

## BRIEF ORIGINAL

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## STRESSFUL EVENTS IN THE ONSET OF CHRONIC FATIGUE SYNDROME

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## ABSTRACT

**Background:** Chronic Fatigue Syndrome (CFS) is a complex and multifactorial disease. Stressful situations experienced could be related to the presentation of the disease. Few studies have determined which factors could trigger CFS. The main objective of this study was to explore the stressful situations which can be associated with CFS presentation.

**Methods:** Retrospective observational case-control study with CFS diagnosed patients according to the Fukuda's criteria. Controls were matched to cases by sex, age and educational level with a 1:1 ratio. Participants aged between 18 and 75 years from the province of Lleida. Information was obtained through personal questionnaires. The measure of association was the odds ratio.

**Results:** In total, 77 cases and 77 controls were included. Association found between stressful life events and presentation of disease were pregnancy ORa=31.7 (CI95%:2.2-456.7), spouse abuse ORa=10.2 (CI95%:1.2-88.4) and mobbing ORa=6.9 (CI95%:1.3-36.9), eating disorders=7.5 (CI95%:1.3-42.1), car accident ORa=5.5 (CI95%:1.7-17.9), economic problems ORa=5.1 (CI95%:2.1-12.6) and changes in sleep habits ORa=2.8 (CI95%:1.1-7.5).

**Conclusions:** Stressful life events as pregnancy, spousal abuse, mobbing, eating disorders, car accident, economic problems and changes in sleep habits felt by those affected must be taken into consideration when compiling background information related to the onset of Chronic Fatigue Syndrome. Adequate identification of these stressful life events in risk people could contribute to early diagnosis of Chronic Fatigue Syndrome.

**Keywords:** Chronic Fatigue Syndrome, Stressful events, Precipitating factors, Early Diagnosis, Logistic Regression, Pregnancy, Violence Against Women, Spouse Abuse, Feeding and Eating Disorders, Poverty, Dysssomnias. Accidents.

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## RESUMEN

## Situaciones estresantes asociadas a la presentación del síndrome de fatiga crónica

**Fundamentos:** El síndrome de fatiga crónica (SFC) es una enfermedad compleja y multifactorial. Situaciones estresantes vividas podrían relacionarse con la presentación de la enfermedad. Son pocos los estudios que han determinado estos factores desencadenantes de la presentación del SFC. El objetivo principal del presente estudio fue explorar cuáles pueden ser las Situaciones estresantes asociadas al desencadenamiento del síndrome de fatiga crónica.

**Métodos:** Estudio observacional retrospectivo de casos y controles con pacientes diagnosticados de SFC según los criterios de Fukuda. Los controles se emparejaron con los casos según sexo, edad y nivel de estudios con una razón 1:1. Ambos tenían edades comprendidas entre los 18 y los 75 años y eran residentes en la provincia de Lleida. Se aplicó una tabla de acontecimientos vitales estresantes (AVE). La información se obtuvo mediante encuestas personales. Se realizó regresión logística binaria calculando la odds ratio como medida de asociación.

**Resultados:** Se incluyeron 77 casos y 77 controles. Se evidenció asociación entre acontecimientos vitales estresantes y presentación de la patología, como embarazo con ORa=31,7 (IC95%: 2,2-456,7), maltrato por parte de la pareja ORa=10,2 (IC95%:1,2-88,4), mobbing ORa=6,9 (IC95%:1,3-36,9), trastornos de la alimentación ORa=7,5 (IC95%:1,3-42,1), accidente de tráfico ORa=5,5 (IC95%:1,7-17,9), problemas económicos ORa=5,1 (IC95%:2,1-12,6) y cambios de hábitos de sueño ORa=2,8 (IC95%:1,1-7,5).

**Conclusiones:** Acontecimientos vitales estresantes como el embarazo, el maltrato por parte de la pareja, mobbing, trastornos de alimentación, accidente de tráfico, problemas económicos y cambios de hábitos de sueño percibidos por los afectados, deben tenerse en cuenta al explorar la información relacionada con el desencadenamiento del síndrome de fatiga crónica. Su hallazgo en personas de riesgo podría contribuir a un diagnóstico precoz del síndrome de fatiga crónica.

**Palabras clave:** Síndrome de fatiga crónica, acontecimientos estresantes, factores desencadenantes, detección precoz de la enfermedad. Análisis de regresión logística. Embarazo. Abuso de la pareja. Trastornos de alimentación y de la ingestión de alimentos. Trastornos del sueño. Accidents

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## INTRODUCTION

The chronic fatigue syndrome (CFS) is a complex disease with a multifactorial etiopathogenesis. The debut of CFS usually occurs in young adults from 20 to 40 years of age and is predominantly found in females (8:1) <sup>(1)</sup>.

It is characterized by the presence of intense, unexplainable and persistent, albeit varying, and weakening fatigue after physical or cognitive activity from which an individual does not recover with rest. The etiopathogenesis of CFS is unknown. It may last more than 6 months and may notably interfere with and reduce occupational, educational, social and personal activities by half and is accompanied by associated symptomatology. The most common criteria used for the diagnosis of CFS are those of Fukuda <sup>(2)</sup>.

It has been estimated that from 5 to 20 % of patients attended in primary care have presented fatigue for more than one month during their life, with the cause of fatigue being identified in more than 65 % of the cases <sup>(3)</sup>.

The lack of objective tests to diagnose CFS has led to doubts as to its actual existence and thus, this syndrome may induce social rejection and incomprehension among family members and friends <sup>(4)</sup>.

Predisposing, triggering and maintenance factors have been described in the multifactorial pathogenesis of CFS. With regard to triggering factors, it has been reported that CFS may debut in relation to stressful events which have taken place in the life of the patient.

Many people with CFS report having experienced a very stressful situation prior to the manifestation of the disease, with some cases describing a concom-

itant infection or other determining factors. Several studies evaluating stress as a trigger of CFS have focused on situations which occurred during infancy and adolescence such as psychological and physical abuse, abandonment, sexual abuse or fights with parents as well as events perceived as stressful by the individual <sup>(5,6,7)</sup>.

These studies concluded that exposure to stress factors during early stages of life is associated with the development of CFS <sup>(8)</sup>, and report that CFS is 2- to 3-fold more frequent in people who were submitted to these stress factors during infancy <sup>(9)</sup>.

Taking into account the hypothesis that different stress factors influence the triggering of CFS, the aim of the present study was to evaluate vital situations which patients have identified as stressful and which may be associated with the triggering of CFS in these patients.

## METHODS

We performed an observational, case-control study including subjects diagnosed with CFS according to the classification criteria of Fukuda <sup>(2)</sup>. All patients provided written informed consent to participate in the study.

The patients included were from 18 to 75 years of age and were attended in the Specialized Hospital Unit of the Department of Rheumatology of the Hospital Universitario Santa Maria in Lleida, Catalunya (Spain).

The control subjects were matched (1:1) with the cases by sex, age ( $\pm 1$  year) and education. Patients with a history of neurological disease or head trauma, severe mental disorder according to axis I of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) TR or a diagnosis of fibromyalgia were excluded.

Among the controls we also excluded individuals with any specific pathology related to CFS such as fibromyalgia, myofascial pain, chronic idiopathic pain, multiple chemical syndrome or other central sensitivity syndromes.

Each case was matched as closely as possible with a control. All controls were evaluated with the Fukuda criteria to ensure that none had CFS.

The control subjects were selected among people attended in the Primary Care Center Primer de Maig of Lleida. Since only 77 effective cases were available and considering the frequency of exposure in the control group (0.5), an alpha error of 0.05 and a power of 0.80 with a bilateral hypothesis, the odds ratio (OR) of the study was  $\geq 2.5$ .

The data were collected from July 2013 to February 2014 in a table of vital stress events (VSE) specifically elaborated for this study taking into account the Stress Inventory Scale by Holmes and Rahe<sup>(10)</sup>, the Traumatic Events Questionnaire (TEQ)<sup>(11)</sup> and the Stressful Life Events Screening Questionnaire (SLESQ)<sup>(12)</sup>.

The questionnaire describes a total of 48 life situations which may be stressful to the participants. Since the questionnaire is self-administered the patients were assisted, if necessary, by the Principal Investigator.

### Statistical analysis

The grade of association was determined by calculation of the crude (cOR) and adjusted OR (aOR) with the corresponding confidence interval of 95 % (CI95%). The adjustment was made using binary logistic regression using the risk factors detected in the univariate analysis. A p value < 0.05 was considered statistically significant. The analyses were performed using the SPSS v 20 statistical package.

The study was carried out following the norms of good clinical practice, guaranteeing the veracity of all the data and results obtained and the anonymity of the participants according to the Organic Law on the protection of personal data<sup>(13)</sup> and Law 14/2007 of biomedical investigation<sup>(14)</sup>. The study was performed according to the principles of the Declaration of Helsinki<sup>(15)</sup> and was approved by the Committee of Ethics and Clinical Investigation of the Health Care Region of Lleida.

## RESULTS

Of a total of 120 eligible cases 13 were excluded because they did not fulfill the inclusion criterion of age. Of the overall study population 14 could

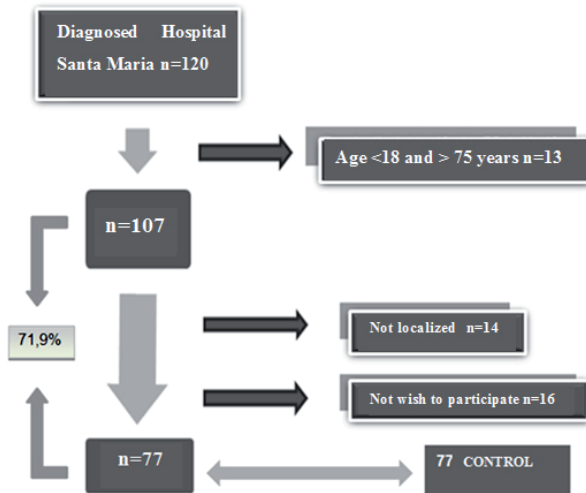
not be localized, and 16 did not wish to participate. Finally, 77 out of 107 (71.9%) cases were included and matched with 77 controls (figure 1).

The mean age of the cases was 50.8 years [standard deviation (SD) 8.5 years] while that of the controls was 51.2 years (SD 8.4; range: 21-68 years). Among the cases and controls 69 (89.7%) were women and 39 (50.7%) had secondary education or higher.

Univariate analysis identified the statistically significant vital events perceived as stressful (table 1).

Table 2 shows the stressful vital events (SVE) which were independently associated in the multivariate analysis: pregnancy (OR 31.7; CI95% 2.2-456.7), partner abuse (OR=10.2; CI95%:1.2-88.4), mobbing (OR=6.9 CI95%:1.3-36.9), eating disorders (OR=7.5; CI95%: 1.3-42.1), traffic accident (OR=5.5; CI95%: 1.7-17.9), economic problems (OR=5.1; CI95%: 2.1- 12.6) and changes in sleeping habits (OR=2.8; CI95%: 1.1-7.5).

**Figure 1**  
**Sequential scheme of sample collection study**



**Table 1**  
**Stressful events associated to Chronic Fatigue Syndrome. Univariate analysis**

AVE	Cases		Controls		p	OR (CI 95%)
	SI n (%)	NO n (%)	SI n (%)	NO n (%)		
School/college problems	26 (33.8)	51 (66.2)	0 (0.0)	77 (100)	0.00	40.5 (5.3-307.3)
Pregnancy	18 (23.4)	59 (76.6)	1 (1.3)	76 (98.7)	0.00	23.2 (3-178.8)
Family abuse	15 (19.5)	62 (82.5)	0 (0.0)	77 (100)	0.00	19.8 (2.5-153.5)
Partner abuse	15 (19.5)	62 (82.5)	1 (1.3)	76 (98.7)	0.00	18.4 (2.4-143.1)
Change in school/college	14 (18.2)	63 (81.8)	1 (1.3)	76 (98.7)	0.00	16.9 (2.2-132)
Marriage	13 (16.9)	64 (83.1)	0 (0.0)	77 (100)	0.00	16.8 (2.1-131.2)
Discussion between parents	13 (16.9)	64 (83.1)	1 (1.3)	76 (98.7)	0.00	15.4 (1.9-121.2)
Sexual abuse	11 (14.3)	66 (85.7)	0 (0.0)	77 (100)	0.00	13.9 (1.7-110.3)
Christmas	11 (14.3)	66 (85.7)	1 (1.3)	76 (98.7)	0.00	12.6 (1.6-100.7)
Sex difficulties	19 (24.7)	58 (75.3)	2 (2.6)	75 (97.4)	0.00	12.3 (2.7-54.9)
Mobbing	18 (23.4)	59 (76.6)	2 (2.6)	75 (97.4)	0.00	11.4 (2.5-51.3)
Eating disorders	18 (23.4)	59 (76.6)	2 (2.6)	75 (97.4)	0.00	11.4 (2.5-51.3)
Unwished pregnancy	7 (9.1)	70 (90.9)	0 (0.0)	77 (100)	0.01	8.8 (1.1-72.0)
Childbirth	19 (24.7)	58 (75.3)	3 (3.9)	74 (96.1)	0.00	8.1 (2.3-28.6)
Extramarital relation	10 (13.0)	67 (87.0)	2 (2.6)	75 (97.4)	0.01	5.6 (1.2-26.5)
Economic problems	26 (33.8)	51 (66.2)	7 (9.1)	70 (90.9)	0.00	5.1 (2.0-12.6)
Traffic accident	23 (29.9)	54 (70.1)	6 (7.8)	71 (92.2)	0.00	5.0 (1.9-13.2)
Trouble with parents	24 (31.2)	53 (68.8)	7 (9.1)	70 (90.9)	0.00	4.5 (1.8-11.3)
Misbirth	16 (20.8)	61 (79.2)	5 (6.5)	72 (93.5)	0.01	3.7 (1.3-10.9)
Change in work conditions	18 (23.4)	59 (76.6)	6 (7.8)	71 (92.2)	0.00	3.6 (1.3-9.7)
Personal injury or illness	41 (53.2)	36 (46.8)	20 (26.0)	57 (74.0)	0.00	3.2 (1.6-6.4)
Change in sleeping habits	30 (39.0)	47 (61.0)	15 (19.5)	62 (80.5)	0.00	2.6 (1.3-5.5)
Change in friendships	18 (23.4)	59 (76.6)	8 (10.4)	69 (89.6)	0.03	2.6 (1.1-6.5)

OR: Odds ratio. CI95%: Confidence interval 95%

AVE	ORc (CI 95%)	ORa (CI 95%)
Pregnancy	23.2 (3.0-178.8)	31.7 (2.2-456.7)
Partner abuse	18.4 (2.4-143.1)	10.2 (1.2-88.4)
Eating disorders	11.4 (2.5-51.3)	7.5 (1.3-42.1)
Mobbing	11.4 (2.5-51.3)	6.9 (1.3-36.9)
Traffic accident	5.0 (1.9-13.2)	5.5 (1.7-17.9)
Economic problems	5.1 (2.1-12.6)	5.1 (2.1-12.6)
Change in sleeping habits	2.6 (1.3-5.5)	2.8 (1.1-7.5)

ORc: crude odds ratio; ORa: adjusted odds ratio CI: Confidence interval 95%

## DISCUSSION

In the present study 7 SVE were identified as independent stress factors including pregnancy, partner abuse, mobbing, eating disorders, traffic accident, economic problems and changes in sleeping habits.

Different hypotheses have been generated in relation to the factors which predispose and trigger CFS. Several studies<sup>(9, 16)</sup> have focused on stressful situations experienced during early stages of life as factors which may favor the presentation of the disease.

It is of note that although there are different studies on SVE and CFS, none have identified the stressful events related to the later appearance of the disease. Indeed, although it has been described that pregnancy may affect the evolution of CFS, no study has associated pregnancy with the presentation of this syndrome<sup>(17)</sup>. Neither have traffic accidents been associated with the posterior presentation of CFS. On the other hand, there are similar studies on fibromyalgia<sup>(18-20)</sup>.

Several studies have described that both physical and psychological abuse<sup>(21)</sup> during different stages of life are related to the appearance of CFS<sup>(16)</sup>.

Eating disorders, mainly anorexia and bulimia, are very frequent among people with CFS. Fisher et al.<sup>(22)</sup> questioned whether an eating disorder acts as a trigger of CFS or is simply a coincidence.

With respect to mobbing at work, Mansilla<sup>(23)</sup> concluded that the therapeutic approach to cases of CFS should include thorough assessment of occupational relationships.

A change in sleeping habits is a factor which is frequently associated with symptomatic CFS. However, this factor has not been previously described as a trigger of this syndrome, although it has been reported to be a possible factor of disease persistence and comorbidity<sup>(24)</sup>.

With regard to economic problems, we found that an unfavorable economic situation was related to the appearance of CFS. Again, no previous studies have attributed this as a factor related to CFS<sup>(25-27)</sup>.

Primary care centers are the doorway through which patients with fatigue are consulted, with nursing professionals providing the easiest access. Nursing consultations provide an excellent opportunity to create a personal link and facilitate evaluation of the associated circumstances. The present study shows that nursing staff are able to adequately assess SVE in subjects with CFS. Considering the numerous SVE detected nurses are able to orient the diagnosis and avoid worsening of the disease, even in cases in which the time interval of the symptoms referred by the patient is of less than the 6 months deemed necessary to achieve the diagnosis.

The main limitation of this study is the possible difficulty in information collection. Since this was a retrospective study and taking into account the symptomatology of CFS, some of the individuals doing the questionnaire may not remember situations which should be evaluated. On the other hand, there may also be a bias among the cases and controls in that the former may remember more stressful situations because they may have been thinking more about situations that may be related to the presentation of the disease.

The use of a non-validated ad hoc questionnaire to evaluate the presence of SVE is a methodological limitation. However, in the absence of a validated medical tool to easily obtain this information this questionnaire may provide a new instrument to evaluate these situations of CFS.

The results of the present study may be useful in primary care in order to reduce the time to achieve a correct diagnosis of CFS. Further studies should be performed to obtain more evidence of the role of SVE as triggering factors of CFS. Moreover, a cohort study is needed to evaluate the factors identified in the multivariate analysis as well as to validate the questionnaire on SVE proposed.

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