



## Attention-deficit hyperactivity disorder in chronic fatigue syndrome patients

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### ABSTRACT

Psychopathological disorders are frequent in chronic fatigue syndrome patients. The present study examines the presence of attention-deficit hyperactivity disorder (ADHD) in a sample of adult chronic fatigue syndrome (CFS) patients, and evaluates its clinical consequences in this population. CFS patients were assessed for childhood and adult ADHD by clinical interview and ADHD-specific scales. Psychopathological comorbidities were evaluated by clinical examination and questionnaires. Forty-seven of 158 CFS patients (29.7%) were diagnosed of childhood ADHD and in 33 (20.9%), the condition persisted into adulthood. CFS patients with adult ADHD had an earlier CFS onset, more severe anxiety and depression symptoms, and a higher risk of suicide than CFS patients without ADHD. Using lineal regression analysis, we found that depressive symptoms and ADHD severity were significant predictors of fatigue intensity. Consequently, ADHD may be common in CFS patients, and is associated with a more severe psychopathologic clinical profile.

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### 1. Introduction

Chronic fatigue syndrome (CFS) is a disabling disorder affecting 0.1–2.5% of the general population. It is characterized by debilitating fatigue associated with other symptoms, including fever, sore throat, lymph node pain, myalgia, arthralgia, headache, postexertional weakness, sleep disorders, and impaired short-term memory or attention (Fukuda et al., 1994). There are no confirmatory physical signs or characteristic laboratory abnormalities, and the diagnosis is based on clinical grounds. The etiology and pathophysiology of CFS remain unclear, although they are likely multifactorial (Wyller, 2007). Current evidence suggests that the Central Nervous System (CNS) is primarily involved in the fatigue, pain, mood, cognitive, and sleep disturbances (Chen et al., 2008). In addition, immune, metabolic, and endocrine abnormalities have been reported. In particular, hypothalamic-pituitary-adrenal (HPA) axis hypofunction has been found in a large percentage of CFS patients, although it is not clear whether this disturbance is cause or consequence of the illness.

CFS can be classified in the spectrum of what might be considered stress-associated syndromes by virtue of its frequent onset after acute or chronic stressors and exacerbation of symptoms during periods of physical or emotional stress (Nater et al., 2011). Several risk factors have been considered in relation to CFS. One is the presence of adverse experiences in childhood, especially childhood abuse, adverse parenting, and lifelong victimization (Heim et al., 2006). Another risk factor, whose influence is not well understood, is extreme energy and a high level of action proneness in childhood before the development of symptoms (Harvey et al., 2009).

Attention-deficit/hyperactivity (ADHD) disorder is highly prevalent worldwide, and is estimated to affect 5% of children and 3% of adults (Polanczyk et al., 2007). The Diagnostic and Statistical Manual of Mental Disorders-Text Revision (DSM-IV-TR) differentiates ADHD into 3 subtypes, inattentive, hyperactive-impulsive, and combined, reflecting possible combinations of the two ADHD core symptoms (inattention and hyperactivity-impulsivity) (American Psychiatric Association, 1994). The expression of ADHD can change with age; hyperactive symptoms appear to be typical of young children, whereas inattention represents a relatively pervasive developmental characteristic (Biederman et al., 2000). Longitudinal studies have shown that ADHD has long-term disabling consequences, for example, school failure, relational problems such as rejection, and family conflicts (Coghill et al., 2008). Furthermore, it is a predictor of mental health problems in adults (Biederman et al., 2010). Therefore,

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ADHD is an important childhood stress factor, which in some patients persists into adulthood.

The relationship between the presence of ADHD and later development of CFS has not been formally evaluated. Considering the observation that chronic stress and hyperactive behavior are risk factors for CFS and that ADHD can be associated with these factors, we hypothesized that ADHD could be common in CFS patients.

The primary aim of this study was to evaluate the presence of child and adult attention-deficit hyperactivity disorder in a sample of adult patients with chronic fatigue syndrome, using a cross-sectional study design. The secondary objective was to describe the clinical consequences of this association.

## 2. Method

### 2.1. Participants

The original sample consisted of 169 consecutive adults referred from primary care to a specialized outpatient program at a university hospital. The sample was collected between September 2009 and December 2010. All patients underwent an extensive medical examination by physicians with experience in CFS at the hospital internal medicine department before psychiatric assessment, in keeping with our diagnostic protocol (Alijotas et al., 2002). The CFS diagnosis was established according to CDC criteria (Fukuda et al., 1994). Comorbidity with other axis I disorders was assessed with the structured clinical interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), Structured Clinical Interview for DSM-IV Axis I Disorders (SCID I, First et al., 1997).

The inclusion criteria were age older than 18 years, CFS diagnosed according to CDC criteria, a complete clinical assessment, and informed consent to participate. The only exclusion criterion was the presence of severe unstable psychiatric disorders, such as psychotic episode, major depressive episode, maniac episode, and anorexia nervosa.

Of the total initial sample, 11 patients were excluded: six because of an associated severe psychiatric comorbidity that could account for some of the CFS symptoms (four major depression, one obsessive-compulsive disorder, one delusional disorder), and five because they did not complete the entire evaluation protocol. The final sample included 158 patients.

All patients provided written informed consent to participate and the research protocol was approved by the hospital ethics committee.

### 2.2. Assessment

#### 2.2.1. Fatigue assessment

The Fatigue Severity Scale (FSS) and Fatigue Impact Scale (FIS) were used to rate fatigue. The FSS, which mainly measures the severity of fatigue, has been specifically designed to differentiate fatigue from clinical depression. It is a self-report scale that includes 9 items rated from 1 to 7. Higher scores (range 7–63) indicate greater fatigue severity (Krupp et al., 1989). The FIS is an informant-based scale that assesses the impact of fatigue on various areas of functioning (physical, psychosocial, and cognitive), rather than fatigue severity or phenomenology. It also gives an overall score. It has 40 items ranging from 0 “never” to 4 “always”. Higher scores (range 0–160) suggest greater functional impairment (Fisk et al., 1994).

#### 2.2.2. ADHD diagnosis

The diagnosis of ADHD was established according to DSM-IV ADHD criteria. The Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID Part II) was administered (Epstein et al., 1999). The CAADID is a semi-structured clinical interview divided into two parts that assess ADHD symptoms according to the DSM-IV in both childhood and adulthood. It also evaluates the pervasiveness and level of impairment. Administration of the CAADID requires 1 h. In order to contrast the ADHD symptoms recorded, information was also collected from a family member or person who knew the patient well from childhood to adulthood. To complete the childhood diagnosis, we used the 61-item version of the Wender Utah Rating Scale (WURS); scores above the cut-off of 36 are suggestive of the diagnosis (Ward et al., 1993). The severity of adult ADHD symptoms was evaluated with the ADHD Rating Scale (ADHD-RS), which is designed to assess the 18 diagnostic criteria of DSM IV (DuPaul et al., 1998). It is a self-reported scale, in which each item is rated from 0 to 3. The cut-off value for a diagnosis of adult ADHD is set at 24.

The Barratt Impulsivity Scale (BISS-11) was used to complete the evaluation of impulsivity at the time of the assessment. It is a 30-item self-reported scale and the median score for the Spanish population is 32.5 (Patton et al., 1995).

#### 2.2.3. Depressive and anxiety comorbidity assessment

The severity of depressive and anxiety symptoms was assessed with the Hospital Anxiety–Depression Scale (HAD) (Zigmond and Snaith (1983)), which is designed to recognize these symptoms in patients with physical illness. It has 14 items divided into two parts that evaluate either depressive or anxiety symptoms. The scores indicate the presence of mild (8–10) to severe (15–21) symptoms. The State-Trait Anxiety Inventory (STAII) (Spielberger et al., 1970) is a self-report scale that was used to complete the assessment of anxiety symptoms. It has 40 items divided into two groups that analyze anxiety, considering it as a transitory situation (state) or a more stable condition (trait). Items are scored on a 4-point scale. The total score for each subscale is calculated by adding the items. Higher scores (range 0–60) indicate greater severity.

Suicide risk was studied with the Plutchick Risk of Suicide Scale (RS) (Plutchik et al., 1989), a 15-item self-report scale with dichotomous responses. Values above the cut-off point of 6 indicate a risk of suicide.

## 2.3. Statistical analysis

Statistical analysis was performed with the PASW statistics package (version 17.0) for Windows (SPSS Inc.; Chicago, Illinois). Continuous measures were described by means and standard deviations, whereas categorical variables were expressed using frequencies and percentages. The sample was divided into two groups according to the presence of the adult ADHD diagnosis. Between-group differences for continuous variables were assessed with the independent *t*-test or Mann–Whitney *U* test, and expressed as the mean difference and 95% confidence interval. The Pearson chi-square test or Fisher exact test were used to assess differences in categorical variables, determining the odds ratio (OR) and 95% confidence interval. Factors related to the presence of adult ADHD in the univariate analysis (*p* < 0.05) were included in a linear regression model, following the forward stepwise method, to identify variables independently associated with more severe fatigue, evaluated with the FIS-40 score. A two-tailed probability (*p*) value of less than 0.05 was considered significant.

## 3. Results

Of the 158 patients assessed, 47 (29.7%) met the criteria for childhood ADHD. In 33 patients from the total (20.9%), ADHD persisted to adulthood (persistence rate, 70.2%). Considering the patients with childhood ADHD, 27 (57%) patients met the criteria for hyperactive–impulsive subtype, 14 (30%) for inattentive, and 6 (13%) for combined. In adulthood, the inattentive subtype was the most common, diagnosed in 21 (64% patients), followed by hyperactive in 7 (21%), and combined in 5 (15%). The subtypes evolution in the 33 patients with adult ADHD is reflected in Table 1. None of these patients had been diagnosed of ADHD previously.

There were no significant differences between the two groups (CFS+ADHD vs. CFS) in terms of age, sex, years of education, working status, or presence of insomnia at the time of the evaluation. In both groups, CFS onset had been progressive and there were no statistical differences in the present fatigue severity according to the FSS and FIS results (Table 2). However, CFS+ADHD patients had an earlier CFS onset (29.66 vs. 34.77; *p*=0.02) and disease duration had been longer (18.16 vs. 13.83 years; *p*=0.05). There were no differences in previous psychiatric disorders (Table 2). A somewhat larger percentage of patients had

**Table 1**

Evolution of subtypes in the 33 patients with adult attention-deficit/hyperactivity disorder (ADHD).

Childhood	Hyperactive-impulsive (n=16)	Inattentive (n=11)	Combined (n=6)
<b>Adults</b>			
Hyperactive-impulsive (n=5)	5	0	0
Inattentive (n=21)	8	10	3
Combined (n=7)	3	1	3

Data refer to the number of patients in each ADHD subtype.

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