

Childhood Trauma and Risk for Chronic Fatigue Syndrome

Association With Neuroendocrine Dysfunction

Christine Heim, PhD; Urs M. Nater, PhD; Elizabeth Maloney, MS, DrPH; Roumiana Boneva, MD, PhD; James F. Jones, MD; William C. Reeves, MD, MSc

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.

Arch Gen Psychiatry. 2009;66(1):72-80

Author Affiliations: Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine (Drs Heim and Nater), and Chronic Viral Diseases Branch, National Center for Zoonotic, Vector-borne, and Enteric Diseases, Centers for Disease Control and Prevention (Drs Nater, Maloney, Boneva, Jones, and Reeves), Atlanta, Georgia.

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 ner-

vous, 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 Univer-

sity 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 al³).

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 definition²¹ 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 al³).

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 ($\alpha=0.63-0.95$) 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 Scale³¹ 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 CFS³⁶⁻³⁸ 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 $\mu\text{g}/\text{dL}$.

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 scores²⁸ 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 rule⁴¹ 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.

