of either an organically based or a purely stress-related disorder, it is imperative to keep an open mind regarding the cause of CFS. Second, aware that many chronically fatigued adolescents and their parents feel the medical profession has categorized CFS as a purely psychosomatic condition, the clinician should perform a careful comprehensive medical and psychosocial evaluation, explore family illness attributions and beliefs, and formulate a diagnostic explanation and treatment plan that is likely to be acceptable. Regardless of cause, it appears that physical deconditioning, somatic symptoms, disrupted sleep cycles, distressing psychological thoughts, withdrawal from age-appropriate activities, and a sense of powerlessness pervade the lives of these adolescents and their concerned parents. It is prudent to recall that these exact same problems are not uncommon in adolescents with cancer or cystic fibrosis. An effective treatment program should emphasize normalization of sleep patterns, graduated incremental physical activity, appropriate pharmacological treatment of targeted symptoms, the use of cognitive behavioral techniques to increase the sense of self-efficacy, and incremental return to normal activities (particularly school).

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