ORIGINAL ARTICLE

Early Adverse Experience and Risk for Chronic Fatigue Syndrome

Results From a Population-Based Study

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Context: Chronic fatigue syndrome (CFS) is an important public health problem. The causes of CFS are unknown and effective prevention strategies remain elusive. A growing literature suggests that early adverse experience increases the risk for a range of negative health outcomes, including fatiguing illnesses. Identification of developmental risk factors for CFS is critical to inform pathophysiological research and devise targets for primary prevention.

Objective: To examine the relationship between early adverse experience and risk for CFS in a population-based sample of clinically confirmed CFS cases and nonfatigued control subjects.

Design, Setting, and Participants: A case-control study of 43 cases with current CFS and 60 nonfatigued controls identified from a general population sample of 56 146 adult residents from Wichita, Kan.

Main Outcome Measures: Self-reported childhood trauma (sexual, physical, and emotional abuse and emotional and physical neglect) and psychopathology (depression, anxiety, and posttraumatic stress disorder) by CFS status.

Results: The CFS cases reported significantly higher levels of childhood trauma and psychopathology compared with the controls. Exposure to childhood trauma was associated with a 3- to 8-fold increased risk for CFS across different trauma types. There was a graded relationship between the degree of trauma exposure and CFS risk. Childhood trauma was associated with greater CFS symptom severity and with symptoms of depression, anxiety, and posttraumatic stress disorder. The risk for CFS conveyed by childhood trauma increased with the presence of concurrent psychopathology.

Conclusions: This study provides evidence of increased levels of multiple types of childhood trauma in a population-based sample of clinically confirmed CFS cases compared with nonfatigued controls. Our results suggest that childhood trauma is an important risk factor for CFS. This risk was in part associated with altered emotional state. Studies scrutinizing the psychological and neurobiological mechanisms that translate childhood adversity into CFS risk may provide direct targets for the early prevention of CFS.

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CHRONIC FATIGUE SYNdrome (CFS) is an important public health problem that affects 400 000 to 900 000 adults in the United States.[1,2] Chronic fatigue syndrome is defined as unexplained persistent or relapsing fatigue that occurs for at least 6 months, is not relieved by rest, and causes substantial reduction in activities. The fatigue must be accompanied by at least 4 of 8 case-defining symptoms, including unusual fatigue after exertion, impaired memory or concentration, unrefreshing sleep, headaches, muscle pain, joint pain, sore throat, and tender lymph nodes.[3] Chronic fatigue syndrome is a debilitating illness that is associated with considerable personal suffering and decreased quality of life in affected individuals.[4] The average duration of the illness in cases identified from the population is 5 to 7 years, and fewer than 20% of cases have been diagnosed by a physician as having CFS.[2] A quarter of affected individuals are unemployed or receive disability, and the average household forgoes $20 000 in lost earnings and wages owing to CFS. The total economic cost of CFS in the United States is an estimated $9.1 billion per year.[5] Despite the substantial public burden of CFS, the causes and pathophysiology of CFS remain unknown, and effective prevention is elusive.

Identifying risk factors for CFS is critical to guide pathophysiological research and devise targets for prevention. Risk factors of CFS identified in prior studies include female sex, genetic disposition, certain personality traits or behavioral styles, and physical and emotional stressors.[6] Our

group[7] reported that patients with CFS (hereafter referred to as CFS patients), identified through a physician surveillance network, were significantly more likely to report histories of stressful life events, repeated infections, or surgeries than were randomly selected matched control subjects. Another study[8] reported that exposure to Hurricane Andrew triggered relapses and symptom exacerbations in CFS patients living in South Florida. The extent of individual emotional and behavioral stress response was the single and strongest predictor of the likelihood and severity of relapse and functional impairment within 4 months after the hurricane. In addition, Gulf War veterans have an increased rate of CFS that is associated with posttraumatic stress disorder (PTSD).[9,10] Our group[11] observed that self-reported chemical, emotional, and physical stressors associated with deployment were linked to the occurrence of CFS-like illness in Gulf War veterans. It thus appears that stress is a risk or a triggering factor of CFS. Stress likely interacts with other risk factors in influencing central nervous, neuroendocrine, and immune systems, resulting in functional changes that lead to fatigue and associated symptoms, such as sleep disruption, cognitive impairment, and pain.[12] Stress-induced alterations in these regulatory systems may also contribute to emotional problems, which often coincide with CFS.[13]

However, not every individual exposed to acute stress will develop CFS, and it is therefore critical to understand sources of individual differences in vulnerability to the pathogenic effects of stress. Thus, preexisting factors known to modulate the organism's ability to compensate in response to emotional or physical challenge might interfere with successful adaptation and convey vulnerability to develop CFS. Recent advances in developmental neurosciences suggest that stress early in life induces persistent changes in neural circuits implicated in the integration of emotional processing, endocrine-autonomic control, and the regulation of arousal and vigilance, resulting in increased reactivity to the environment, cognitive impairment, pain sensitivity, depression, anxiety, and altered sleep.[14-16] Several of the neurobiological and behavioral effects of early-life stress parallel features of CFS.[13] Given that CFS is frequently triggered by an acute challenge[6] and is associated with changes in regulatory outflow systems,[17] it is conceivable that adverse experience in childhood is causally associated with developing CFS, particularly in response to a challenge.

Epidemiological studies provide strong evidence that early adverse experience (eg, child abuse, neglect, and family dysfunction) is associated with a significantly increased risk for a variety of adverse health outcomes.[18-24] Evidence from community-based studies also suggests that childhood abuse is associated with elevated levels of fatigue.[25,26] However, few studies have tested the hypothesis that childhood adversity is a risk factor for CFS. In 2 clinical studies, patients with CFS more frequently reported abusive victimization[27] and more exposure to an overprotective parenting style[28] during their childhood compared with controls. Both studies recruited treatment-seeking patients from tertiary care clinics, and sampling biases of subjects with psychosocial problems cannot be excluded, particularly given that individuals with childhood adversity more frequently use health care services.[29] The only published community-based study on the relationship between childhood adversity and CFS assessed sexual and physical abuse in one question each and did not find significant associations with CFS.[30] However, chronic fatigue cases diagnosed as having a primary psychiatric disorder were treated as a separate group in this study, and rates of abuse were markedly elevated in this group. Unfortunately, these psychiatric disorders were not specified, and it remained unclear whether these disorders corresponded to those defined as exclusionary for CFS in the 1994 research case definition. In a subsequent report based on the same sample,[31] childhood abuse was found to predict fatigue and anxiety disorders, including PTSD, which are not exclusionary of CFS. In sum, the association between childhood adversity and the risk for CFS warrants further investigation. The failure to use psychometrically validated dimensional instruments to measure multiple types of childhood trauma has been a particular difficulty in previous studies of CFS.[27-30]

Since 1997, the Centers for Disease Control and Prevention (CDC) have conducted a population-based surveillance study of CFS in Wichita, Kan.[2] The present study was conducted as part of a larger clinical evaluation for CFS in individuals identified in this survey as described elsewhere.[32] Our aims were to assess multiple types of childhood adversity and psychopathology in CFS cases vs controls and to estimate risk of CFS associated with childhood stress. We further examined associations between childhood trauma and CFS severity and considered the relationship between psychopathology and CFS after childhood stress. Our goal was to provide impetus for the development of future hypothesis-driven studies that further scrutinize the association between childhood stress and CFS, including identification of the psychobiological mechanisms that mediate this relationship.

METHODS

SUBJECTS

This study adhered to the human experimentation guidelines of the Helsinki Declaration and was approved by the institutional review boards of the CDC and Emory University, Atlanta. All subjects gave informed consent. The study enrolled subjects who had participated from 1997 through 2000 in the Wichita CFS Surveillance Study.[2,32] A random-digit-dialing telephone survey was used to screen 56 146 adult residents, 18 to 69 years of age, living in Wichita in 1997. Based on the screening survey, a total of 5295 persons with fatigue of 1 month's duration or longer were identified. These persons were contacted to participate in a detailed telephone interview, and 3528 agreed to participate, along with a subset of 3634 nonfatigued (NF) persons. The detailed interview was used to identify cases with fatigue for 6 months or longer, who did not feel better after rest, who did not report any fatigue-associated medical or psychiatric conditions, and who reported at least 4 of the 8 CFS case-

defining symptoms (CFS-like cases). A total of 555 CFS-like cases were identified and invited to participate in a clinical examination to confirm CFS. Of those, 299 agreed to participate. Participants and nonparticipants did not differ in age, sex, income, and duration of illness.[2] Randomly selected NF persons matched to CFS-like cases based on age, sex, race, and body mass index (calculated as weight in kilograms divided by height in meters squared) were also invited to undergo the same tests to confirm their status and rule out other conditions. All persons who participated in the baseline clinical evaluation and had no permanent exclusion were invited to complete follow-up detailed telephone interviews in 1998, 1999, and 2000, along with persons whose status had changed over time, making them eligible for a detailed interview in subsequent years. Among eligible persons, interviews were conducted with 4228 in 1998, 3980 in 1999, and 3474 in 2000, representing 69%, 65%, and 56% of the original sample, respectively. Among eligible subjects who completed detailed interviews, 67% completed clinical evaluations at 12 months, 70% at 24 months, and 68% at 36 months of follow-up. The study yielded information on prevalence, incidence, and clinical course of CFS as described elsewhere.[2,33]

In 2002, all subjects ever having met criteria for clinically confirmed CFS in the surveillance study were invited to participate in the current study. Thus, we invited the 70 people who were classified as having CFS at least once during the 4-year surveillance study to participate in the current study. Of those, 58 (83%) agreed to participate. We randomly selected an equal number of surveillance participants who had unexplained fatigue for 6 months or longer at least once during the 4-year surveillance study but who did not meet full CFS criteria in the past, and 59 (84%) were enrolled. An equal number of NF controls matched to lifetime CFS cases on sex, age, race, and body mass index were randomly selected. All subjects were admitted to a Wichita hospital research unit for 2 days. On admission, subjects underwent reevaluation in terms of current CFS symptoms and exclusionary conditions. At the clinic, 43 current CFS cases were confirmed. These consisted of past CFS cases who still had CFS, as well as new-onset CFS cases derived from chronically fatigued persons who previously did not meet CFS criteria. Persons with insufficient symptoms of fatigue at the time of the clinic visit were not included in this report. We included the 60 controls who remained eligible and were NF at the time of the clinic evaluation. Because invited controls were individually matched to cases with a CFS diagnosis in the past 4 years and subjects were reclassified according to current diagnostic status, individual matching could not be maintained. Owing to the small sample size, we included all available CFS cases and controls in this report. The groups were demographically comparable. The mean age of the sample was 50.5 years and mean body mass index was 29.2. The sample included 19 men (18%) and 7 nonwhite individuals (7%).[32]

ASSESSMENT AND CLASSIFICATION OF CFS

To identify exclusionary medical conditions,[3,34] subjects provided a standardized medical history and a review of current medications, underwent a standardized physical examination, and provided blood and urine samples for routine analysis. Licensed and specifically trained psychiatric interviewers conducted the Diagnostic Interview Schedule for *DSM-IV*[35] to diagnose current Axis I psychiatric disorders. Exclusionary psychiatric illnesses were current or lifetime bipolar disorder, psychosis, substance abuse within 2 years, and eating disorders within 5 years.[3,34]

Subjects were diagnosed as having CFS if they met criteria of the 1994 case definition.[3] Criteria of the 1994 case definition were applied following recommendations of the International Chronic Fatigue Syndrome Study Group regarding measurement of the major illness domains.[34] Subjects completed a series of well-validated and reliable rating scales to assess symptoms of CFS and functioning, including the 36-Item Short-Form Health Survey,[36] the Multidimensional Fatigue Inventory,[37] and the CDC Symptom Inventory.[38] The 36-Item Short-Form Health Survey assesses function in different areas, including general health, physical functioning, social functioning, mental health, and limitations in role activities because of physical or emotional health problems. The Multidimensional Fatigue Inventory quantifies symptoms of fatigue, including general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity. The CDC Symptom Inventory measures the occurrence, intensity, and frequency of 19 symptoms related to CFS, resulting in a multiplied total score. An additional case definition score considers the 8 symptoms included in the case definition.[3] Classification as a current CFS case was based on cutoff scores in these rating scales with respect to the 3 dimensions of CFS specified in the case definition, ie, impairment, fatigue, and accompanying symptoms.[32] Subjects meeting these criteria at the time of the study were classified as CFS cases (n=43). Subjects with no evidence of fatigue in the Multidimensional Fatigue Inventory were classified as NF controls (n=60). By definition, case and control groups differed on all scales (all $P<.001$).[32]

ASSESSMENT OF EARLY ADVERSE EXPERIENCE

We assessed childhood adverse experience using the short form of the Childhood Trauma Questionnaire (CTQ).[39] This self-report questionnaire measures 5 categories of childhood trauma experience in separate subscales, including emotional, physical, and sexual abuse and emotional and physical neglect. Each subscale is measured in 5 items. Examples of questions are: "People in my family called me stupid, lazy, or ugly" (emotional abuse item); "People in my family hit me so hard that it left bruises or marks" (physical abuse item); "Someone threatened to hurt me or tell lies about me unless I did something sexual with them" (sexual abuse item); "I knew there was someone to take care of me and protect me" (emotional neglect inverse item); and "There was someone to take me to the doctor if I needed it" (physical neglect inverse item). Subjects rate each item on a 5-point Likert scale from 1 (never true) through 5 (very often true). Such Likert-type items create dimensional scales providing quantitative scores that have enhanced reliability and maximized statistical power.[39] In addition, cutoff scores for none-to-low, low-to-moderate, moderate-to-severe, and severe-to-extreme exposure are provided for each scale. We used the moderate-to-severe cutoff scores for each subscale to classify subjects as positive for a history of childhood trauma category. The cutoff scores are 13 or higher for emotional abuse, 10 or higher for physical abuse, 8 or higher for sexual abuse, 15 or higher for emotional neglect, and 10 or higher for physical neglect.[40] Being identified as positive for a category corresponds with endorsing a substantive number of experiences as often true. The CTQ has been extensively tested for psychometric properties. The questionnaire demonstrated good internal consistency (0.63-0.95) and criterion-related validity (0.50-0.75) in clinical and community samples. Convergent reliability with therapist assessments of abuse histories is high. Good specificity and sensitivity of cutoff scores to classify maltreated subjects has been reported as well.[39,40]

Table 1. Mean CTQ Scores in CFS Cases and NF Controls Identified From the General Population in Wichita, Kan

CTQ Score	Mean Score (95% CI)		Statistic, $F_{1,102}$	*P* Value
	CFS (n = 43)	NF (n = 60)		
Emotional abuse	10.6 (8.9-12.4)	7.7 (6.8-8.5)	10.8	.001
Physical abuse	8.0 (6.8-9.2)	6.5 (6.0-6.9)	6.85	.01
Sexual abuse	8.0 (6.5-9.6)	5.7 (5.1-6.3)	9.89	.002
Emotional neglect	12.1 (10.3-13.9)	8.1 (7.2-9.0)	19.1	<.001
Physical neglect	7.1 (6.3-8.0)	5.9 (5.5-6.3)	7.82	.006
Total score	45.9 (39.9-51.9)	33.9 (31.5-36.3)	17.3	<.001

Abbreviations: CFS, chronic fatigue syndrome; CI, confidence interval; CTQ, Childhood Trauma Questionnaire; NF, nonfatigued.

ASSESSMENT OF PSYCHOPATHOLOGY

Lifetime and current *DSM-IV* Axis I psychiatric disorders were assessed using the Diagnostic Interview Schedule for *DSM-IV*.[35] We diagnosed psychiatric disorders that are not exclusionary for CFS,[3,34] including nonmelancholic major depression, anxiety disorders, and PTSD. We measured current symptom severity using psychometrically validated dimensional rating scales. Depression severity was assessed using the Self-rating Depression Scale.[41] The scale provides an index score and categories reflecting no (<50), mild (50-59), moderate (60-69), and severe (≥70) depression. Anxiety was assessed using the State-Trait Anxiety Inventory,[42] which provides a continuous score and percentile population norms. The Davidson PTSD Scale[43] was used to measure frequency and severity of PTSD symptoms in the following 3 clusters: intrusion, avoidance, and hyperarousal. A total score of 40 or higher indicates clinically relevant PTSD. Subjects rated this scale in relation to their most stressful or traumatic life event.

STATISTICAL ANALYSIS

We first compared cases and controls regarding CTQ scores. We used multivariate analysis of variance to compare groups across CTQ subscales while considering correlations between subscales. A significant omnibus effect rejects the null hypothesis and allows for comparison of the groups on subscales. To determine which of the 5 CTQ subscales were most effective in discriminating between CFS cases and NF controls, we used nonparametric canonical discriminant analysis. A quadratic discriminant function was applied to the 5 CTQ subscales to compute standardized canonical coefficients and an eigenvalue.

We next created groups with and without any exposure to childhood trauma as well as multiple exposure categories based on moderate-to-severe CTQ cutoff scores[40] and compared distributions using χ^2 and Mann-Whitney tests. We then used unconditional logistic regression modeling to compute odds ratios and 95% confidence intervals as estimates of the relative risk of having CFS as a function of these categorical predictor variables, adjusting for age, sex, and race. Graded associations between exposure level and CFS risk were explored by entering ordinal (number of exposure categories) and continuous (CTQ total score) predictor variables in logistic regression models. To examine associations between trauma exposure and CFS severity, we compared mean CDC Symptom Inventory scores between CFS cases with and without childhood trauma using multivariate analysis of variance.

To address the role of psychopathology, we compared groups in terms of psychiatric status and computed Pearson correlation coefficients between CTQ and psychiatric symptom scores. To examine the effect of psychopathology in moderating the risk of CFS related to childhood trauma exposure, we stratified the CFS group on the basis of low vs high levels of psychopathology. We then used multinominal logistic regression analysis to estimate risk of belonging to either case group as a function of childhood trauma. The level of significance was set at $P<.05$ for all tests.

RESULTS

Subjects with CFS had significantly higher overall childhood trauma scores than controls ($F_{5,97}=4.099$; $P=.002$; **Table 1**). Mean scores were in the moderate range for each trauma type in the CFS group, except for the sexual abuse score, which reached the moderate-to-severe cutoff. Because scores for the 5 individual CTQ subscales were highly correlated, we applied a discriminant analysis to the 5 CTQ subscales. After mutual adjustment for the effects of all subscales on each other, the emotional neglect and sexual abuse subscales were the most effective for discriminating CFS and NF groups (standardized canonical coefficients of 1.08 and 0.38, respectively).

When cutoff scores for moderate-to-severe trauma exposure were applied,[40] more CFS cases had scores above the cutoff compared with NF controls in each trauma category (all, $P<.05$). Twenty-seven CFS cases (63%) met at least 1 cutoff score for any childhood trauma type compared with 22 controls (37%) ($\chi^2_1=6.85$; $P=.009$). The CFS cases more frequently experienced multiple types of trauma than controls ($z=3.21$; $P=.001$). Exposure to childhood trauma was associated with 3- to 8-fold increased risk of CFS, depending on the type of trauma (**Table 2**). There was a graded relationship between the degree of exposure and the risk for CFS. The risk of having CFS increased by 77% (95% confidence interval, 1.28-2.45; $P<.001$) with each increase in the number of exposure categories and by 6% (95% confidence interval, 1.03-1.09; $P<.001$) with each point increase in CTQ total score. The Hosmer-Lemeshow statistic for assessing model fit was significant for the linear associations between the number of exposure categories ($P=.005$) or the CTQ total score ($P=.002$) and CFS risk. Exposure to childhood trauma was also associated with CFS severity. The CFS cases with childhood trauma had higher CDC Symptom Inventory scores ($F_{5,37}=3.72$; $P=.008$) compared with CFS cases without childhood trauma (**Figure**).

Table 2. Logistic Regression Models Estimating the Likelihood of Having CFS Relative to Childhood Trauma Exposure in CFS Cases and NF Controls Identified From the General Population in Wichita, Kan*

Predictor	No. (%) Above the Cutoff: CFS (n = 43)	No. (%) Above the Cutoff: NF (n = 60)	OR (95% CI)	*P* Value†
Any category				
Yes	27 (63)	22 (37)	3.35 (1.43-7.88)	.006
No	16 (37)	38 (63)	1.00	
Emotional abuse				
Yes	18 (42)	12 (20)	2.87 (1.19-6.70)	.02
No	25 (58)	48 (80)	1.00	
Physical abuse				
Yes	12 (28)	6 (10)	4.28 (1.35-13.60)	.01
No	31 (72)	54 (90)	1.00	
Sexual abuse				
Yes	12 (28)	3 (5)	8.00 (2.02-31.70)	.003
No	31 (72)	57 (95)	1.00	
Emotional neglect				
Yes	26 (60)	17 (28)	4.58 (1.90-11.00)	.001
No	17 (40)	43 (72)	1.00	
Physical neglect				
Yes	7 (16)	2 (3)	5.90 (1.15-30.30)	.03
No	36 (84)	58 (97)	1.00	

Abbreviations: CFS, chronic fatigue syndrome; CI, confidence interval; NF, nonfatigued; OR, odds ratio.

*Exposure to childhood trauma was based on the following Childhood Trauma Questionnaire cutoff scores for moderate-to-severe trauma[40]: emotional abuse, ≥13; physical abuse, ≥10; sexual abuse, ≥8; emotional neglect, ≥15; and physical neglect, ≥10. All models were adjusted for age, sex, and race.

†Based on Wald χ^2 tests.

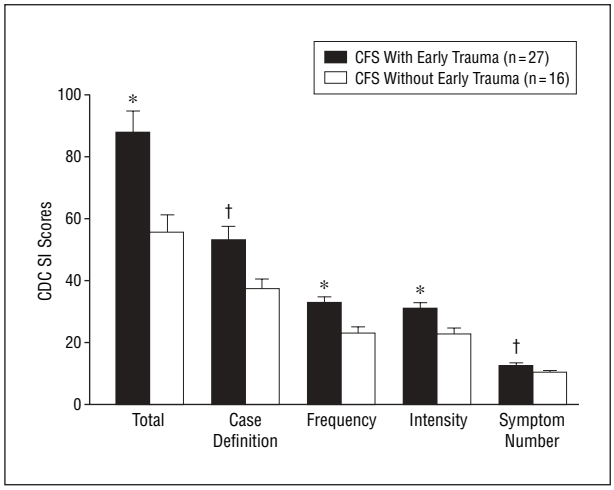

Figure. Childhood trauma and the severity of chronic fatigue syndrome (CFS). Mean Centers for Disease Control and Prevention Symptom Inventory (CDC SI) scores are shown as a function of exposure to childhood trauma in cases with CFS. Error bars reflect standard error of the mean. *$P<.01$. †$P<.05$.

Subjects with CFS reported more psychopathology than did NF controls (**Table 3**). Relative to controls, a greater proportion of CFS cases had more severe depression ($z=6.46$; $P<.001$). Significantly more CFS cases had high state anxiety (≥75th percentile) and met the cutoff score for clinically significant PTSD compared with controls. Clinically relevant symptoms of depression and PTSD were noted only in CFS cases and not in controls. In the Diagnostic Interview Schedule for *DSM-IV*, a greater proportion of CFS cases than controls were diagnosed as having current (7 cases [16%] vs 1 control [2%]; $P=.009$) and lifetime (13 cases [30%] vs 5 controls [8%]; $P=.004$) anxiety disorders, including PTSD, whereas there was only a trend for increased lifetime major depression.

There were significant correlations between the overall CTQ scores and the symptom scores for depression, anxiety, and PTSD (all $P<.001$). These correlations remained unchanged when analysis was restricted to CTQ subscales for emotional neglect and sexual abuse. To estimate the effects of current psychopathology on CFS risk related to emotional neglect and/or sexual abuse, we stratified the CFS group into those with low vs high levels of psychopathology. Multinominal logistic regression models showed that the risk for CFS as a function of exposure varied with levels of psychopathology (**Table 4**). Childhood trauma was associated with an elevated risk for CFS even in the presence of low levels of psychopathology. Risk for CFS increased further in the presence of high levels of psychopathology.

COMMENT

We explored associations between CFS and multiple forms of childhood trauma and psychopathology using dimensional rating scales in clinically confirmed CFS cases compared with controls identified from the population. Childhood trauma was an important risk factor for CFS and the association demonstrated a graded response. Childhood trauma was associated with CFS severity and symptoms of depression, anxiety, and PTSD. Risk of CFS as a function of childhood trauma increased with altered emotional state. Our findings are in agreement with previous studies in tertiary care patients that found an association between CFS and victimization starting in childhood[27] or exposure to adverse parenting.[28] We also confirm and extend findings suggesting that childhood abuse predicts PTSD symptoms in individuals with chronic fatigue.[31] Our results are concordant with the findings from community surveys reporting elevated rates of fatigue in women with childhood abuse experience[25,26] and with studies that identified childhood trauma as a risk factor for functional somatic syndromes in general.[44-49] We also confirmed the well-known relationship between childhood trauma and depression and anxiety,[50] which in turn are associated with functional somatic disorders.[13] In sum, it appears that CFS is part of a spectrum of disorders that are associated with childhood adversity. In adulthood, these disorders frequently manifest or worsen in relation to an acute stress or challenge.[6] High emotional reactivity is a risk factor for all of these disorders.[6,51-53] Thus, enhanced stress and mood reactivity can be assumed to be a central feature common to this spectrum of disorders. In fact, these disorders might reflect the brain's inability to adapt or compen-

Table 3. Mean Scores and Frequency of Severity Categories in the Self-rating Depression Scale, State Anxiety Inventory, and Davidson PTSD Scale in CFS Cases and NF Controls Identified From the General Population in Wichita, Kan

Scale	CFS (n = 43)	NF (n = 60)	Statistic	*P* Value
Self-rating Depression Scale				
Mean score (95% CI)	54.6 (52.2-57.1)	37.6 (33.8-37.1)	$t = 11.09$	<.001
No. (%) of subjects				
No depression (score, <50)	13 (30)	54 (90)	$z = 6.46$	<.001
Mild depression (score, 50-59)	15 (35)	6 (10)		
Moderate depression (score, 60-69)	13 (30)	0		
Severe depression (score, ≥70)	2 (5)	0		
State Anxiety Inventory				
Mean score (95% CI)	37.3 (34.1-40.6)	26.6 (24.9-28.2)	$t = 6.44$	<.001
No. (%) of subjects ≥75th percentile (score, ≥40)	17 (40)	1 (2)	Fisher exact	<.001
Davidson PTSD Scale*				
Mean intrusion score (95% CI)	6.6 (4.3-8.9)	1.6 (0.8-2.3)	$F_{1,95} = 21.66$	<.001
Mean avoidance score (95% CI)	8.0 (5.0-10.9)	0.7 (0.3-1.2)	$F_{1,95} = 31.96$	<.001
Mean hyperarousal score (95% CI)	13.7 (11.1-16.4)	3.2 (2.1-4.1)	$F_{1,95} = 71.92$	<.001
Mean total score (95% CI)	28.3 (21.2-35.5)	5.4 (3.6-7.1)	$F_{1,95} = 51.59$	<.001
No. (%) likely PTSD cases (score, ≥40)	11 (29)	0	Fisher exact	<.001

Abbreviations: CFS, chronic fatigue syndrome; CI, confidence interval; NF, nonfatigued; PTSD, posttraumatic stress disorder.
*Two CFS cases and 5 NF controls did not complete the Davidson PTSD scale.

Table 4. Multinominal Logistic Regression Models Estimating the Likelihood of Having CFS with High vs Low Levels of Psychopathology Compared With NF Status as a Function of Childhood Trauma Exposure in Subjects Identified From the General Population in Wichita, Kan*

Predicted Outcome Variable	Exposure	No. (%) of Subjects	OR (95% CI)	*P* Value†
CFS + high-level depression (n = 15)	Yes	11 (73)	8.07 (2.11-30.80)	.002
	No	4 (27)	1.00	
CFS + low-level depression (n = 28)	Yes	16 (57)	3.52 (1.33-9.33)	.01
	No	12 (43)	1.00	
NF (n = 60)	Yes	18 (30)		
	No	42 (70)		
CFS + high-level anxiety (n = 17)	Yes	12 (71)	7.77 (2.19-27.40)	.001
	No	5 (29)	1.00	
CFS + low-level anxiety (n = 26)	Yes	15 (58)	3.39 (1.25-9.19)	.02
	No	11 (42)	1.00	
NF (n = 60)	Yes	18 (30)		
	No	42 (70)		
CFS + high-level PTSD (n = 11)‡	Yes	7 (64)	6.53 (1.44-29.70)	.02
	No	4 (36)	1.00	
CFS + low-level PTSD (n = 30)‡	Yes	18 (60)	3.73 (1.41-9.82)	.008
	No	12 (40)	1.00	
NF (n = 55)‡	Yes	17 (31)		
	No	38 (69)		

Abbreviations: CFS, chronic fatigue syndrome; CI, confidence interval; NF, nonfatigued; OR, odds ratio; PTSD, posttraumatic stress disorder.
*Exposure to childhood trauma is based on Childhood Trauma Questionnaire cutoff scores for moderate-to-severe emotional neglect and/or sexual abuse.[40] Psychopathology groups are based on the cutoff scores given in Table 3 (moderate cutoff for depression). All logistic regression models are adjusted for age, sex, and race.
†Based on Wald χ^2 testing.
‡Two CFS cases and 5 NF subjects did not complete the Davidson PTSD Scale.

sate in response to challenge, leading toward maladaptive responses and ultimately disease.

As we noted, stress early in life, during critical periods of heightened brain plasticity, permanently affects brain regions involved in cognitive-emotional processing and control of regulatory outflow systems (eg, the endocrine, autonomic, and immune systems). Behavioral and physiological effects of early stress in animal models are similar to symptoms of CFS. For example, adverse rearing conditions in nonhuman primates induce decreased basal cortisol secretion.[54,55] Such hypocortisolism has also been described for patients with CFS,[17] other functional somatic syndromes, and PTSD.[13,56] Low cortisol levels might lead to disinhibition of immune mediators and central-autonomic stress responses that in turn could evolve into fatigue, pain,

cognitive impairment, and emotional symptoms.[13] Mild adrenal dysfunction and increased circulating cytokines have been reported for adult women with histories of childhood abuse.[50] In sum, childhood adversity appears to alter the same regulatory systems that convey vulnerability to stress and that have been implicated in the pathophysiology of CFS.

However, early-life stress does not always lead to CFS, and resiliency factors must be considered. It is likely that certain dispositional factors, ie, genes and sex, moderate the relationship between early-life stress and CFS, possibly by influencing the brain's response to stress. On the other hand, our results also clearly demonstrate that not all CFS cases have a history of childhood trauma. We also found that childhood trauma was related to clinical features of CFS. Thus, there may be important subtypes of CFS that differ in causality and disease profiles. Although early stress and PTSD have been related to profound neuroendocrine changes that are similar to those in CFS,[13] surprisingly, these factors have not been controlled for in previous neuroendocrine studies of CFS, which might have contributed to inconsistent findings. Consideration of childhood experience might also have important implications for therapeutic decisions in CFS. For example, patients with chronic forms of depression[57] or functional gastrointestinal tract disorders[58] are differentially responsive to psychotherapy vs pharmacotherapy, depending on the presence of childhood adverse experiences. Childhood trauma may thus be a predictor of response to specific treatments in CFS, and therapeutic trials should stratify subjects by childhood exposures.

There are several important limitations of the present study. First, the sample size was small. However, the sample consisted of current CFS cases who were identified through a 4-year surveillance study of the population in Wichita, and 83% of cases ever identified as having CFS in the survey agreed to participate. Controls were identified from the same population. Thus, results can be extrapolated and are not restricted to a clinically referred group. However, we cannot exclude the possibility that CFS cases with childhood trauma were more likely to participate in the survey than were CFS cases without childhood trauma or controls with childhood trauma. A second important limitation is reliance on retrospective and uncorroborated self-reports of childhood experiences. Problems concerning the credibility of self-reports of childhood trauma include simple forgetting, nonawareness, nondisclosure, and reporting biases due to mood states.[59] Moreover, declarative biographical memory before the age of 5 years is sparse because the hippocampus is not fully developed. Early trauma itself leads to hippocampal damage, which might impair recall of childhood experiences.[60] However, a recent meta-analysis of studies using external corroboration of self-reports revealed that false-negative reports are more frequent than false-positive ones, leading to downward biases in estimated associations between early adversity and outcome variables. The use of validated psychometric instruments and focus on moderate-to-severe early trauma increased validity of self-reports.[59] It should be noted that rates of moderate-to-severe childhood trauma in our control group are comparable to rates reported in other studies.[21-25] However, we cannot exclude that subjects with CFS have increased preexisting sensitivity to even minor adverse events relative to controls that resulted in differential reporting of trauma. A third limitation concerns the types of trauma we measured. We focused on familial childhood trauma and did not consider occurrences outside the family or other types of events such as childhood illnesses. We also did not differentiate between contact sexual abuse and noncontact harassment. Finally, we did not consider effects of adulthood traumas and life stresses that might mediate the relationship between childhood adversity and CFS. Individuals with early adverse experience more frequently experience adulthood stresses and, moreover, are sensitized to the effects of such stressors.[50] Owing to the cross-sectional design, we cannot determine whether psychopathology preceded early adversity, mediated between early adversity and CFS, or more frequently occurred secondary to CFS in cases with early adversity.

CONCLUSIONS

Results of this exploratory study should be considered as preliminary. Nevertheless, our observations lend support for the hypothesis that CFS represents a disorder of adaptation that is promoted by early environmental insults, leading to failure to compensate in response to challenge. We hope our results will serve as an impetus for generating more specific hypotheses and developing future studies designed to scrutinize the relationship between childhood adversity and CFS. Longitudinal studies are needed to provide information on the causal relationship between childhood trauma and CFS and to systematically evaluate developmental trajectories, as well as mediators and moderators of this relationship. Mechanistic studies should identify specific neurobiological pathways that translate early adverse experience into CFS. The impact of childhood trauma on the clinical course of CFS and response to treatment should be evaluated. Such studies, taken together, have the potential to elucidate the pathophysiology, identify subtypes, and devise strategies for preventing and treating CFS. Integrating our findings with results from developmental neuroscience emphasizes the need to revise prevailing dichotomous approaches that differentiate between psychological and biological contributors to CFS.

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