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Undiagnosed and comorbid disorders in patients with presumed chronic fatigue syndrome [☆]

An Mariman ^{a,b,*}, Liesbeth Delesie ^{a,b}, Els Tobback ^{a,b}, Ignace Hanoulle ^a, Erica Sermijn ^a, Peter Vermeir ^a, Dirk Pevernagie ^{c,d}, Dirk Vogelaers ^{a,b,d}

^a Department of General Internal Medicine, Infectious Diseases and Psychosomatic Medicine, University Hospital Ghent, Belgium

^b Center for Neurophysiologic Monitoring, University Hospital Ghent, Belgium

^c Sleep Medicine Center, Kempenhaeghe Foundation, Heeze, The Netherlands

^d Department of Internal Medicine, Faculty of Medicine and Health Sciences, University of Ghent, Belgium

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ABSTRACT

Objective: To assess undiagnosed and comorbid disorders in patients referred to a tertiary care center with a presumed diagnosis of chronic fatigue syndrome (CFS).

Methods: Patients referred for chronic unexplained fatigue entered an integrated diagnostic pathway, including internal medicine assessment, psychodiagnostic screening, physiotherapeutic assessment and polysomnography + multiple sleep latency testing. Final diagnosis resulted from a multidisciplinary team discussion. Fukuda criteria were used for the diagnosis of CFS, DSM-IV-TR criteria for psychiatric disorders, ICSD-2 criteria for sleep disorders. **Results:** Out of 377 patients referred, 279 (74.0%) were included in the study [84.9% female; mean age 38.8 years (SD 10.3)].

A diagnosis of unequivocal CFS was made in 23.3%. In 21.1%, CFS was associated with a sleep disorder and/or psychiatric disorder, not invalidating the diagnosis of CFS. A predominant sleep disorder was found in 9.7%, 19.0% had a psychiatric disorder and 20.8% a combination of both. Only 2.2% was diagnosed with a classical internal disease. In the total sample, a sleep disorder was found in 49.8%, especially obstructive sleep apnea syndrome, followed by psychophysiological insomnia and periodic limb movement disorder. A psychiatric disorder was diagnosed in 45.2%; mostly mood and anxiety disorder.

Conclusions: A multidisciplinary approach to presumed CFS yields unequivocal CFS in only a minority of patients, and reveals a broad spectrum of exclusionary or comorbid conditions within the domains of sleep medicine and psychiatry. These findings favor a systematic diagnostic approach to CFS, suitable to identify a wide range of diagnostic categories that may be subject to dedicated care.

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Introduction

Chronic fatigue syndrome (CFS) is characterized by long lasting, unexplained fatigue with a disabling impact on professional, social and daily functioning. The absence of any obvious underlying disease and the presence of a number of associated clinical features are fundamental to this disorder. Several case definitions have been introduced, including the revised CDC (Centers for Disease Control and Prevention) criteria published by Fukuda et al. in 1994 [1]. These are now the standard criteria in the US and are widely used in other countries as well. To establish the diagnosis of CFS, the Fukuda definition requires a major criterion of unexplained, incapacitating fatigue of at least six month duration, in combination with at least four out of eight minor criteria. These minor criteria include postexertional malaise lasting for at least 24 h, sore throat, tender cervical or axillary lymph nodes, muscle pain, multi-joint pain without swelling or redness, headache of a new type, pattern or severity, memory and concentration impairment and unrefreshing sleep.

Abbreviations: AASM, American Academy of Sleep Medicine; AHI, apnea-hypopnea index; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CFS, chronic fatigue syndrome; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th edition – text revision; ICSD-2, International Classification of Sleep Disorders, 2nd edition; MSLT, multiple sleep latency test; MUS, medically unexplained symptoms; OSA, obstructive sleep apnea; PLMD, periodic limb movement disorder; PLM, periodic limb movements; PSG, polysomnography; REM, rapid eye movements; UCF, unexplained chronic fatigue; SD, standard deviation.

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* Corresponding author at: Dept of General Internal Medicine, Infectious Diseases and Psychosomatic Medicine, University Hospital Ghent, De Pintelaan 185, B-9000 Ghent, Belgium. Tel.: +32 9 332 37 08; fax: +32 9 332 38 95.

E-mail address: an.mariman@ugent.be (A. Mariman).

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Fatigue, the main feature of CFS, is a complex, heterogeneous and multidimensional phenomenon. It is a common denominator referring to various aspects of impaired physical, mental, emotional and neuro-cognitive functioning [2–4]. Fatigue is a frequent manifestation of a variety of medical, neurological and psychiatric conditions but it may also appear as a side effect of pharmacological treatment.

With regard to fatigue and associated symptoms, the syndromal definition of CFS overlaps with other entities such as insomnia [5,6], obstructive sleep apnea (OSA) [7], fibromyalgia [8] and mood disorders [9]. The Fukuda case definition stipulates limited exclusion criteria within the domain of primary psychiatric disorders, such as past or present diagnosis of a major depression with psychotic features, melancholic depression, bipolar affective disorders, schizophrenia of any subtype, delusional disorders of any subtype, dementia of any subtype, and anorexia nervosa or bulimia nervosa [1]. As a result, the presence of a mood disorder does not exclude a diagnosis of CFS according to the Fukuda criteria. In this case definition, however, the extent to which this disorder needs to be treated is not specified, whereas the major criterion requires the absence of a medical or psychiatric disorder that in itself may sufficiently explain abnormal fatigue. Within the primary sleep disorders, sleep apnea, without indication of severity, and narcolepsy are conditions that exclude a diagnosis of CFS [1]. Primary and secondary insomnia (Diagnostic and Statistical Manual of Mental Disorders 4th edition – text revision, DSM-IV-TR) [10] do not feature within the Fukuda exclusions, although insomnia can explain the somatic symptoms in a number of presumed CFS patients [5,11].

Unexplained chronic fatigue (UCF) is best approached from a biopsychosocial perspective [12] within a multidisciplinary setting. A monodisciplinary approach may lead to a spurious diagnosis of CFS as treatable psychiatric or sleep disorders may go unnoticed.

Patients with UCF in whom previous clinical investigations had not revealed any medical or psychiatric disease were referred to our tertiary care center to confirm or exclude a presumed diagnosis of CFS. The aim of the current study was to identify nosological entities that are either exclusionary or comorbid to CFS and to assess the prevalence of these disorders in the group of patients referred with UCF to our center.

Methods

Patient recruitment took place between June 2010 and February 2011. Patients were admitted to our tertiary care referral center for further clinical investigation of UCF. Prior to referral they had been examined by conventional methods in primary and/or secondary care settings. These previous assessments did not reveal any underlying medical or psychiatric disease that would obviously explain the severity and duration of the reported chronic fatigue.

Criteria for enrollment were UCF persisting for at least six months, and a minimum age of 18 years. Participants gave written informed consent. The study was approved by the institutional Ethical Review Board of the University Hospital Ghent, Belgium.

Multidisciplinary assessment

Assessment of UCF at our center follows a holistic approach that is based on the biopsychosocial model by Wessely et al. [12]. The initial diagnostic part of the integrated diagnostic pathway (Fig. 1) involves internal medicine assessment, psychodiagnostic screening, rehabilitation assessment, and polysomnography (PSG) combined with a multiple sleep latency test (MSLT). The internal medicine assessment consists of comprehensive history taking, also considering any previous medical diagnoses or investigations, and a physical examination. If indicated, routine lab tests, chest radiography and echography of the abdomen are carried out. A rehabilitation physician evaluates whether any musculoskeletal comorbidity is present that is potentially suitable for physiotherapeutic management. Psychodiagnostic screening, performed by a medical psychologist, includes history taking, the

administration of validated questionnaires (Table 1) and psychological tests. Psychiatric consultation is scheduled when the history is remarkable for a past or present psychiatric disorder, and whenever hints for the presence of a psychiatric disorder emerge from the psychodiagnostic evaluation or from the multidisciplinary discussion (Fig. 1). Psychiatric diagnosis complies with DSM-IV-TR criteria [10]. Final diagnosis results from a subsequent multidisciplinary team discussion with definition of an individually tailored management plan.

Sleep assessment

Sleep history is based on an interview that integrates the results of relevant sleep questionnaires (Table 1). Sleep diagnosis is in keeping with the International Classification of Sleep Disorders (ICSD-2) nosology [13].

PSG and MSLT are recorded and scored according to the American Academy of Sleep Medicine (AASM) manual [14]. Sleep parameters derived from PSG include time in bed, total sleep time, sleep efficiency, sleep latency, rapid eye movements (REM) sleep latency, time spent in the different sleep stages, wakefulness after sleep onset, arousal index, apnea-hypopnea index (AHI) and presence of periodic limb movements (PLM). MSLT consists of taking four naps and assessing mean sleep latency and presence of REM sleep at sleep onset.

OSA is defined by an AHI ≥ 5 /h in combination with associated symptoms (e.g. excessive daytime sleepiness, fatigue, or impaired cognition). Severity of OSA is classified as mild ($5 \leq \text{AHI} < 15$), moderate ($15 \leq \text{AHI} < 30$) or severe ($\text{AHI} \geq 30$).

Patients were asked to withdraw from hypnotics (benzodiazepines and z-drugs) at least three weeks before PSG was performed.

Diagnostic decision making and categories

The outcome of the multidisciplinary discussion is a diagnostic decision regarding unequivocal CFS, CFS with comorbidity, or a condition that excludes CFS.

In unequivocal CFS, no symptoms or signs of coexisting sleep or psychiatric disorders are observed. CFS with comorbidity is defined as a combination of UCF meeting the major and minor Fukuda criteria, with a comorbid condition that may contribute to, but does not sufficiently explain the degree of reported impairment. Typically, coexisting mood disorder or sleep disorders (e.g. OSA, insomnia, or periodic limb movement disorder (PLMD)) are being considered 'comorbid' in a number of patients. Predominant sleep and/or psychiatric disorders are judged exclusionary to CFS, as they tentatively explain the full clinical picture, including fatigue. In this case, the diagnosis of CFS is not assumed in the first instance, but may be reconsidered in a subsequent stage, pending insufficient symptomatic relief following adequate treatment of the primary disorder. Nevertheless, this study focuses on the initial diagnostic classification without further follow-up of patients after treatment.

Diagnostic categories include: 1) CFS without comorbidity (unequivocal CFS), 2) CFS with comorbidity, 3) a predominant sleep disorder, 4) a predominant psychiatric disorder, 5) a combination of a sleep and psychiatric disorder, 6) a classical internal medicine disease (with or without associated psychiatric or sleep disorders), 7) no final diagnosis (complaints of chronic fatigue remaining unresolved).

Statistical analysis

Descriptive statistics were performed with SPSS Statistics version 19.

Results

Inclusion and demographics

Three hundred seventy-seven patients were referred for evaluation of UCF (Fig. 2). Seven patients (1.9%) were excluded because of the age criterion. Fifty-eight patients

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