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Chronic fatigue syndrome (CFS) symptom-based phenotypes in two clinical cohorts of adult patients in the UK and The Netherlands

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ABSTRACT

Objective: Studies have provided evidence of heterogeneity within chronic fatigue syndrome (CFS), but few have used data from large cohorts of CFS patients or replication samples.
Methods: 29 UK secondary-care CFS services recorded the presence/absence of 12 CFS-related symptoms; 8 of these symptoms were recorded by a Dutch tertiary service. Latent Class Analysis (LCA) was used to assign symptom profiles (phenotypes). Regression models were fitted with phenotype as outcome (in relation to age, sex, BMI, duration of illness) and exposure (in relation to comorbidities and patient-reported measures).
Results: Data were available for 7041 UK and 1392 Dutch patients. Almost all patients in both cohorts presented with post-exertional malaise, cognitive dysfunction and disturbed/unrefreshing sleep, and these 3 symptoms were excluded from LCA. In UK patients, six phenotypes emerged: 'full' polysymptomatic (median 8, IQR 7-9 symptoms) 32.8%; 'pain-only' (muscle/joint) 20.3%; 'sore throat/painful lymph node' 4.5%; and 'oligosymptomatic' (median 1, IQR 0-2 symptoms) 4.7%. Two 'partial' polysymptomatic phenotypes were similar to the 'full' phenotype, bar absence of dizziness/nausea/palpitations (21.4%) or sore throat/painful lymph nodes (16.3%). Women and patients with longer duration of illness were more likely to be polysymptomatic. Polysymptomatic patients had more severe illness and more comorbidities. LCA restricted to 5 symptoms recorded in both cohorts indicated 3 classes (polysymptomatic, oligosymptomatic, pain-only), which were replicated in Dutch data.
Conclusions: Adults with CFS may have one of 6 symptom-based phenotypes associated with sex, duration and severity of illness, and comorbidity. Future research needs to determine whether phenotypes predict treatment outcomes, and require different treatments.

Introduction

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME) or, more recently, systemic exertion intolerance disease (SEID) [24], is defined as persistent or recurrent debilitating fatigue that is not lifelong, or the result of ongoing exertion, or alleviated by rest, or explained by other conditions, and which results in a substantial reduction in activity [36]. CFS imposes a huge burden on patients, carers and families [23,34,46]. In the UK, adults who attend NHS specialist CFS services have been ill for a median duration of 3°years, and half of those who were employed at the onset of their illness have ceased working [12]. A meta-analysis of prevalence studies based on clinically-confirmed cases in several countries indicates a prevalence of 0.76% (95% CI 0.23% to 1.29%) [28].

CFS is an illness of unknown aetiology and pathogenesis, and of varied symptomatology [43]. Heterogeneity in the symptom profile of CFS can be confusing for clinicians, fuelling debate over diagnostic criteria, and posing an obstacle to biomedical research that aims to find biomarkers of CFS [26]. Several studies have investigated heterogeneity (phenotypes) in adult [21,22,25,48,49,55,57] and paediatric [33] CFS patients. Despite between-study variation in the factors analysed and the methods used, these studies have demonstrated some consistency in classifying CFS phenotypes, including: a 'polysymptomatic' phenotype; a 'sore throat/painful lymph node' phenotype; phenotypes classified according to the presence/absence of musculoskeletal pain; and a dose-response effect in the number of symptoms and the overall severity of CFS. However, only one of the above studies conducted a replication analysis [2].

The relationship between CFS phenotypes and treatment outcomes remains relatively unexplored. Three studies have shown that CFS patients who present with pain symptoms have less favourable outcomes [10,14,30]. If symptom-based CFS phenotypes predict treatment outcomes, then simple decision-making algorithms based on symptom profiles could be used by clinicians and therapists to deliver individualised treatments.

In our study, we aimed to delineate symptom-based CFS phenotypes using data from a large clinical cohort of CFS patients from the UK, and

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to replicate our results in a clinical cohort of Dutch CFS patients. We aimed to investigate how these phenotypes were related to age, sex, and duration of illness, common CFS comorbidities (migraine, irritable bowel syndrome, anxiety and depression), and patient-reported measures of illness severity and quality-of-life.

Methods

UK CFS patient cohort

Study population

Patient data were extracted from the CFS National Outcomes Database (NOD). The NOD is a centralized repository of pseudonymised clinical assessment and patient-reported outcome data which are routinely collected by NHS specialist CFS services across England. The NOD has been hosted by the University of Bristol since 2006, primarily for the purpose of evaluating NHS adult and paediatric CFS services. For this study, we used data from patients assessed and treated by 29 NHS services during the period 01/06/2010 to 31/05/2013.

Symptoms, comorbidities and patient-reported measures

Clinical teams either sent photocopies of clinical assessment forms and patient questionnaires to the NOD team in Bristol for data entry or they entered data into their own local database which were transferred electronically to the NOD team at regular intervals. A CFS diagnosis was made (or confirmed) at an initial clinical assessment appointment in accordance with NICE guidelines [36]. The latter include a set of 12 persistent/recurrent symptoms, namely: sleep disturbance/unrefreshing sleep; joint pain; muscle pain; headaches; painful lymph nodes; sore throat; cognitive dysfunction; post-exertional malaise; general malaise/flu-like symptoms; dizziness; nausea; palpitations. Clinicians recorded the presence/absence of each symptom, with the guidance that the symptom should have persisted/recurred during 4 or more consecutive months, did not predate the fatigue and was not caused by some other medical condition. The recording of symptomatology in NHS specialist CFS services is part of the overall triage and assessment process, with multidisciplinary input from clinicians and therapists who have extensive experience in the diagnosis and treatment of CFS. Clinicians also record the presence/absence of 6 common comorbidities (migraine, irritable bowel syndrome, fibromyalgia, chronic regional pain disorder, depression, and anxiety), the patient's height and weight, and the duration of illness (months since onset of chronic fatigue). At assessment patients complete standard questionnaires which provide quantitative measures of fatigue (Chalder Fatigue Scale [11]), physical function (RAND SF-36 [56]), mood (Hospital Anxiety & Depression Scale (HADS) [47]), pain (visual analogue pain rating scale), self-efficacy (Stanford Self-Efficacy for Managing Chronic Disease 6-Item Scale [32]), sleepiness (Epworth Sleepiness Scale [27]), and quality-of-life (EQ-5D [16]). Psychiatric comorbidity that could explain the presence of fatigue was ruled out by clinical interview at the specialist service with experienced clinicians, using the HADS questionnaire.

Dutch CFS patient cohort (replication sample)

Study population

The Dutch cohort comprised adults diagnosed with CFS at a tertiary specialist care centre during the period 2007–2012 in accordance with Centers for Disease Control and Prevention (CDC) criteria [19,45] and Dutch guidelines [8,42]. A Checklist Individual Strength (CIS20-R) fatigue severity subscale score ≥ 35 [53] and a Sickness Impact Profile (SIP) score ≥ 700 were used as operational criteria for fatigue that was severe enough to cause substantial functional impairment [29]. Consultants of the outpatient clinic of the Department of Internal Medicine assessed the medical status of all patients and decided whether patients had been sufficiently evaluated to rule out a medical explanation for the fatigue. If patients had not been sufficiently examined, they were seen for full physical examination, case history evaluation and laboratory tests. Psychiatric comorbidity that could explain the presence of fatigue was ruled out by clinical interview at the specialist service with experienced clinical psychologists using Beck Depression Inventory for Primary Care (BDI-PC) [5,7] and Symptom Checklist 90 (SCL-90) [1] questionnaires.

Symptoms, comorbidities and patient-reported measures

CDC diagnostic criteria include a set of 8 persistent/recurrent symptoms occurring during 6 or more consecutive months: unrefreshing sleep; pain in several joints; muscle pain; headache; tender lymph nodes; sore throat; impaired memory; impaired concentration; and feeling ill after exertion. Patients were asked "Which of the following complaints did you experience during the last 6 months?" and, if affirmative, whether the symptom had been experienced for "less than" or "longer than" 6 months. We coded responses of "not at all" and "sometimes (each month)" as 'symptom absent' and responses of "sometimes (each week)" and "daily" as 'symptom present'. The latter also required the symptom to have been experienced for "longer than" 6 months. 'Post-exertional malaise' was in response to a question asking whether symptoms were worse after physical effort; 'cognitive dysfunction' was based on an affirmative response to one or both of two separate questions about forgetfulness and concentration; 'Sleep disturbance' was in response to a question asking whether the patient woke up unrefreshed. Responses were recorded by self-completed questionnaire. At assessment patients complete standard questionnaires which provide quantitative measures of: fatigue (Chalder Fatigue Scale [11] and CIS20-R [53]); physical functioning (RAND SF-36 [56]); mood (BDI-PC); and a 7-item self-efficacy scale [41].

Ethical approvals

The North Somerset & South Bristol Research Ethics Committee determined that collection and analysis of these CFS patient data did not require ethical review by an NHS Research Ethics Committee or approval by NHS Research and Development offices (REC ref. 07/Q2006/48). The medical-ethical committee of the Radboud University Nijmegen Medical Centre ruled that the collection and analysis of Dutch CFS patient data did not require ethical review. Dutch CFS patient data were collected as part of routine clinical practice.

Statistical methods

CFS phenotypes (primary and replication analyses)

Our latent class analysis (LCA) was based on symptoms recorded in UK and Dutch patient data. We planned to conduct our primary analysis using 12 symptoms recorded in UK patients, and our replication analysis using the restricted set of 8 symptoms recorded in both UK and Dutch patient data. All analyses were carried out using Mplus version 7.11 [58].

LCA identifies subtypes of related cases (latent classes, or 'phenotypes') from multivariate categorical data — in this case, responses to questions about presence/absence of each symptom [44]. LCA aims to determine the minimum number of latent classes that describe the observed patterns of responses in the data. In LCA, each individual is 'assigned' (probabilistically) to one of a pre-defined number of discrete latent classes on the basis of their responses to the symptom questions. The optimum class solution, i.e. the optimum number of classes, is selected by inspection and comparison of various model fit statistics [39], including: 1) Bayesian Information Criterion (BIC); 2) bivariate model fit — a test of the conditional independence assumption (within each class, there should be no association of one symptom with another, because all associations between symptoms are accounted for by class membership); 3) entropy – a measure of how well individuals have been classified (based on class membership probabilities) – a value of '1' indicates perfect separation of the classes; 4) Lo–Mendell–Rubin