ORIGINAL ARTICLE

Childhood Trauma and Risk for Chronic Fatigue Syndrome

Association With Neuroendocrine Dysfunction

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Context: Childhood trauma appears to be a potent risk factor for chronic fatigue syndrome (CFS). Evidence from developmental neuroscience suggests that early experience programs the development of regulatory systems that are implicated in the pathophysiology of CFS, including the hypothalamic-pituitary-adrenal axis. However, the contribution of childhood trauma to neuroendocrine dysfunction in CFS remains obscure.

Objectives: To replicate findings on the relationship between childhood trauma and risk for CFS and to evaluate the association between childhood trauma and neuroendocrine dysfunction in CFS.

Design, Setting, and Participants: A case-control study of 113 persons with CFS and 124 well control subjects identified from a general population sample of 19 381 adult residents of Georgia.

Main Outcome Measures: Self-reported childhood trauma (sexual, physical, and emotional abuse; emotional and physical neglect), psychopathology (depression, anxiety, and posttraumatic stress disorder), and salivary cortisol response to awakening.

Results: Individuals with CFS reported significantly higher levels of childhood trauma and psychopathological symptoms than control subjects. Exposure to childhood trauma was associated with a 6-fold increased risk of CFS. Sexual abuse, emotional abuse, and emotional neglect were most effective in discriminating CFS cases from controls. There was a graded relationship between exposure level and CFS risk. The risk of CFS conveyed by childhood trauma further increased with the presence of posttraumatic stress disorder symptoms. Only individuals with CFS and with childhood trauma exposure, but not individuals with CFS without exposure, exhibited decreased salivary cortisol concentrations after awakening compared with control subjects.

Conclusions: Our results confirm childhood trauma as an important risk factor of CFS. In addition, neuroendocrine dysfunction, a hallmark feature of CFS, appears to be associated with childhood trauma. This possibly reflects a biological correlate of vulnerability due to early developmental insults. Our findings are critical to inform pathophysiological research and to devise targets for the prevention of CFS.

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CHRONIC FATIGUE SYNdrome (CFS) affects up to 2.5% of the US adult population,[1-3] with an estimated total economic loss of $9.1 billion per year.[4] 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 to devise targets for prevention. Risk factors of CFS identified in prior studies include female gender, genetic disposition, and certain personality traits or behavioral styles.[5] Moreover, physical and emotional stressors are risk or triggering factors of CFS.[5] Stress in interaction with other risk factors likely triggers CFS symptoms through its effects on 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.[6] However, obviously not every individual exposed to a stressor goes on to develop CFS, and it is therefore of critical importance to understand sources of individual differences in vulnerability to the pathogenic effects of stress.

We previously suggested that early adverse experience such as childhood abuse, neglect, and loss might be a predisposing factor that interferes with successful adaptation to stress, thereby conveying risk to develop CFS.[7] This hypothesis was based on evidence from developmental neurosciences suggesting that stress early in life within a genetic window of vulnerability

permanently programs the organism's responsiveness to subsequent stress throughout the lifespan. These long-term consequences of early-life stress occur through direct effects on brain circuits implicated in the mediation of cognitive-emotional regulation, vigilance, arousal, and the integration of endocrine, autonomic, and immune regulatory systems.[8-10] Of note, similar changes in these circuits and regulatory outflow systems have been implicated in the pathophysiology of CFS.[11,12] It is therefore conceivable that adverse experience in childhood is causally associated with developing CFS, particularly in response to challenge.

In support of this line of reasoning, we recently reported preliminary results from a population-based study of CFS in Wichita, Kansas, suggesting that childhood trauma is an important risk factor for CFS.[7] Our results confirmed and extended observations in tertiary clinical samples.[13,14] However, these previous studies failed to consider psychobiological mechanisms that might mediate the relationship between early adversity and CFS risk.

A primary candidate in investigating the link between childhood trauma and CFS risk is the hypothalamic-pituitary-adrenal (HPA) axis, which constitutes the organism's main neuroendocrine stress response system. Activation of the HPA axis results in the synthesis and secretion of glucocorticoids from the adrenal cortex. Glucocorticoids exert multiple metabolic, behavioral, and immune-regulatory effects that help the organism adapt to challenge. Insufficient glucocorticoid signaling has been associated with increased immune activation and inflammatory responses, potentially promoting symptoms of fatigue and pain.[11,15] Dysfunction of the HPA axis characterized by lower-than-normal cortisol secretion is one of the hallmark biological features of CFS.[11,12] Of note, similar hypocortisolism has also been observed in animal models of early-life stress[16,17] and in adults with childhood adverse experience.[18,19] Hypocortisolism is also a prominent feature of posttraumatic stress disorder (PTSD),[20] which often coincides with CFS.[7] However, despite the obvious overlap of the effects of childhood trauma with findings in CFS, the contribution of childhood adversity to neurobiological findings in CFS remains obscure.

In this study, we therefore sought to replicate our previous preliminary results on the association between childhood trauma and CFS risk in an independent population-based study of CFS in metropolitan, urban, and rural regions of Georgia and to extend our previous findings by considering the contribution of childhood trauma to neuroendocrine dysfunction in CFS. We hypothesized that childhood trauma would be associated with increased CFS risk and that hypocortisolism in CFS would be associated with early adverse experience, reflecting a biological marker of developmental risk rather than a correlate of the disorder itself.

METHODS

SUBJECTS

This study adhered to human experimentation guidelines of the Declaration of Helsinki and was approved by the Centers for Disease Control and Prevention (CDC) and Emory University institutional review boards. All of the subjects gave informed consent. This study was part of a larger population-based survey of CFS in Georgia conducted between September 23, 2004, and July 30, 2005.[3] A random-digit-dialing telephone survey was used to screen 19 381 adult residents (96.4% response) aged 18 to 59 years in Georgia. The screening survey identified 3425 persons with fatigue for 1 month or longer, 5122 persons who were unwell for 1 month or longer but were not fatigued, and 10 834 well persons. The next survey step encompassed a detailed telephone interview. Of those identified as fatigued, 2438 (71.2%) completed the detailed telephone interview. We randomly selected 2134 persons identified as unwell but not fatigued, of whom 1429 (67.0%) completed the detailed telephone interview. We also randomly selected 3113 well persons, and 1756 (56.4%) completed the detailed interview. The detailed interview identified persons who had fatigue for 6 months or longer, were not feeling better after rest, did not report any fatigue-associated medical or psychiatric conditions, and reported at least 4 of the 8 CFS case-defining symptoms (CFS-like). A total of 469 individuals with CFS-like illness without self-reported medical or psychiatric exclusions were identified and invited to participate in a clinical examination to confirm CFS, and 292 of these individuals (62.3%) agreed to participate. Participants and nonparticipants did not differ in age, sex, income, and duration of illness. Based on random selection, 505 chronically unwell persons with or without fatigue and 641 well or not chronically unwell persons, matched to CFS-like cases by age (±3 years), sex, race/ethnicity, and geographic strata, were also invited to undergo the same clinical examination to confirm their status and rule out other conditions. During the clinical evaluation, 113 cases of CFS were confirmed, 264 participants had an unexplained illness, and 124 persons were classified as well. This article focuses on the 113 individuals with CFS and 124 well persons (control subjects). These groups were demographically comparable. The mean age of the sample was 44 years. Among the sample, 21.9% were male, 24.5% were nonwhite, and 3.8% were Hispanic (for details, see the article by Reeves et al[3]).

ASSESSMENT AND CLASSIFICATION OF CFS

To identify exclusionary medical and psychiatric conditions,[21,22] subjects provided a standardized medical history and a review of current medications, underwent a standardized physical examination, and provided blood and urine for routine analysis. Licensed and specifically trained psychiatric interviewers conducted the Structured Clinical Interview for *DSM-IV* to diagnose Axis I psychiatric disorders.[23] Exclusionary psychiatric illnesses were current or lifetime bipolar disorder, psychosis, substance abuse within 2 years, and eating disorders within 5 years.[21,22]

Subjects were diagnosed with CFS if they met criteria of the 1994 case definition[21] as applied following recommendations of the International Chronic Fatigue Syndrome Study Group regarding measurement of the major illness domains.[22] Subjects completed a series of rating scales to assess symptoms of CFS and functioning, including the 36-Item Short Form Health Survey,[24] the Multidimensional Fatigue Inventory,[25] and the CDC Symptom Inventory.[26] 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.[3] Subjects meeting these criteria at the time of the study were classified as having CFS (n=113). Subjects who met no criteria were classified as well (n=124). By definition, case and control groups differed on all scales (all $P < .001$) (details in the article by Reeves et al[3]).

ASSESSMENT OF EARLY ADVERSE EXPERIENCE

We assessed childhood adverse experience using the Short Form of the Childhood Trauma Questionnaire (CTQ).[27] The CTQ is a self-report questionnaire that measures 5 categories of childhood trauma experience, including emotional, physical, and sexual abuse as well as emotional and physical neglect. Each subscale is measured in 5 items rated 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.[27] 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 in that category. 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.[28] The CTQ has good internal consistency (α=0.63-0.95) and criterion-related validity (r=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 have been reported as well.[27,28]

ASSESSMENT OF PSYCHOPATHOLOGY

Lifetime and current *DSM-IV* Axis I psychiatric disorders were assessed with the Structured Clinical Interview for *DSM-IV*.[23] Depression severity was assessed using the Self-Rating Depression Scale.[29] 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 Anxiety Inventory.[30] We computed a 75th-percentile cutoff score based on the entire sample to classify subjects as having high (≥39) vs low (<39) state anxiety. The Davidson PTSD Scale[31] was used to measure frequency and severity of PTSD symptoms in 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. Subjects who could not report any major stressful or traumatic life event did not complete the PTSD scale.

NEUROENDOCRINE ASSESSMENT

To assess HPA axis function, we measured salivary cortisol responses to awakening on a regular workday within 3 days of the clinic visit. Cortisol secretion follows a distinct circadian pattern with high levels in the morning and lower levels in the evening and has a steep increase occurring within the first 30 minutes after awakening.[32] Measurement of cortisol in saliva provides an economical and noninvasive method to reliably assess circulating free cortisol levels.[33] The salivary cortisol response to awakening has received considerable scientific attention[34,35] and has been shown to be sensitive to detect HPA axis dysregulation related to stress and disease, including CFS[36-38] and early adverse experience.[39,40] Subjects received salivette collection devices (Sarstedt Inc, Newton, North Carolina) and written instructions by mail before their clinic visit and brought the salivettes to the clinic visit. They collected saliva immediately on awakening (0 minutes) and 30, 45, and 60 minutes after awakening, and they recorded exact collection times. They were also instructed to not brush their teeth, smoke, drink, or eat during the saliva collection period. Analyses used data from those subjects who complied with the collection schedule. Data from subjects providing samples deviating more than 10 minutes from the instructed collection times were not included in the analyses. Saliva was stored at −20°C until assayed for free cortisol concentrations by a commercial laboratory using a radioimmunoassay (Esoterix, Inc, Calabasas, California). The interassay coefficient of variance was 12.6% and the assay sensitivity was 0.05 μg/dL.

STATISTICAL ANALYSIS

We used multivariate analysis of variance to compare individuals with CFS and well control subjects across CTQ subscales while considering correlations between subscales. Cases and controls with missing values on CTQ scales were excluded listwise, resulting in sample sizes of 106 individuals with CFS and 122 well control subjects in these comparisons. A significant omnibus effect rejects the null hypothesis and allows for comparing groups on subscales. We used nonparametric canonical discriminant analysis to determine which of the 5 CTQ subscales were most effective in discriminating between CFS cases and controls. A quadratic discriminant function was applied to the 5 subscales to compute standardized canonical coefficients, and an eigenvalue was calculated as a measure of overall variance between the CFS and well groups accounted for by each subscale. 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[28] and compared distributions using χ^2 and Mann-Whitney U tests. We then used unconditional logistic regression modeling to compute odds ratios (ORs) and 95% confidence intervals (95% CIs) as estimates of relative risk of CFS as a function of these categorical predictor variables, adjusting for age, sex, race, and ethnicity. We explored graded associations between exposure level and CFS risk 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 computed Pearson correlation coefficients between CTQ and CDC Symptom Inventory scores. 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 based on low vs high levels of psychopathological symptoms. We then used multinomial logistic regression analysis to estimate the risk of belonging to either case group as a function of childhood trauma.

Next we stratified CFS and control groups based on the presence or absence of moderate to severe exposure to any type of childhood trauma and compared the 4 resultant subgroups regarding cortisol awakening responses by using repeated-measures multivariate analysis of covariance. We computed areas under the curve (AUC) using the trapezoidal rule[41] and compared AUC between the groups by analysis of covariance. We used logarithm-transformed data to normalize distribution. All of the analyses were controlled for age, sex, race, and ethnicity. Of note, 20 individuals with CFS and 7 control subjects were using medication with a possible effect on the endocrine system. To maintain the population-based sample and yield representative results, we first analyzed cortisol data across all of the subjects with medication intake as a covariate. We then confirmed the results by repeating all of the analyses without individuals with CFS and control subjects using medication. We correlated cortisol measures with CTQ, CDC Symptom Inventory, and psychopathology scores using the Pearson correlation coefficient. Finally, we used stepwise multiple regression modeling to predict AUC when considering demographic and clinical variables simultaneously. The level of statistical significance was set at $P<.05$ for all tests.

Table 1. Childhood Trauma Questionnaire Scores

CTQ Subscale[a]	CTQ Scores, Mean (95% CI)		$F_{1,227}$	*P* Value
	Individuals With CFS (n=106)	Well Control Subjects (n=122)		
Emotional abuse	10.6 (9.6-11.7)	7.3 (6.7-7.9)	31.5	<.001
Physical abuse	9.0 (8.1-9.8)	6.9 (6.5-7.3)	20.5	<.001
Sexual abuse	8.6 (7.4-9.7)	5.8 (5.4-6.3)	21.7	<.001
Emotional neglect	11.0 (10.1-11.9)	7.9 (7.2-8.5)	30.8	<.001
Physical neglect	7.6 (6.9-8.3)	5.9 (5.5-6.2)	23.0	<.001
Total	46.7 (43.1-50.4)	33.7 (32.0-35.5)	44.8	<.001

Abbreviations: CFS, chronic fatigue syndrome; CI, confidence interval; CTQ, Childhood Trauma Questionnaire.
[a] Multivariate analysis of variance across subscales: Hotelling Trace $F_{5,222}=9.11$; $P<.001$.

Table 2. Logistic Regression Models Estimating the Likelihood of Having Chronic Fatigue Syndrome Relative to Childhood Trauma Exposure[a]

Predictor	No. (%) Over Cutoff[b]		OR (95% CI)	*P* Value[c]
	Individuals With CFS (n=106)	Well Control Subjects (n=122)		
Any category				
Yes	66 (62.3)	29 (23.8)	5.6 (3.1-10.0)	<.001
No	40 (37.7)	93 (76.2)	1 [Reference]	
Emotional abuse				
Yes	35 (33.0)	9 (7.4)	6.4 (2.9-14.3)	<.001
No	71 (67.0)	113 (92.6)	1 [Reference]	
Physical abuse				
Yes	35 (33.0)	12 (9.8)	4.7 (2.6-9.7)	<.001
No	71 (67.0)	110 (90.2)	1 [Reference]	
Sexual abuse				
Yes	35 (33.0)	13 (10.7)	4.2 (2.0-8.6)	<.001
No	71 (67.9)	109 (89.3)	1 [Reference]	
Emotional neglect				
Yes	27 (25.5)	11 (9.0)	3.5 (1.6-7.6)	.001
No	79 (74.5)	111 (91.0)	1 [Reference]	
Physical neglect				
Yes	26 (24.5)	6 (4.9)	6.5 (2.5-16.7)	<.001
No	80 (75.5)	116 (95.1)	1 [Reference]	

Abbreviations: CFS, chronic fatigue syndrome; CI, confidence interval; OR, odds ratio.
[a] All of the models are adjusted for age, sex, and race.
[b] Exposure to childhood trauma is based on Childhood Trauma Questionnaire cutoff scores for moderate to severe trauma: emotional abuse, 13 or higher; physical abuse, 10 or higher; sexual abuse, 8 or higher; emotional neglect, 15 or higher; and physical neglect, 10 or higher.
[c] *P* values are based on Wald χ^2 tests.

RESULTS

Persons with CFS had significantly higher overall childhood trauma scores than control subjects (Hotelling Trace $F_{5,222}=9.11$; $P<.001$) (**Table 1**). Mean scores were in the moderate range for each trauma type in the CFS group except for the sexual abuse score, which was higher than the moderate to severe cutoff. Because scores for the 5 individual CTQ subscales were highly correlated (all $P<.001$), we applied a nonparametric discriminant analysis to the CTQ subscales. The combination of results obtained using all 5 CTQ subscales significantly discriminated between individuals with CFS and well control subjects ($P<.001$). After mutual adjustment for the effects of all subscales on each other, the 3 CTQ subscales that were most informative in discriminating between individuals with CFS and well control subjects were sexual abuse, emotional abuse, and emotional neglect as evidenced by their standardized canonical coefficients (0.45, 0.40, and 0.36, respectively).

When applying cutoff scores for moderate to severe trauma exposure,[28] more individuals with CFS had scores higher than the cutoff compared with control subjects in each trauma category (all $P<.01$). A total of 62.3% of individuals with CFS met at least 1 cutoff score for any childhood trauma type compared with 23.8% of control subjects ($\chi^2_1=34.6$; $P<.001$). Individuals with CFS more frequently experienced increasing numbers of multiple types of trauma than control subjects ($Z=6.23$; $P<.001$). Exposure to any childhood trauma was associated with a 5.6-fold increased risk of CFS. The relative risk of CFS ranged between 3.5-fold and 6.5-fold increases depending on the type of trauma (**Table 2**). There was a graded relationship between the degree of exposure and risk of

Table 3. Logistic Regression Model of Gradual Relationship Between Childhood Trauma Exposure and Chronic Fatigue Syndrome Risk[a]

Predictor, No. of Categories[b]	Childhood Trauma Exposure, No. (%)		Increase in Risk of Having CFS	
	Individuals With CFS (n=106)	Well Control Subjects (n=122)	OR (95% CI)[c]	*P* Value[d]
0	40 (37.7)	93 (76.2)	2.1 (1.6-2.7)	<.001
1	23 (21.7)	17 (13.9)		
2	16 (15.1)	6 (4.9)		
3	12 (11.3)	3 (2.5)		
4	8 (7.5)	2 (1.6)		
5	7 (6.6)	1 (0.8)		

Abbreviations: CFS, chronic fatigue syndrome; CI, confidence interval; OR, odds ratio.
[a]Model is adjusted for age, sex, and race.
[b]The number of childhood trauma categories is based on cutoff scores for moderate to severe trauma (Table 2).
[c]The OR reflects an increase in risk with each level of increase in exposure categories.
[d]*P* value is based on Wald χ^2 test.

Table 4. Mean Scores and Frequency of Severity Categories in the Self-rating Depression Scale, State Anxiety Inventory, and Davidson Posttraumatic Stress Disorder Scale

Scale	Individuals With CFS (n=112)	Well Control Subjects (n=124)	Statistic[a]	*P* Value
Self-rating depression scale[b]				
Score, mean (95% CI)	56.2 (54.4-58.0)	36.5 (35.4-37.6)	$F_{1,231}=349.9$	<.001
No depression, No. (%)	27 (24.8)	119 (96.7)		
Mild depression, No. (%)	37 (33.9)	4 (3.3)	$Z=11.18$	<.001
Moderate depression, No. (%)	35 (32.1)	0		
Severe depression, No. (%)	10 (9.2)	0		
State Anxiety Inventory				
Score, mean (95% CI)	38.1 (35.7-40.5)	25.7 (24.6-26.8)	$F_{1,232}=95.5$	<.001
≥75th Percentile, No. (%)[c]	48 (44.0)	8 (6.5)	$\chi^2_1=44.9$	<.001
Davidson PTSD Scale[d]				
Intrusion score, mean (95% CI)	7.5 (5.6-9.4)	1.5 (0.9-2.1)	$F_{1,179}=39.0$	<.001
Avoidance score, mean (95% CI)	7.5 (5.2-9.8)	0.7 (0.2-1.1)	$F_{1,179}=34.9$	<.001
Hyperarousal score, mean (95% CI)	10.2 (7.8-12.6)	0.3 (0.1-0.6)	$F_{1,179}=70.4$	<.001
Total score, mean (95% CI)	25.2 (19.2-31.2)	2.5 (1.4-3.5)	$F_{1,179}=57.2$	<.001
Likely PTSD case, No. (%)	22 (25.0)	0	$\chi^2_1=26.2$	<.001

Abbreviations: CFS, chronic fatigue syndrome; CI, confidence interval; PTSD, posttraumatic stress disorder.
[a]Variable *df* reflect missing values.
[b]No depression indicates a score less than 50; mild depression, a score from 50 to 59; moderate depression, a score from 60 to 69; and severe depression, a score of 70 or higher.
[c]A score of 37 or higher.
[d]Subjects with no traumatic experience did not complete the Davidson PTSD Scale. A likely PTSD case is one with a total score of 40 or higher.

CFS inasmuch as the risk of having CFS doubled with each increase in the number of exposure categories (95% CI, 1.6-2.7; $P<.001$) (**Table 3**). The risk of CFS increased by 7.2% (95% CI, 1.0-1.1; $P<.001$) with each point increase in the CTQ total score. The Hosmer-Lemeshow statistic for assessing the model fit confirmed linear associations between the number of exposure categories or CTQ total score and the CFS risk. The CTQ total score was correlated with the number of CFS symptoms and mental fatigue within the CFS group ($P=.03$ for both).

Subjects with CFS exhibited more psychopathological symptoms than control subjects (**Table 4**). Relative to control subjects, a greater proportion of individuals with CFS had more severe depression ($Z=11.18$; $P<.001$). Significantly more individuals with CFS had high state anxiety (≥75th percentile) and met the cutoff score for clinically significant PTSD compared with control subjects. Clinically relevant symptoms of depression and PTSD were noted only in subjects with CFS and not in control subjects. In the Structured Clinical Interview for *DSM-IV*, a greater proportion of individuals with CFS than control subjects was diagnosed with current mood disorders (30.1% vs 0.0%, respectively; $P<.001$) or anxiety disorders (45.5% vs 8.9%, respectively; $P<.001$), including PTSD. There were significant correlations between the CTQ total score and symptom scores for depression ($r=0.346$; $P=.004$), anxiety ($r=0.213$; $P=.001$), and PTSD ($r=0.319$; $P<.001$). There were also significant correlations between the CDC Symptom Inventory total score and symptom scores for depression ($r=0.346$; $P<.001$), anxiety ($r=0.282$; $P<.001$), and PTSD ($r=0.346$; $P<.001$). To estimate the effects of current psychopathology on CFS risk related to childhood trauma, we strati-

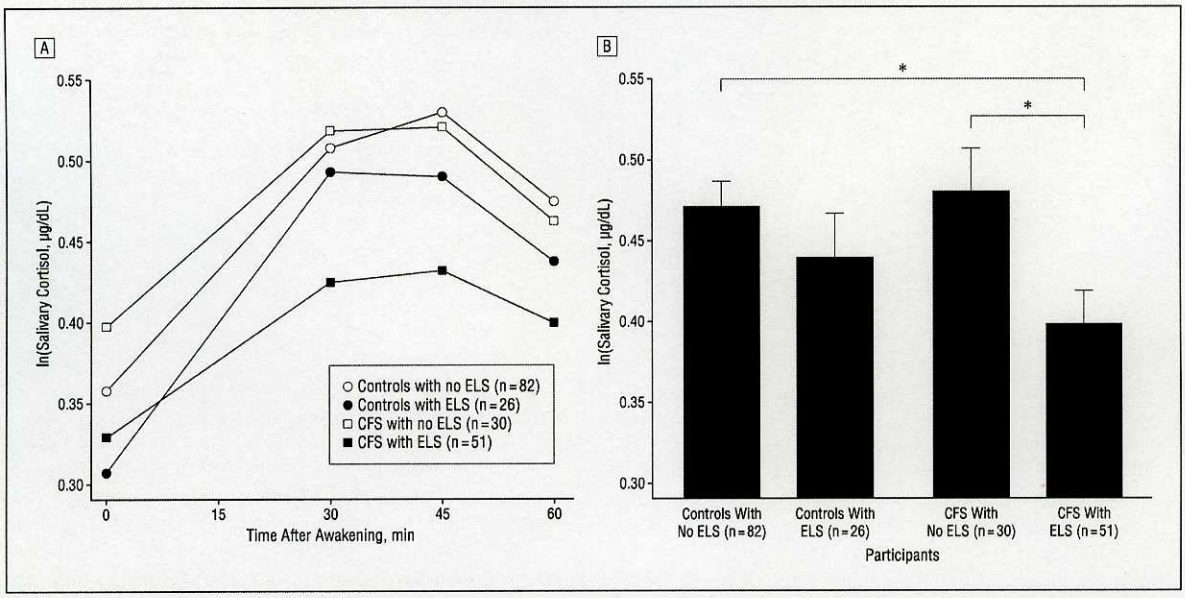

Figure. Logarithm-transformed mean salivary cortisol concentrations in response to awakening (A) and mean (SE) areas under the curve (B) in individuals with chronic fatigue syndrome (CFS) and well control subjects randomly identified from the general population in Georgia and stratified by the presence or absence of histories of childhood trauma (early-life stress [ELS]). There were significant main effects for group indicating decreased cortisol response and areas under the curve in individuals with CFS and childhood trauma but not in individuals with CFS without childhood trauma relative to control subjects and individuals with CFS with no childhood trauma. *$P<.05$.

fied the CFS group into those with low vs high levels of psychopathological symptoms. Multinomial logistic regression models showed that childhood trauma was associated with a markedly increased risk of CFS even in the absence of depression (OR=5.1; 95% CI, 2.6-10.1; $P<.001$), anxiety (OR=6.7; 95% CI, 3.3-13.7; $P<.001$), or PTSD (OR=5.1; 95% CI, 2.6-9.9; $P<.001$). Remarkably, with the presence of high levels of PTSD symptoms, the risk of having CFS as a function of childhood trauma further increased to more than a 9-fold elevated risk (OR=9.4; 95% CI, 3.1-28.8; $P<.001$).

Individuals with CFS had flattened cortisol awakening response profiles compared with well control subjects ($F_{3,567}=4.1$; $P=.007$). However, when stratifying CFS and control groups depending on the presence vs absence of moderate to severe childhood trauma exposure, only those individuals with CFS and childhood trauma exposure exhibited decreased mean cortisol levels after awakening (group effect: $F_{3,180}=3.0$; $P=.03$) (**Figure**, A) and a lower mean total AUC awakening response (group effect: $F_{3,180}=3.0$; $P=.03$) (Figure, B) compared with control subjects and individuals with CFS without childhood exposure (all contrasts: $P<.05$). Remarkably, individuals with CFS without childhood trauma experience did not differ from control subjects (Figure). Sex, race, and medication use had significant effects on cortisol awakening responses that were controlled for in the analysis of covariance. All of the group differences were confirmed when subjects using medications with potential effects on the endocrine system were excluded.

Cortisol levels at 0, 30, and 45 minutes after awakening and total cortisol response (AUC) were negatively correlated with emotional abuse scores (all $P<.05$). Cortisol levels 30 minutes after awakening were additionally negatively correlated with emotional neglect, CTQ total, and PTSD symptom scores (all $P<.05$). There were no correlations between cortisol levels and CFS symptom measures. When entering demographics, medication use, CFS status, and childhood trauma exposure in a stepwise multiple regression analysis, exposure to childhood trauma was a significant predictor of total cortisol response ($\beta=-0.199$; $t=-0.2846$; $P=.005$), whereas CFS status was excluded from the model. The effect of childhood trauma was maintained when additionally entering psychopathological symptoms, ie, PTSD levels.

COMMENT

Our results confirm childhood trauma as an important risk factor of CFS.[7] In addition, neuroendocrine dysfunction manifested by decreased salivary cortisol awakening response was associated with childhood trauma in CFS, likely reflecting a biological correlate of vulnerability due to early developmental insults. The associations observed in this study are particularly important because we evaluated persons with CFS and well control subjects identified from the Georgia population rather than clinical settings. Thus, the results can be generalized to the population of persons with CFS.

Our current results obtained in the Georgia population provide substantial replication of the preliminary findings from our previous study conducted in Wichita, Kansas.[7] It is remarkable that the group means of self-reported exposure to childhood trauma among CFS cases in Georgia are identical to those found in CFS cases in Wichita. Also similar to findings in Wichita,[7] we identi-

fied sexual abuse and emotional maltreatment as the best predictors of CFS status. The association between childhood trauma and CFS demonstrated a graded response. Childhood trauma was associated with CFS severity and psychopathological symptoms. While childhood trauma was an independent risk factor of CFS when stratifying cases into those with high vs low levels of psychopathological symptoms, CFS risk as a function of childhood trauma exposure nearly doubled with the presence of current PTSD symptoms. These identical results were found even though the Wichita[7] and Georgia[3] studies used a different epidemiological approach to identify cases and controls from the population.

Our current findings are in agreement with previous studies in tertiary care patients that found associations between CFS and victimization starting in childhood[13] or exposure to adverse parenting.[14] We also confirm findings that childhood abuse predicts PTSD symptoms in chronically fatigued individuals.[42] Our results are concordant with findings from community surveys reporting elevated rates of fatigue in women with childhood abuse experience.[43,44] Our results further substantiate the idea that CFS is part of a spectrum of disorders that are associated with childhood adversity, including depression, anxiety, and other functional somatic disorders.[7] Because all of these disorders often manifest or worsen in relation to acute stressors, enhanced stress reactivity as a potential consequence of early adversity may be a central feature common to this spectrum of disorders.

Of note, several disorders that have been related to early stress in epidemiological and clinical studies have also been associated with hypocortisolism in the neuroendocrine literature.[11] Relative decreases in cortisol secretion have been observed in nonhuman primates reared under insecure attachment conditions as well as in adult humans with childhood adversity.[16-20] Therefore, the second aim of this study was to investigate the contribution of childhood trauma exposure to HPA axis dysfunction in CFS. In accordance with our hypothesis, we found that decreased cortisol responses to awakening were observed in only those individuals with CFS who reported exposure to childhood trauma but not in individuals with CFS without such exposure. Of note, when considered as a whole, the CFS group did demonstrate a flattened response compared with control subjects in accordance with the published literature.[11,12] Only when stratifying CFS cases and controls by the presence or absence of childhood trauma did it emerge that decreased cortisol secretion was in fact associated with a risk factor more prevalent among CFS cases, ie, childhood trauma. The association between cortisol levels and childhood trauma was also confirmed by correlational analyses. Thus, our results may suggest that hypocortisolism in CFS reflects a biological marker of developmental risk for CFS rather than a correlate of the disorder itself. It should be noted that a recent study[45] reported decreased cortisol responses to a combined dexamethasone/corticotropin-releasing factor test in tertiary care patients with CFS without childhood trauma, whereas responses in patients with CFS and childhood trauma were comparable to those in control subjects. Cortisol responses in this test reflect feedback sensitivity of the HPA axis; therefore, these results are not directly comparable to our results. It may be speculated that changes at specific regulatory levels of the HPA axis are associated with risk or resilience factors vs illness state in CFS. It has further been suggested that hypocortisolism might be a consequence of having CFS because low cortisol secretion has been associated with illness features such as inactivity.[46] Whether hypocortisolism is a cause or consequence of CFS remains to be evaluated in longitudinal studies. Our results raise the possibility that childhood trauma is associated with certain illness features that are also associated with hypocortisolism.

The idea that hypocortisolism may be a preexisting risk factor for CFS is well in line with the potential physiological effects of decreased cortisol availability under conditions of stress. There are several avenues through which lack of cortisol effects might lead to characteristic symptoms of pain, fatigue, and anxiety and stress sensitivity.[11,15] First, glucocorticoids secreted during stress induce gluconeogenesis, mobilize free fatty acids, and reduce the use of amino acids for protein synthesis, thereby increasing the organism's energy supplies. Altered metabolism during stress due to hypocortisolism might lead to exhaustion and fatigue. Second, glucocorticoids exert inhibitory effects on the secretion of proinflammatory cytokines such as interleukin 6 and tumor necrosis factor α during stress and help return these cytokines to baseline levels after stress. These cytokines regulate cellular immunity and mediate pain. Increased or prolonged cytokine activity in the brain leads to impaired cognitive function and mood and anxiety symptoms through stimulation of corticotropin-releasing factor and noradrenergic systems.[11,15] Third, cortisol has direct effects on the brain and behavior by exerting negative feedback effects on locus ceruleus noradrenergic cells.[47] Relatively decreased cortisol output may have permissive effects toward an increased and sustained activation of corticotropin-releasing factor and noradrenergic systems, perhaps in concert with elevated cytokine levels, leading toward central stress sensitization, anxiety, and further stimulation of the immune system promoting fatigue and pain.[11,20] Based on these considerations, we suggest that hypocortisolism as a consequence of childhood trauma might be a preexisting risk factor that is associated with failure of the organism to adapt and compensate in response to challenge and thereby promotes the development of CFS and associated emotional and somatic disorders.[11] Consequently, maintaining normal cortisol function after childhood trauma, as seen in our control group, may reflect an important resilience factor that protects against developing CFS and other disorders.

There are several limitations of this study. A major 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.[48] Moreover, declarative biographical memory before age 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.[49] A recent meta-

analysis of studies using external corroboration of self-reports revealed that false negatives are more frequent than false positives, 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 the validity of self-reports.[48] It should be noted that rates of moderate to severe childhood trauma in our control group are comparable to rates reported in other studies. However, we cannot exclude that subjects with CFS have increased preexisting sensitivity to even minor adverse events relative to control subjects that resulted in differential reporting of trauma or might have been more likely to participate in the survey. A second 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. Finally, we did not consider effects of adulthood traumas and life stresses that might mediate the relationship between childhood adversity and CFS. Owing to the cross-sectional design, we cannot determine whether psychopathological symptoms preceded early adversity, mediated between early adversity and CFS, or more frequently occurred secondary to CFS in cases with early adversity.

In conclusion, our results lend further 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. Hypocortisolism might potentially be a biological substrate of such vulnerability induced by early-life stress. Longitudinal studies are needed to provide information on the causal relationship between childhood trauma, hypocortisolism, and CFS and to systematically evaluate developmental trajectories as well as mediators and moderators of this relationship. Such studies have the potential to elucidate the pathophysiology, identify subtypes, and devise strategies for preventing and treating CFS. Our findings emphasize the need to revise prevailing dichotomous approaches that differentiate between psychological and biological contributors to CFS.

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