Systemic exertion intolerance disease diagnostic criteria applied on an adolescent chronic fatigue syndrome cohort: evaluation of subgroup differences and prognostic utility

Tarjei Torre Asprusten,1 Dag Sulheim,2 Even Fagermoen,3 Anette Winger,4 Eva Skovlund,5,6 Vegard Bruun Wyller1,7

ABSTRACT

Objective Existing case definitions for chronic fatigue syndrome (CFS) all have disputed validity. The present study investigates differences between adolescent patients with CFS who satisfy the systemic exertion intolerance disease (SEID) diagnostic criteria (SEID-positive) and those who do not satisfy the criteria (SEID-negative).

Methods 120 adolescent patients with CFS with a mean age of 15.4 years (range 12–18 years) included in the NorCAPITAL project (ClinicalTrials ID: NCT01040429) were post-hoc subgrouped according to the SEID criteria based on a comprehensive questionnaire. The two subgroups were compared across baseline characteristics, as well as a wide range of cardiovascular, inflammatory, infectious, neuroendocrine and cognitive variables. Data from 30-week follow-up were used to investigate prognostic differences between SEID-positive and SEID-negative patients.

Results A total of 45 patients with CFS were SEID-positive, 69 were SEID-negative and 6 could not be classified. Despite the fact that clinically depressed patients were excluded in the NorCAPITAL project, the SEID-positive group had significantly higher score on symptoms suggesting a mood disorder (Mood and Feelings Questionnaire); 23.2 vs 13.4, difference 9.19 (95% CI 5.78 to 12.6). No other baseline characteristics showed any group differences. When accounting for multiple comparisons, there were no statistically significant differences between the groups regarding cardiovascular, inflammatory, infectious, neuroendocrine and cognitive variables. Steps per day and Chalder Fatigue Questionnaire at week 30 showed no differences between the groups.

Conclusion The findings question the discriminant and prognostic validity of the SEID diagnostic criteria in adolescent CFS, and suggest that the criteria tend to select patients with depressive symptoms.

BACKGROUND

Chronic fatigue syndrome (CFS) is a disabling and long-lasting disorder characterised by symptoms such as fatigue, postexertional malaise (PEM), sleeping difficulties, widespread pain, cognitive problems and orthostatic intolerance.1–3 The prevalence estimates among adolescents vary from 0.1% to 1.0%,1,5 and the disorder may have a substantial negative impact on school attendance,6 quality of life6 and family functioning.7

The pathophysiology of CFS remains poorly understood. However, some studies report certain characteristics such as attenuation of the hypothalamus–pituitary–adrenal axis,8 9 which may be associated with PEM,10 altered autonomic cardiovascular control11 12 and impaired cognitive function.13 14

No biomarker association has been established in CFS, and a diagnosis therefore depends on symptom-based diagnostic criteria only. More than 20 case definitions exist. Most of them require between 3 and 6 months of unexplained fatigue, but vary considerably regarding requirement of additional symptoms.1 3 15 In a systematic review

What is already known on this topic?

► There exist more than 20 diagnostic definitions of chronic fatigue syndrome (CFS).
► A new definition and a new label (systemic exertion intolerance disease, SEID) have recently been proposed.
► The validity of the SEID criteria has not been established, either in adults or in adolescents.

What this study hopes to add?

► The present study questions the discriminant and prognostic validity of the SEID diagnostic criteria in adolescent CFS.
► It suggests that the criteria tend to select patients with depressive symptoms.
from 2014, Brurberg et al. could not draw firm conclusions concerning the validity of any of these criteria due to weak methodology and inconsistent results of the 38 included validation studies.

In 2015, the Institute of Medicine (IOM) in the USA proposed new diagnostic criteria for CFS (Box 1) and coined a new term: systemic exertion intolerance disease (SEID). In line with previous CFS criteria, the SEID criteria are also based on the requirement of specific symptoms assumed to correspond to certain pathophysiological characteristics.

The IOM report found strong evidence of slowed cognitive processing speed and orthostatic intolerance in CFS and that certain infections (such as Epstein-Barr virus (EBV) infection) often precipitate the disorder. The IOM report underlined the importance of empirically testing the SEID criteria, and that a multidisciplinary committee review should be undertaken within 5 years.

A diagnostic category should be regarded valid when at least one of two conditions is met: (1) if the diagnostic entity is clearly separated from neighbouring conditions and (2) if the diagnostic entity can be associated with a specific underlying disease process. Discriminant validity in this study concerns whether the two groups defined by the SEID criteria (SEID-positive and SEID-negative) differ in terms of variables reflecting underlying disease mechanisms, whereas prognostic validity concerns to what degree there are differences in outcomes between the two groups.

Some studies have compared the SEID criteria with existing case definitions, showing differences in prevalence, symptom severity and grade of impairment, but to the best of our knowledge the SEID definition has not been firmly validated, either in adolescent or adult patients with CFS. The aims of this study were to (1) investigate the prevalence of SEID-positive patients in a group of 120 adolescent patients with CFS, (2) evaluate the SEID criteria by investigating differences in background and disease markers between SEID-positive and SEID-negative patients, and (3) evaluate the prognostic impact of the SEID criteria by investigating differences in activity measure and fatigue between the groups at 30-week follow-up.

METHODS

Design

This study is part of the NorCAPITAL project (The Norwegian Study of Chronic Fatigue Syndrome in Adolescents: Pathophysiology and Intervention Trial; ClinicalTrials ID: NCT01040429, post-results). NorCAPITAL is a combined cross-sectional and randomised controlled trial that primarily aimed to investigate the pathophysiology of adolescent CFS and to assess low-dose clonidine pharmacotherapy to this group of patients; the design has been described in detail elsewhere. In the present study, we used baseline data and follow-up data from week 30. Data were collected between March 2010 and October 2012. Informed, written consent was obtained from all participants and from parents or next of kin if required.

Recruitment of patients with CFS

All hospital paediatric departments in Norway (n=20), primary care paediatricians and general practitioners were invited to refer adolescents with CFS aged 12–18 years consecutively to our department, which is a national referral centre for young patients with CFS. To be eligible for the NorCAPITAL project, we required 3 months of unexplained chronic/relapsing fatigue of new onset, and in line with clinical guidelines the patients were not required to meet any additional symptom criteria. A standard form required the referral unit to confirm the result of clinical investigations considered compulsory to diagnose paediatric CFS according to national Norwegian recommendations (evaluation by paediatric specialist, extensive haematology and biochemistry analyses, chest X-ray, abdominal ultrasound, and MRI of the brain). Also, the referring units were required to confirm that the patient (1) was hindered from normal school attendance due to fatigue; (2) was not permanently bedridden; (3) was not struck by a medical or psychiatric disorder (including depression) and/or did not go through any concurrent demanding life event, both could possibly account for the present fatigue; and (4) did not use medicines (including hormone contraceptives) regularly. Patients considered eligible were summoned to our study centre; a final decision on inclusion was made after a separate clinical examination combined with quality assessment of the previously conducted screening programme. Details of the recruitment procedure and inclusion/exclusion criteria are described elsewhere.

All participants underwent an identical investigational programme at baseline, 8 weeks and 30 weeks, which included a 1-day assessment in hospital consisting of...
clinical examination, blood sampling, autonomic testing and cognitive testing. Immediately afterwards, daily physical activity was monitored for seven consecutive days using the activPAL accelerometer device (PAL Technologies, Glasgow, Scotland), and a self-administered questionnaire was completed.

**Questionnaires**

A CFS symptom inventory for adults has previously been used to develop an analogous inventory for adolescents. A total of 24 common symptoms are evaluated in terms of frequency during the last month (5-point Likert scale ranging from never/rarer than once a month to present every day/almost every day, scored from 1 to 5).

In addition, validated inventories were used to assess the following:

1. Fatigue (Chalder Fatigue Questionnaire, CFQ): CFQ contains 11 questions reflecting different aspects of fatigue. It is scored in two ways; we used dichotomous scoring, where the respective answers are scored 0-0-1-1, giving a maximum score of 11.

2. Fatigue Severity Scale. Nine statements related to fatigue last month are scored on a Likert scale from 1 to 7, ranging from ‘strongly disagree’ to ‘strongly agree’, giving a maximum sum score of 63.

3. Sleep disturbances (Karolinska Sleep Questionnaire): Each symptom is scored 1-6 on a Likert scale, with lower scores indicating poorer sleep. A subscale measuring insomnia is constructed by taking the mean across four items addressing insomnia problems during the preceding month.

4. Symptoms of autonomic dysfunction (Autonomic Symptom Profile): A version for children and adolescents provides subscores on six functional areas. The score reflecting orthostatic intolerance is used in the present paper. Patients were asked whether they get dizzy when rising up from supine position (maximum score of 2), and whether they have felt dizzy or not in seven specific situations (score of 1 each), giving a maximum total score of 9.

5. Depressive symptoms (Mood and Feelings Questionnaire, MFQ): Patients were asked 34 questions on what they had been feeling and doing the preceding 2 weeks; each question was indicated as ‘Not true’, ‘Sometimes true’ or ‘True’, scored 0, 1 and 2, giving a maximum total sum score of 68. Seven items were removed in a sensitivity analysis because they were likely to be positively answered by a fatigued patient.

6. Quality of life (Pediatric Quality of Life Inventory, PedsQL): PedsQL covers four dimensions of quality of life: physical (eight items), emotional (five items), social (five items) and school functioning (five items). Twenty-three items are scored from 0 to 4 on a Likert scale, ranging from ‘never’ to ‘almost always’. Raw scores are transformed, providing a mean score that ranges from 0 to 100.

7. Functional disability (Functional Disability Inventory, FDI): FDI addresses difficulties related to participation in different activities, each item scored 0–4 on a Likert scale, extending from ‘No trouble’ to ‘Impossible’. The maximum total score is 60.

**Subgrouping according to the SEID criteria**

The IOM report presents the SEID criteria with an explanation of presumed core symptoms; these symptoms are considered mandatory to receive the diagnosis. We used variables from the above-mentioned set of questionnaires to operationalise the criteria, and then used baseline data to decide whether a patient fulfilled the SEID criteria or not (see online supplementary table 1).

**Disease markers**

All methods for disease marker investigation have been thoroughly described in previous publications from the NorCAPITAL project. In short, inflammation markers were investigated by examining plasma CRP (C-reactive protein) level through a high-sensitive assay (Roche Diagnostics, Indianapolis, Indiana, USA), and by measuring 27 plasma cytokines using a multiplex technique (Bio-Plex Human Cytokine 27-Plex; Bio-Rad Laboratories, Hercules, California, USA). Specific antibody responses against EBV and Cytomegalovirus (CMV) were assessed using anti-EBV EBNA IgG (Bio-Rad, Dreieich, Germany), anti-EBV VCA IgG and IgM (Hiss Diagnostics, Freiburg, Germany), and anti-CMV IgG and IgM (Architect, Abbott, Illinois, USA). Autonomic cardiovascular control of orthostasis was investigated using the Task Force Monitor (TFM; Model 3040i, CNSystems Medizintechnik, Graz, Austria), a combined hardware and software device for non-invasive continuous recording of cardiovascular variables. The patients were subjected to a low-intensity 20° head-up tilt test. Power spectral analysis of heart rate variability (HRV) was automatically provided by the TFM, power was calculated in the low-frequency (LF) range (0.05–0.17 Hz) and high-frequency (HF) range (0.17–0.4 Hz). Vagal (parasympathetic) activity is the main contributor to HF variability, whereas both vagal and sympathetic activities contribute to LF variability; the LF:HF ratio is considered an index of sympathovagal balance. Cognitive function was assessed using the digit span test from the Wechsler Intelligence Scale for Children, Fourth Edition, the conditions 1–3 of Color-Word Interference Test from the Delis-Kaplan Executive Function System, and the total recall part of Hopkins Verbal Learning Test-Revised (HVLT-R).

**Statistical analysis**

One hundred and twenty adolescent patients with CFS were included in the NorCAPITAL project. Presupposing the same number of SEID criteria positive and negative patients and a significance level of 5%, the power to detect an effect size of 0.6 (difference/SD) was estimated to be 90%; the power to detect an effect size of 0.5 would be a minimum of 75%. A difference in sample size of <2:1 only had insignificant impact on the power estimates.
IBM SPSS statistics 24 (IBM, New York, USA) and iNZight (Department of Statistics, University of Auckland, New Zealand) were used for statistical analyses. Comparison of the SEID-positive and SEID-negative groups was performed by applying t-test, Mann-Whitney U test, χ² test or Fisher’s exact test as appropriate, and analysis of covariance (ANCOVA) was used to evaluate group differences at week 30. Multiple linear regression analyses were performed to explore possible confounding effects of baseline characteristics on between-group differences. A P value ≤0.05 was considered statistically significant. Due to multiple comparisons, a Holmes-Bonferroni correction was considered appropriate for all across-group tests (a total of 44), resulting in a level of significance equal to 0.05/44=0.00114. All tests were two-sided.

**RESULTS**

Of the 120 adolescent patients with CFS included in NorCAPITAL, 45 patients were classified as SEID-positive and 69 as SEID-negative. Six patients were excluded due to insufficient data (table 1).

The SEID-positive group had statistically significantly higher score on symptoms suggesting a mood disorder from the MFQ inventory (total score 23.2 vs 13.4, P≤0.001). We performed a sensitivity analysis by removing seven items from the MFQ likely to be positively answered by any fatigued person, but the difference remained statistically significant (total score 14.8 vs 8.46, P≤0.001). No other baseline characteristics were different between the two groups.

Preliminary analyses showed statistically significant differences at baseline on variables reflecting HF power, LF power, LF:HF ratio, plasma cortisol level and digit span sum score (table 2). However, when multiple comparisons were taken into account, none of the differences were considered statistically significant. Also, when adjusting for the possible confounding effects of total score of MFQ, total score of CFQ and steps per day in multiple linear regression analyses, all P values were >0.05.

An ANCOVA model featuring steps per day and CFQ at week 30 as outcome variables showed no differences between SEID groups (table 3).

**DISCUSSION**

The following are the main findings of this study: (1) No cardiovascular, infectious, inflammatory, neuroendocrine or cognitive biomarker differed significantly between the SEID-positive and the SEID-negative groups. (2) When controlled for baseline values, there were no differences in steps per day or CFQ at 30 weeks between the SEID-positive and the SEID-negative groups. (3) The SEID-positive group had significantly more depressive symptoms. Taken together, the findings question the validity of the SEID diagnostic criteria in adolescent CFS, and suggest that the criteria tend to select patients with depressive symptoms.

The SEID criteria have been criticised for not having predefined exclusion criteria, enabling patients with major depressive disorders to be diagnosed with CFS. The present sample should not contain patients with...
Table 2  Biomarkers possibly associated with the SEID diagnostic criteria

|                                | SEID-negative (n=69) | SEID-positive (n=45) | Difference/95% CI of difference/OR | P value, not adjusted | P value, adjusted* |
|--------------------------------|----------------------|----------------------|----------------------------------|-----------------------|---------------------|
| **Cardiovascular variables, supine** |                      |                      |                                  |                       |                     |
| Heart rate, beats/min, mean (SD) | 69.5 (9.0)           | 73.7 (13.1)          | 4.21 −0.23 to 8.64              | 0.063                 |                     |
| MAP, mm Hg, mean (SD)            | 78.7 (7.9)           | 79.2 (9.2)           | 0.54 −2.66 to 3.73              | 0.740                 |                     |
| TPRI, mm Hg/L/min/m² ×10⁻³, mean (SD) | 8.70 (2.12)        | 9.39 (16.6)          | 0.69 −0.05 to 1.43              | 0.067                 |                     |
| **LFnuRRI, normalised units, mean (SD)** | 38.7 (16.2)          | 46.1 (13.0)          | 7.43 1.72 to 13.1               | 0.011                 | 0.104               |
| **HFnuRRI, normalised units, mean (SD)** | 61.3 (16.3)          | 53.9 (13.0)          | −7.39 −13.1 to −1.67            | 0.012                 | 0.106               |
| **LFabsRRI, ms², median (IQR)** | 632 (805)            | 451 (774)            | −182 −516 to 136                | 0.159                 |                     |
| **HFabsRRI, ms², median (IQR)** | 1016 (1974)          | 495 (1662)           | −521 −1239 to 22                | 0.014                 | 0.051               |
| **LF:HF ratio, median (IQR)**    | 0.63 (0.56)          | 0.92 (0.88)          | 0.29 0.05 to 0.52               | 0.008                 | 0.082               |
| **Cardiovascular variables, delta values†** |                      |                      |                                  |                       |                     |
| Heart rate, beats/min, mean (SD) | 5.19 (4.39)          | 4.60 (3.22)          | −0.58 −2.09 to 0.93             | 0.418                 |                     |
| MAP, mm Hg, mean (SD)            | 1.02 (4.02)          | 1.32 (3.43)          | 0.30 −1.14 to 1.74              | 0.684                 |                     |
| TPRI, mm Hg/L/min/m² ×10⁻³, mean (SD) | 6.24 (8.09)          | 6.46 (6.63)          | −0.02 −0.29 to 0.34             | 0.895                 |                     |
| **LFnuRRI, normalised units, mean (SD)** | 9.22 (10.1)          | 5.32 (12.5)          | −3.90 −8.12 to 0.32             | 0.083                 |                     |
| **HFnuRRI, normalised units, mean (SD)** | −9.19 (10.1)         | −5.32 (12.5)         | 3.87 −0.55–8.28                 | 0.086                 |                     |
| **LFabsRRI, ms², median (IQR)**  | −94.3 (428)          | −101 (316)           | −7.2 −126 to 166                | 0.739                 |                     |
| **HFabsRRI, ms², median (IQR)**  | −355 (961)           | −153 (815)           | 202 −103 to 539                 | 0.075                 |                     |
| **LF:HF ratio, median (IQR)**    | 0.24 (0.66)          | 0.21 (0.80)          | −0.02 −0.43 to 0.29             | 0.092                 |                     |
| **Infectious variables**         |                      |                      |                                  |                       |                     |
| Anti-EBV EBNA IgG, n (%)         | 32 (49.2)            | 25 (56.8)            | 0.74 0.34 to 1.59               | 0.436                 |                     |
| Positive                        | 33 (50.8)            | 19 (43.2)            |                                  |                       |                     |
| Anti-EBV VCA IgM, n (%)         | 67 (98.5)            | 43 (95.6)            | 0.36 0.37 to 35.4               | 0.562                 |                     |
| Negative                        | 1 (1.5)              | 2 (4.4)              |                                  |                       |                     |
| Anti-EBV VCA IgG, n (%)         | 29 (65.9)            | 21 (67.7)            | 0.92 0.35 to 2.45               | 0.868                 |                     |
| Negative                        | 15 (34.1)            | 10 (32.3)            |                                  |                       |                     |
| Anti-CMV IgM, n (%)             | 67 (100)             | 45 (100)             |                                  |                       |                     |
| Negative                        | 0 (0)                | 0 (0)                |                                  |                       |                     |
| Anti-CMV IgG, n (%)             | 38 (55.9)            | 24 (53.3)            | 1.11 0.52 to 2.36               | 0.790                 |                     |
| Negative                        | 30 (44.1)            | 21 (46.7)            |                                  |                       |                     |
| **Inflammatory variables**       |                      |                      |                                  |                       |                     |
| Serum hsCRP, mg/L, median (IQR) | 0.44 (0.97)          | 0.46 (0.62)          | 0.02 −0.25 to 0.21              | 0.526                 |                     |
| Serum IL-1β, pg/mL, median (IQR)| 2.03 (2.12)          | 2.31 (2.31)          | 0.28 −0.92 to 1.06              | 0.620                 |                     |
| Serum IL-6, pg/mL, median (IQR) | 6.56 (5.54)          | 7.39 (7.29)          | 0.83 −1.66 to 3.00              | 0.481                 |                     |
| Serum IL-10, pg/mL, median (IQR)| 3.49 (3.35)          | 4.07 (6.88)          | 0.59 −1.25 to 3.16              | 0.936                 |                     |
| Serum TNF, pg/mL, median (IQR)  | 45.5 (39.1)          | 46.8 (46.1)          | 1.34 −13.3 to 15.5              | 0.674                 |                     |
| **Neuroendocrine variables**     |                      |                      |                                  |                       |                     |
| Plasma norepinephrine, pmol/L, mean (SD) | 1972 (722)           | 2017 (893)           | 45 −258 to 348                  | 0.770                 |                     |
| Plasma epinephrine, pmol/L, mean (SD) | 316 (104)            | 323 (125)            | 6.36 −37.4 to 50.1              | 0.774                 |                     |
| Plasma cortisol, nmol/L, mean (SD) | 345 (135)            | 400 (156)            | 55 −0.06 to 110                 | 0.050                 |                     |

Continued
clinical depression disorder, given the predefined exclusion criteria of NorCAPITAL; however, patients with varying degrees of depressive symptoms were eligible. Our finding of higher depressive symptom scores among SEID-positive patients might theoretically be explained from overlapping symptoms in depression and chronic fatigue states. However, in a sensitivity analysis removing possibly overlapping items, the differences between the groups remained, strengthening the finding that the SEID-positive group has a greater depressive symptom burden.

Opinions diverge whether chronic fatigue is a general, continuous phenomenon, or may be divided into discrete subgroups that are separate entities with regard to biological profile, treatment and prognosis.38 39 The Fukuda et al criteria1 are the most frequently used in both clinical practice and research, but questionable validity has been revealed.16 A recently published validation study on the Canadian Consensus Criteria reported few differences in biomarkers and no prognostic difference between adolescent patients with CFS who did and did not satisfy the criteria.40 The results from the present study corroborate these previous findings, and taken together these findings question more fundamentally the validity of classifying chronic fatigued patients based on symptom expressions alone.

Despite not being detected as statistically significant in the present study, variables reflecting HRV give the impression that autonomous cardiovascular control may be of importance in the further search for relevant and valid subgrouping of patients with chronic fatigue. This goes well with earlier findings showing significant changes in autonomous cardiovascular control in patients with CFS.11

**Strengths and limitations**

A strength of this study is the low rate of missing data. A limitation might be that data acquisition in the NorCAPITAL project was carried out before the SEID criteria were published. In particular, the phenomenon of PEM,
which was highlighted in the IOM report, was not specifically attended to in the NorCAPITAL project. However, we find it justified that the SEID criteria regard ‘increased fatigue after activity’ as a proxy for other PEM symptoms, in line with a previous study.57

CONCLUSION

This study questions the discriminant and prognostic validity of the SEID diagnostic criteria in adolescent CFS, and suggests that the criteria tend to select patients with depressive symptoms. These results corroborate earlier findings and question the concept of classifying fatigued patients based on symptom phenotype. A new approach may be to perform cluster analysis on biological markers to look for subgroups on a basal level with potentially different treatments, prognosis and others.

Acknowledgements We thank Kari Gjersum for secretariat assistance, Hansama Chandrakumar, Esther Gangas, Adelheid Holm, Anna Marie Thorendal Ryenbakken and Marianne Svendsen for practical assistance, Thor Ueland, Pål Aukrust, Fredrik Müller, Kristin Godang, J Philip Saul and Peter C Rowe for discussions on study design and results, and Line Sletner and Peter C Rowe for reflections and comments on the present paper.

Contributors TTA and VBW conceptualised and designed the study, carried out the statistical analyses, drafted the initial manuscript, and reviewed and revised the manuscript. EF, DS and AW collected the data and contributed to drafting the manuscript. ES supervised statistical analyses, and critically reviewed and revised the manuscript.

Funding This study was funded by Health South-East Hospital Trust and the University of Oslo.

Competing interests None declared.

Patient consent Obtained.

Ethics approval The study was approved by the Norwegian National Committee for Ethics in Medical Research and the Norwegian Medicines Agency and adhered to the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non-Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/ © Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

1. Fukuda K, Straus SE, Hickie I, et al. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Ann Intern Med* 1994;121:953–9.

2. IOM(Institute of Medicine). *Beyond myalgic encephalomyelitis/chronic fatigue syndrome: Redefining an illness*. Washington (DC): National Academies Press (US), 2015. http://www.nationalacademies.org/hmd/Reports/2015/MC-FS.aspx.

3. Carruthers BM, Jain AK, De Meirleir KL, et al. Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols. *J Chronic Fatigue Syndr* 2003;11:7–116.

4. Nijhof SL, Maijer K, Bieijenberg G, et al. Adolescent chronic fatigue syndrome: prevalence, incidence, and morbidity. *Pediatrics* 2011;127:e1169–e1175.

5. Crawley EM, Emond AM, Sterne JA. Unidentified Chronic Fatigue Syndrome/myalgic encephalomyelitis (CFS/ME) is a major cause of school absence: surveillance outcomes from school-based clinics. *BMJ Open* 2011;1:e000252.

6. Kennedy G, Underwood C, Belch JJ. Physical and functional impact of chronic fatigue syndrome/myalgic encephalomyelitis in childhood. *Pediatrics* 2010;125:e1324–30.

7. Mäenpää A, Hollingworth W, Eaton N, et al. The financial and psychological impacts on mothers of children with chronic fatigue syndrome (CFS/ME). *Child Care Health Dev* 2012;38:505–12.

8. Sulheim D, Fagermoen E, Winger A, et al. Disease mechanisms and clonidine treatment in adolescent chronic fatigue syndrome: a combined cross-sectional and randomized clinical trial. *JAMA Pediatr* 2014;168:351–60.

9. Papadopoulos AS, Cleare AJ. Hypothalamic–pituitary–adrenal axis dysfunction in chronic fatigue syndrome. *Nat Rev Endocrinol* 2012;8:22–32.

10. Hall DL, Lattie EG, Antoni MH, et al. Stress management skills, cortisol awakening response, and post-exertional malaise in Chronic Fatigue Syndrome. *Psychoneuroendocrinology* 2014;49:26–31.

11. Wyller VB, Due R, Saul JP, et al. Usefulness of an abnormal cardiovascular response during low-grade head-up tilt-test for discriminating adolescents with chronic fatigue from healthy controls. *Am J Cardio* 2007;98:997–1001.

12. Wyller VB, Vitelli V, Sulheim D, et al. Altered neuroendocrine control and association to clinical symptoms in adolescent chronic fatigue syndrome: a cross-sectional study. *J Transl Med* 2016;14:121.

13. NICE. *Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (or Encephalopathy): Diagnosis and Management of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (or Encephalopathy) in Adults and Children*. London: Excellence NIHTaC, 2007.

14. Sulheim D, Fagermoen E, Sivertsen GS, et al. Cognitive dysfunction in adolescents with chronic fatigue syndrome: a cross-sectional study. *Arch Dis Child* 2015;100:838–44.

15. Royal College of Paediatrics and Child Health. *Evidence Based Guideline for the Management of CFS/ME (Chronic Fatigue Syndrome/Myalgic Encephalopathy) in Children and Young People*. London: Royal College of Paediatrics and Child Health, 2004.

16. Brurberg KG, Fenhus MS, Larun L, et al. Case definitions for chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME): a systematic review. *BMJ Open* 2014;4:e003973.

17. Kendall R, Jablensky A. Distinguishing between the validity and utility of psychiatric diagnoses. *Am J Psychiatry* 2003;160:4–12.

18. Jason LA, McManimen S, Sunnquist M, et al. Examining the institute of medicine’s recommendations regarding chronic fatigue syndrome: clinical versus research case definitions. *J Neurol Psychol* 2015;2015(Suppl 2).

19. Jason LA, McManimen S, Sunnquist M, et al. Clinical criteria versus a possible research case definition in chronic fatigue syndrome/myalgic encephalomyelitis. *Fatigue* 2017;5:89–102.

20. Wagner D, Nisenbaum R, Heim C, et al. Psychometric properties of the CDC Symptom Inventory for assessment of chronic fatigue syndrome. *Popul Health Metr* 2005;3:8.

21. Chalder T, Berelowitz G, Pawlikowska T, et al. Development of a fatigue scale. *J Psychosom Res* 1993;37:147–53.

22. Knupp LB, LaRocca NG, Muir-Nash J, et al. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol* 1989;46:1121–3.

23. Krcliund G, Åkerstedt T. The psychometric properties of the Karolinska Sleep Questionnaire. *J Sleep Res* 1992;1(Suppl 1):113.

24. Åkerstedt T, Knutsson A, Westerholm R, et al. Sleep disturbances, work stress and work hours: a cross-sectional study. *J Psychosom Res* 2002;53:741–8.

25. Suarez GA, Opfer-Gehrking TL, Offord KP, et al. The autonomic symptom profile: A new instrument to assess autonomic symptoms. *Neurology* 1999;52:523–8.
26. Costello EJ, Angold A. Scales to assess child and adolescent depression: checklists, screens, and nets. J Am Acad Child Adolesc Psychiatry 1988;27:726–37.
27. Varni JW, Seid M, Rode CA. The PedsQL: measurement model for the pediatric quality of life inventory. Med Care 1999;37:126–39.
28. Walker LS, Greene JW. The functional disability inventory: measuring a neglected dimension of child health status. J Pediatr Psychol 1991;16:39–58.
29. Wyller VB, Sørensen O, Sulheim D, et al. Plasma cytokine expression in adolescent chronic fatigue syndrome. Brain Behav Immun 2015;46:80–6.
30. Fortin J, Habenbacher W, Heller A, et al. Non-invasive beat-to-beat cardiac output monitoring by an improved method of transthoracic bioimpedance measurement. Comput Biol Med 2006;36:1185–203.
31. Bianchi AM, Mainardi LT, Meloni C, et al. Continuous monitoring of the sympatho-vagal balance through spectral analysis. IEEE Eng Med Biol Mag 1997;16:64–73.
32. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Circulation 1996;93:1043–65.
33. Wechsler D. Wechsler intelligence scale for children. 4th edn. San Antonio, TX: The Psychological Corporation, 2003.
34. Delis D, Kaplan E, Kramer J. Delis-Kaplan Executive Function System (D-KEFS)(Norwegian version). Stockholm, Sweden: Pearson System, 2001.
35. Benedict RHB, Schretlen D, Groninger L, et al. Hopkins verbal learning test ? revised: normative data and analysis of inter-form and test-retest reliability. The Clinical Neuropsychologist 1998;12:43–55.
36. Holms S. A simple sequentially rejective multiple test procedure. Scandinavian Journal of Statistics 1979;6:65–70.
37. Jason L, Sunnquist M, Kot B, et al. Unintended consequences of not specifying exclusionary illnesses for systemic exertion intolerance disease. Diagnostics 2015;5:272–86.
38. Fink P, Toft T, Hansen MS, et al. Symptoms and syndromes of bodily distress: an exploratory study of 978 internal medical, neurological, and primary care patients. Psychosom Med 2007;69:30–9.
39. Maes M, Twisk FN, Johnson C. Myalgic Encephalomyelitis (ME), Chronic Fatigue Syndrome (CFS), and Chronic Fatigue (CF) are distinguished accurately: results of supervised learning techniques applied on clinical and inflammatory data. Psychiatry Res 2012;202:754–60.
40. Asprusten TT, Fagermoen E, Sulheim D, et al. Study findings challenge the content validity of the Canadian Consensus Criteria for adolescent chronic fatigue syndrome. Acta Paediatr 2015;104:498–503.