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LENGTH OF ILLNESS DOES NOT PREDICT COGNITIVE DYSFUNCTION IN CHRONIC FATIGUE SYNDROME

Abstract

Neuropsychological studies have shown cognitive impairment in Chronic Fatigue Syndrome (CFS), particularly in information processing speed. The aim of this study was to examine the evolution of cognitive impairment in CFS. The evolution is one the most disabling aspects of the CFS, and it has received little attention in literature. Fifty-six women with CFS were assessed with neuropsychological tests. Patients were divided into 3 groups based on the duration of the disease. There were no differences between groups in terms of cognitive function. The cognitive impairment in CFS was not found to be more severe with longer disease duration. These data suggest that there is no progressive cognitive impairment in patients with CFS. Therefore, the cognitive deficits in CFS should be treated with cognitive rehabilitation programs focused on improving emotional distress associated to the illness and promoting functional abilities.

Introduction

Fatigue is a common complaint in the general population, but when it occurs in the clinical entity known as chronic fatigue syndrome (CFS), it can produce distress and suffering, and have negative repercussions on the patient's quality of life. CFS is characterized by prolonged, unexplained fatigue for at least 6 months, experienced as severe mental and physical exhaustion. Case definition is used to aid diagnosis, being the most frequent the US Centers for Disease Control and Prevention (CDC, Fukuda, et al., 1994) and the Oxford (Sharpe, et al., 1991) criteria. They define CFS on the basis of the concurrent presence of at least 4 of the following criteria: self-reported memory alteration, painful swallowing, tender cervical or axillary lymph nodes, myalgia, recent onset of headaches or headaches of a new type, pain in several joints without signs of inflammation, unrefreshing sleep, and maliase following exertion and lasting more than 24 hours. For this study we have focused in cognitive impairments and their evolution using a neuropsychological examination to asses the cognitive impairments.

Cognitive impairment is one of the most common symptoms in CFS. Figures from general population studies show prevalences of CFS ranging from 0.007% to 2.8% and the 89% of these people experiencing memory and concentration problems (Jason, et al., 1999). Many people with CFS describe their cognitive difficulties as one of the more disabling and troubling symptoms of their illness (Abbey & Garfinkel, 1991). The cognitive complaints frequently reported by these patients are difficulties with concentration, decreased memory for recent events, poor word-finding ability, and slowing of information processing (Grafman, et al., 1993). These deficits are included in the diagnostic criteria of the syndrome, however, CFS patients´ cognitive functioning performance, including memory, attention, and concentration tests; does not reflect their high level of cognitive complaints.

Studies assessing the cognitive performance of CFS patients with standardized neuropsychological tests have obtained inconsistent results. The most constant findings include slowed information processing speed, impaired working memory, and slowed reaction time (Busichio, Tiersky, Deluca, & Natelson, 2004; Cockshell & Mathias, 2010; Michiels & Cluydts, 2001). The origins of the cognitive dysfunction associated with CFS remain unknown, although increasingly more studies are attempting to objectively determine and answer this question.

Some authors have described anatomical alterations in these patients (Lange, et al., 1999), In a recent study, a reduction in prefrontal cortical volume was found in patients with CFS relative to a healthy control group (de Lange, et al., 2008). In addition, neuroendocrine studies have provided evidence suggesting functional dysfunctions in the hypothalamic-pituitary-adrenal axis. A reduction in cortisol levels and increased serotonergic neurotransmission has been observed in patients with CFS (Cleare, et al., 1995), and this could also be related to alterations in the cognitive capacity. Some research has included as control group patients with multiple sclerosis, a neurological disease whose cognitive impairments are similar to the patient with CFS and worse as the disease progresses (Daly, Komaroff, Bloomingdale, Wilson, & Albert, 2001).

Another hypothesis is that depression and anxiety could be associated with cognitive deficits. However, the data about the role of these factors in cognitive functioning in CFS are not consistent. Some authors have found a relationship between symptoms of depression and anxiety and cognitive deficits in a variety of cognitive measures (Michiels, Cluydts, & Fischler, 1998; L. A. Tiersky, Matheis, Deluca, Lange, & Natelson, 2003) whereas others report that the deficit is not secondary to the emotional status (Busichio, et al., 2004; Dickson, Toft, & O'Carroll, 2009; Short, McCabe, & Tooley, 2002). Nowadays, the evidence

suggests that impaired cognition in chronic fatigue syndrome cannot be explained solely by the presence of a psychiatric condition.

Most patients report a progressive worsening in cognitive symptoms with longer disease duration. Currently there are few studies that focus on this hypothesis. There is one study that examined long-term change in neuropsychological functioning in individuals with CFS over a range 24-63 months. This study showed no changes in attention (forward and backward digits) and memory functions (California Verbal Learning Test, Rey–Osterreith Complex Figure Test) over the time (Lana A. Tiersky, et al., 2001). Other studies associated changes in cognitive function with improvement in patients with CFS. Cope et al, studied 14 patients with CFS over the course of an average of 4,4 months, showing that patients significantly improved on a block design task, a learning task, and a verbal paired associates task (Cope, Pernet, Kendall, & David, 1995). Vercoulen et al. (1996) found subjective concentration difficulties significantly decreased over time in patients with CFS when they improve (Vercoulen, et al., 1996). However, there are some limitations in these studies: the small sample size, the short duration of follow-up, the reduced neuropsychological batteries. In addition, the studies about the course of CFS showed that the symptoms persist in more than half of patients (Cairns & Hotopf, 2005).

The purpose of the study is to assess the cognitive impairment throughout the disease course. Based on studies documenting the worsening in the evolution of the disease (Cairns & Hotopf, 2005) and on our clinical data, we hypothesized that patients with CFS would show an increase in cognitive impairment with progression of the disease.

Material and methods

Patients

The study sample included 56 patients diagnosed with CFS according to the criteria of Fukuda by an internal doctor from the Chronic Fatigue Unit of Vall d'Hebron University Hospital in Barcelona (Spain). Patients were recruited between October 2008 and October 2009. The criteria for inclusion were a diagnosis of CFS and age between 18 and 65 years. Patients were excluded if they had a severe mental disorder (eg, bipolar disorder, psychotic disorder, borderline personality), were drug abusers, or if they were currently affected by, or had a history of, neurological disorders or other organic diseases that involve cognitive alterations. The sociodemographic and clinical characteristics of the patients are summarized in Table 1.

Table 1. Sociodemographic and clinical characteristics of the sample

Variables	N=56
Age, years [a]	46.75 (7.67)
Caucasian[b]	56 (100)
Education level[b]	
Attended elementary school	14 (25.1)
Elementary school graduate	13 (23.2)
Secondary education	18 (32.1)
College education	11 (19.6)
Currently working [b]	20 (35.7)
Diagnosis CFS (months)[a]	46.84 (39.07)
Age at onset of CFS[a]	36.65 (10.85)

[a]Mean (SD), [b]Frequency (percentages)

Assessment

The sociodemographic and disease data, were collected from the information provided by the patients. The presence of psychopathology was assessed by a clinical interview following Diagnostic Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria (American Psychiatric Association, 2001). The degree of fatigue was evaluated with the Fatigue Impact Scale, (FIS, Fisk, et al., 1994). The Hospital Anxiety and Depression Scale (HADS Zigmond & Snaith, 1983) was also administered.

The neuropsychological assessment consisted of administration of an extensive battery of neuropsychological tests previously translated and transculturally adapted. This battery was validated in an own sample of 250 healthy subjects, confirming no significant differences with the original parameters.

The battery was designed to comprehensively assess five cognitive domains: attention and concentration, reaction time, memory, motor functioning and executive functioning. *Attention and concentration*: Digit Span WAIS-III (Wechsler, 1999), Mental Control (WMS-III) (Wechsler, 2004), Symbol Digit Modalities Test (SDMT) (Smith, 1982), Paced Auditory Serial Addition Test (PASAT) (Gronwall, 1977); *reaction time*: California Computerized Assessment Package (CalCAP) (Miller, 1990); *memory*: Rey Auditory Verbal Learning Test (AVLT) (A. Rey, 1964) and Rey-Osterreith Complex Figure (ROCF, immediate and delayed recall) (A. Rey, 1987); Psychomotor speed: Grooved pegboard (Klove, 1963); and *executive functioning*: Stroop Test (Golden, 1994) Trail-Making Test (TMT) (Reitan & Wofson, 1985), verbal fluency test (FAS) (Benton & Hamsher, 1978), and Tower of London Test (Shallice, 1982). Premorbid intellectual capacity was assessed by the vocabulary subtest of the WAIS-III (Wechsler, 1999). The great majority of these tests were frequently used to assess cognitive performance in CFS (Cockshell & Mathias, 2010). In addition, we included mental

control to assess concentration, a deficit frequently referred by patients with CFS. All the tests were administered according to standardized procedures published in each test's manual.

Procedure

The patients comprising our sample were consulting at the Chronic Fatigue Unit of our hospital. Based on their arrival at the Unit and following the inclusion criteria, they were referred to the Psychiatry Department to undergo a psychological examination. The assessment was carried out in 2 sessions. In the first, a clinical psychologist interviewed the patient, recorded sociodemographic and clinical data, and conducted a psychopathological examination. In the second session, which took place within 2 weeks, neuropsychological assessment was performed by a neuropsychologist. All sessions were performed under the same conditions and each one lasted no more than 2 hours.

All the participants received information before the evaluations were carried out, including aim of the study, the benefits we were attempting to achieve, and the procedure to follow, with emphasis on the voluntary nature of their role. After receiving this information, patients signed an informed consent form to participate. This study was approved by the by the ethics committee of the Vall d'Hebron University Hospital.

Design

A cross-sectional study design was used, consisting of evaluation of the cognitive status of CFS patients at a specific time point during the course of the condition. The variables examined included sociodemographic data (age, sex, educational level, and work status), clinical variables related to the disease (time since the diagnosis, time since the onset of symptoms, and degree of fatigue), the presence of depression (assessed by clinical interview and the HADS), and variables referring to the data obtained in the neuropsychological tests.

Patients were divided into 3 groups based on the time since the disease was diagnosed: less than 12 months, from 12 to 48 months, and more than 48 months.

Statistical analysis

To achieve the proposed objectives of the study, data analyses were performed with SPSS for Windows (version 15.0; SPSS Inc., Chicago). A descriptive univariate analysis was carried out in order to describe the sample. The raw scores on the tests were adjusted according to normative data and transformed to T scores (mean=50, dt=10), correcting for the effect of age and education level on neuropsychologic performance. This allowed us to obtain a score, and tests with a T score of less than 40 were considered to indicate impairment, as considered by Busichio et al. (2004). As a result, a profile of cognitive impairment consisting of percentages of impairment in each group was obtained. The distribution of sociodemographic and clinical variables in the 3 groups of patients with differing disease duration was analyzed with one-factor ANOVA or chi-square tests, depending on the type of variable. The percentage of cognitive impairment over the three groups was compared using chi-square tests.

Results

The distribution of the sociodemographic and clinical variables in the 3 groups (Table 2) was homogeneous.

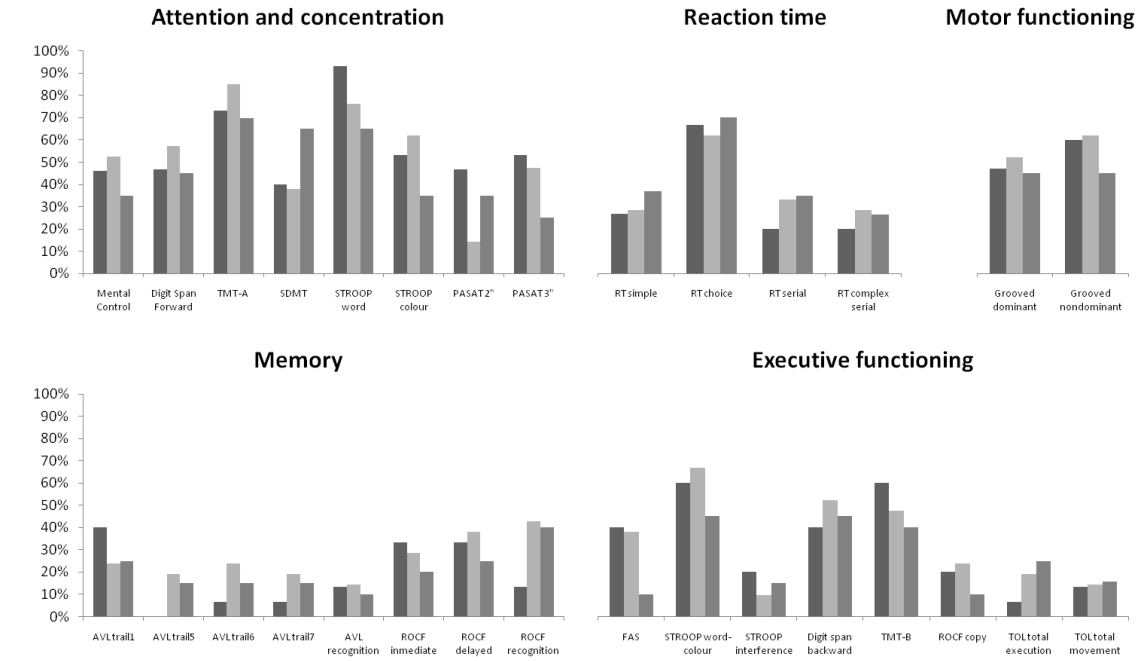
Table 2. Comparison of sociodemographic and clinical variables in the 3 CFS groups, divided according to disease duration

Variables	CFS <12 months (n=15)	CFS 12-48 months (n=21)	CFS >48 months (n=20)	*P*
Age[a]	47.20(4.71)	47.24 (8.20)	45.95 (8.88)	.828[c]
Years of education[a]	11.33 (3.70)	10.24 (3.62)	12.05 (4.23)	.269[c]
Currently working[b]	8 (53.3)	8 (38.1)	4 (20.0)	.084[d]
HADS[a]	21.93 (7.69)	23.05 (7.74)	24.84 (8.88)	.574[c]
Age at onset of CFS[a]	41.67 (6.95)	35.52 (11.58)	34.10 (11.39)	.098[c]
FIS[a]	129.79 (30.07)	134.26 (21.27)	139 (17.25)	.540[c]
Premorbid intelligence level[a]	55.36 (7.53)	57.00 (8.75)	56.85 (8.12)	.826[c]

[a]Mean (SD), [b]Frequency (percentages), [c]ANOVA, [d]chi-square test
HADS indicates Hospital Anxiety and Depression Scale; FIS, Fatigue Impact Scale

More than half of the patients showed a score above 40 (impairment) in processing speed (specifically in the CalCAP, TMT, and Stroop tests) and psychomotor functioning (Grooved pegboard test). Results for the remaining tests were within normal limits.

Figure 1. Percentage of impaired patients (T scores above 40) by neuropsychological tests according to disease duration



12 months, 12-48 months, >48 months. AVL indicates Rey Auditory Verbal Learning test; ROCF, Rey –Osterrieth Complex Figure; RT, reaction time; TMT, Trail Making Test; TOL, Tower of London

The cognitive profile of the sample of CFS patients is shown in Figure 1. Comparison of the neurophysiologic profile between the 3 CFS groups showed no statistically significant differences.

Discussion

To our knowledge the present study is one of the first to examine the evolution of cognitive impairment along the illness in CFS, using groups of patients with different duration of illness. We opted to research this topic because there is a relative lack of previous research despite that many patients consider these cognitive symptoms to be the main source of their disability (Moss-Morris, Petrie, Large, & Kydd, 1996).

Consistent with previous studies, impairment scores were found in test that measure information processing speed, assessed with the CalCAP, TMT, and Stroop Test, Grooved pegboard (Cockshell & Mathias, 2010; Michiels & Cluydts, 2001). The punctuations of these tests in our study is located at one standard deviation below normal, suggesting the presence of mild cognitive impairment (Busichio, et al., 2004). So it is important to follow-up these patients to see their evolution. The study of the evolution of cognitive functioning, it is also necessary to know the impact of the disease on cognition, similar to other diseases that present neuropsychological disorders such as multiple sclerosis. Hence, this group of patients was compared to CFS patients (Daly, et al., 2001).

We hypothesized that patients with CFS would show an increase in cognitive impairment with progression of the disease. Nonetheless, the data did not support this hypothesis, as there were no significant differences in the neuropsychological tests scores between the 3 groups of patients with different disease durations.

These data point out that the cognitive impairment in CFS patients does not worsen over the course of the condition. It must be noted, other variables that can have an influence on cognitive performance, such as age and the educational level, were distributed homogeneously among the 3 groups. The same was true regarding the prevalence of depression, another factor known to affect cognitive function.

These data contradicts the longitudinal studies that show improvement in some cognitive functions (Cope, et al., 1995; Lana A. Tiersky, et al., 2001; Vercoulen, et al., 1996). However, these studies have some limitations. Cope et al., used a very small sample with 14 patients and a short test-retest interval of 4.4 months, so the improvement showed in the neuropsychological tests could be the result of practice effect. The practice effect is associated to repeated examinations of the same neuropsychological assessment, this have been studied in healthy subjects and patients with different illness (Lezak, 1995). In the present study, there is not any practice effect, because it is a cross-sectional study, with only one examination.

Tiersky et al. (2001), included measures of attention (PASAT, forward and backward digit) and memory (CVLT and ROCFT), but this study didn´t incorporate other cognitive tests in which patients' performance is impaired such as Stroop reaction time, AVLT and motor Functioning (Cockshell & Mathias, 2010). So, to study how the length of the illness affects cognitive impairment in CFS patients, we should include a neuropsychological battery with measures that have been shown to be altered in these patients. Finally, Vercoulen et al. (1996), used subjective measures of concentration, so these data are less objective than neuropsychological tests.

The possible progression of the disease to irreversible cognitive impairment, is one of the main concerns in patients with CFS. This data suggests that cognitive impairment does not worsen along the course of CFS. However, patients with CFS present cognitive deficits that should be treated. An alternative could be through the incorporation of cognitive rehabilitation programs in the management of these patients. There are some studies that found an association of neuropsychological deficits with functional impairment in patients with chronic fatigue syndrome, similar to other illnesses than HIV, multiple sclerosis, Alzheimer's disease, and stroke (Christodoulou, et al., 1998). Cognitive impairment has

functional implications in patients' lives, so the intervention programs could focus on developing compensational strategies and promoting active use of preserved functions, as well as providing psychoeducation about the impairment and emotional interventions for cases that might require this treatment. In this line, cognitive behavioral therapy has been shown to improve the health of SFC patients (Prins, van der Meer, & Bleijenberg, 2006; Siessmeier, et al., 2003), also increasing the volume of prefrontal cortex (de Lange, et al., 2008). This brain area is involved in cognitive functions altered in patients with CFS. Based on these results, future studies should broaden the knowledge of the effect of psychological treatment on cognitive deficits in CFS.

The main limitation of this study is the absence of longitudinal data to follow-up the sample at different time points. Nevertheless the use of cross-sectional designs reduces the practice effects on performance in neuropsychological tests. Although this study didn´t include a healthy control group , all the normative data used was extracted from the same local sample. Future studies in this line could include a group without CFS, determine the baseline cognitive performance in both groups, and then perform additional assessments over time. In addition, no objective validation of the performance of the subjects was included although it was clinically assessed. Further studies could include objective effort measures like the Test of memory malingering (TOMM, Tombaugh, 1996; cited in Busichio, et al., 2004). Finally, it must be noted that in order to homogenize the sample of patients and taking into account the influence of gender on cognitive function (Lezak, 1995) men were excluded from this study. Considering that the prevalence of CFS in women is higher than men (Jason, et al., 1999), men representativeness would require a much more larger sample of patients. Although in our study the language and ethnic characteristics of the sample was very homogeneous, it should also be taken into account in future studies.

In conclusion, the cognitive impairment occurring on CFS patients was not found to be more severe with longer disease duration. This fact would support the implementation of rehabilitation programs to optimize the patients' cognitive resources, improve their quality of life, and increase their self-confidence.

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