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Chronic fatigue syndrome (CFS/ME) symptom-based phenotypes and 1-year treatment outcomes in two clinical cohorts of adult patients in the UK and The Netherlands

Simon M. Collin[a,*], Jon Heron[a], Stephanie Nikolaus[b], Hans Knoop[b], Esther Crawley[a]

[a] Population Health Sciences, Bristol Medical School, University of Bristol, Oakfield House, Oakfield Grove, Bristol BS8 2BN, UK
[b] Academic Medical Centre, Department of Medical Psychology, University of Amsterdam, Amsterdam Public Health Research Institute, Amsterdam, The Netherlands

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ABSTRACT

Objective: We previously described symptom-based chronic fatigue syndrome (CFS/ME) phenotypes in clinical assessment data from 7041 UK and 1392 Dutch adult CFS/ME patients. Here we aim to replicate these phenotypes in a more recent UK patient cohort, and investigate whether phenotypes are associated with 1-year treatment outcome.

Methods: 12 specialist CFS/ME services (11 UK, 1 NL) recorded the presence/absence of 5 symptoms (muscle pain, joint pain, headache, sore throat, and painful lymph nodes) which can occur in addition to the 3 symptoms (post-exertional malaise, cognitive dysfunction, and disturbed/unrefreshing sleep) that are present for almost all patients. Latent Class Analysis (LCA) was used to assign symptom profiles (phenotypes). Multinomial logistic regression models were fitted to quantify associations between phenotypes and overall change in health 1 year after the start of treatment.

Results: Baseline data were available for N = 918 UK and N = 1392 Dutch patients, of whom 416 (45.3%) and 912 (65.5%) had 1-year follow-up data, respectively. 3- and 4-class phenotypes identified in the previous UK patient cohort were replicated in the new UK cohort. UK patients who presented with 'polysymptomatic' and 'pain-only' phenotypes were 57% and 67% less likely (multinomial odds ratio (MOR) 0.43 (95% CI 0.19-0.94) and 0.33 (95% CI 0.13-0.84)) to report that their health was "very much better" or "much better" than patients who presented with an 'oligosymptomatic' phenotype. For Dutch patients, polysymptomatic and pain-only phenotypes were associated with 72% and 55% lower odds of improvement (MOR 0.28 (95% CI 0.11, 0.69) and 0.45 (95% CI 0.21, 0.99)) compared with oligosymptomatic patients.

Conclusions: Adult CFS/ME patients with multiple symptoms or pain symptoms who present for specialist treatment are much less likely to report favourable treatment outcomes than patients who present with few symptoms.

1. Introduction

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis (ME) or, more recently in the USA, systemic exertion intolerance disease (SEID) [1], 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 that results in a substantial reduction in activity [2,3]. A meta-analysis of studies based on clinically-confirmed cases in several countries indicated a prevalence of 0.76% (95% CI 0.23% to 1.29%) [4]. CFS/ME imposes a huge burden on patients, careers and families [5,6]. In the UK, adults who attend NHS specialist CFS/ME services have been ill for a median duration of 3 years, and half of those employed at the onset of their illness have ceased working [7].

In a previous study, we used latent class analysis to identify CFS/ME 'phenotypes' based on symptoms in CFS/ME patients attending UK specialist CFS/ME services from 2010 to 2013 [8]. Post-exertional malaise, cognitive dysfunction and disturbed/unrefreshing sleep were near universal symptoms. The other 5 symptoms (muscle pain, joint pain, headache, sore throat, and painful lymph nodes) delineated 3 phenotypes, characterized as 'polysymptomatic', 'oligosymptomatic', and 'pain-only' [8]. We replicated these 3 phenotypes in a cohort of CFS/ME patients attending a Dutch specialist CFS/ME service and, in both cohorts, the phenotypes were strongly associated with patient-

* Corresponding author.
E-mail address: simon.collin@bristol.ac.uk (S.M. Collin).

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reported measures of illness severity and with comorbidities.

The two aims of the present study were: 1) to replicate the original symptom-based CFS/ME phenotypes in a new UK cohort of CFS/ME patients; and 2) to investigate whether phenotypes were related to patient-reported treatment outcomes in the new UK cohort and in the original Dutch patient cohort.

2. Methods

2.1. UK CFS/ME patient cohort

Patients were recruited from 11 specialist CFS/ME services across England (10 NHS services, 1 registered independent provider) during the period 01/06/2014 to 30/09/2016. Patients were eligible if they were ≥ 18 years old and had a CFS/ME diagnosis made or confirmed at an initial clinical assessment appointment in accordance with NICE guidelines [2]. Patients were assessed and treated by clinicians and therapists who have specialist training and experience in the diagnosis and treatment of CFS/ME. The assessment included recording the presence/absence of 12 pre-specified symptoms, under guidance that the symptom should have persisted/recurred during ≥ 4 consecutive months, did not predate the fatigue and was not caused by some other medical condition. The 12 symptoms were: 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 also recorded the presence/absence of common comorbidities, including migraine, Irritable Bowel Syndrome (IBS), Fibromyalgia, depression, and anxiety. At the time of their initial assessment, patients completed standard questionnaires to obtain quantitative measures of fatigue (Chalder Fatigue Scale [9] and Checklist Individual Strength (CIS20-R) [10]) and physical function (RAND SF-36 [11]). Approximately 12 months after their initial clinical assessment, patients were asked to rate changes in their overall health on a Clinical Global Impression scale. They were asked "Overall, how much do you feel your health has changed since you first came to the CFS/ME service?" with possible responses of "very much", "much" or "a little" better, "no change", or "very much", "much" or "a little" worse. Patients who didn't respond were contacted by the clinical team via phone or email on up to 2 further occasions to elicit a response. Outcomes were coded as 'Much better' (="Very much better" or "Much better"), 'Worse' (="Very much worse" or "Much worse") or 'Unchanged' (="A little better", "No change" or "A little worse").

2.2. Dutch CFS/ME patient cohort

The Dutch cohort comprised adults diagnosed with CFS/ME and treated at a tertiary specialist care centre during the period 2007–2012 in accordance with Centers for Disease Control and Prevention (CDC) criteria [3,12] and Dutch guidelines [13,14]. A Checklist Individual Strength (CIS20-R) fatigue subscale score ≥ 35 [10] and a Sickness Impact Profile (SIP) score ≥ 700 were used as operational criteria for fatigue that was severe enough to cause substantial functional impairment [15]. Consultants in 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 an alternative explanation for their fatigue. Patients were given a full physical examination (unless this had already been completed), case history evaluation and laboratory tests. 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. Patients completed the CIS20-R after 12 months' follow up. Patients were classified as 'Much better' if their 12-month follow-up CIS20-R fatigue and SF-36 physical function subscale scores were 'normal' (< 35 and ≥ 65, respectively) [15] and if their fatigue had decreased by ≥ 8 points (corresponding to 1.96 × Reliable Change Index (RCI), where RCI = $\sqrt{2} \times SD_{healthy\ population} \times \sqrt{(1 - Cronbach\ \alpha)}$ [16]. For the CSI20-R fatigue subscale, $\alpha = 0.93$ and $SD_{healthy\ population} = 10.75$ [17]. Patients' health was classified as 'Worse' if their fatigue score had increased, and all other patients were classified as 'Unchanged'.

2.3. Ethical approvals

The UK study had NHS Research Ethics Committee approval (14/NW/0242), and all patients provided written informed consent. The medical-ethical committee of the Radboud University Nijmegen Medical Centre ruled that the collection and analysis of Dutch CFS/ME patient data did not require ethical review. Dutch CFS/ME patient data were collected as part of routine clinical practice.

2.4. Statistical methods

2.4.1. CFS/ME phenotypes

CFS/ME phenotypes in the UK patient cohort were explored using the same method as described in our earlier study [8]. Post-exertional malaise, cognitive dysfunction and disturbed/unrefreshing sleep were near universal symptoms, therefore we based our analysis on the five other symptoms recorded in both cohorts, namely: muscle pain, joint pain, headache, sore throat, and painful lymph nodes (dizziness, nausea, and palpitations were recorded only in the UK cohort). We used latent class analysis (LCA) to identify subtypes of related cases (latent classes, or 'phenotypes') according to presence/absence of each symptom [18]. Patients are 'assigned' (probabilistically) to one of a predefined number of discrete latent classes based on the presence or absence of symptoms. The optimum class solution, i.e. the optimum number of classes, is selected by inspection and comparison of various model fit statistics [19], 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 adjusted likelihood ratio test for c compared with c-1 classes; and 5) bootstrapped likelihood ratio test (BLRT) for c compared with c-1 classes. Selection of the optimum latent class solution, particularly when the statistical selection criteria are inconclusive, may also be informed by subjective input, including: clinical/biological plausibility, prior knowledge of likely heterogeneity within CFS/ME, and the clinical and epidemiological utility of any solution. The probabilities of reporting each symptom across the latent classes obtained from the original and new UK patient datasets were compared by visual inspection.

2.4.2. Associations of CFS/ME phenotypes with patient-reported outcome

Multinomial odds ratios (MORs) adjusted for age and sex were estimated using multinomial logistic regression with a 3-level ordinal