A comparison of cognitive function, sleep and activity levels in disease-free breast cancer patients with or without cancer-related fatigue syndrome

Ollie Minton, Patrick C Stone

ABSTRACT

Background Chronic fatigue is a feature in a subset of women successfully treated for breast cancer but is not well characterised. This study examines differences in objective cognitive function, activity levels and sleep in disease-free women who do and do not meet criteria for cancer-related fatigue syndrome (CRFS).

Methods Women between 3 months and 2 years after completion of any primary therapy were recruited from a cancer centre follow-up clinic. On the basis of a diagnostic semi-structured interview they were classified as being CRFS cases or non-fatigued controls. Participants underwent objective cognitive testing using a computerised battery, wore an activity monitor for 1 week and completed quality of life and fatigue questionnaires.

Results 114 women were recruited (69 controls and 45 CRFS cases). There were significant differences between groups on fatigue, mood, sleep and quality of life scores, and in objective cognitive testing (tests of sustained attention, reaction time and verbal memory all p<0.03). There was an overall difference in daytime activity (p=0.03) from actigraphy recordings. There were no differences on objective measures of sleep or in routine laboratory measures.

Conclusions Our preliminary results suggest that disease-free women with CRFS after successful breast cancer treatment have significantly lower subjective quality of life and mood. Additionally, objective cognitive impairment in certain domains may play an important role in the subjective manifestation of these symptoms. There is also objective evidence on actigraphy of differing levels of activity. The subjective sleep disturbance and higher prevalence of insomnia do not correlate with objective measures.

INTRODUCTION

Two thirds of women diagnosed with breast cancer today are likely to survive for at least 20 years. As a result more women are living with the longer-term side-effects of treatment. These can include neurocognitive changes, sleep disturbance, quality of life impairment and persistent fatigue. Of the many symptoms associated with cancer and its treatment, fatigue is probably the most under-recognised and poorly managed.

We have previously undertaken a systematic review of the literature regarding the prevalence of fatigue in breast cancer survivors (BCS). Many of the early studies of fatigue in cancer populations were limited by the use of poorly validated assessment instruments and the lack of a coherent definition of cancer-related fatigue syndrome (CRFS). However, in 1998 Cella and colleagues proposed the introduction of diagnostic criteria for CRFS, which have now been successfully applied in a number of clinical studies. These criteria are based on similar principles to those used to diagnose patients with chronic fatigue syndrome (CFS). Most recently, our own group rigorously applied the diagnostic criteria to BCS between 3 months and 2 years after completion of treatment. We found the prevalence of CRFS to be 30%.

CRFS is a clinical diagnosis and as such relies on the subjective reports of patients. Broadly speaking, patients’ complaints of fatigue relate to either decrements in motor performance (physical fatigue) or impaired cognitive abilities (mental fatigue). Unfortunately, the same term can be used to describe both an objective physical or mental decrement in performance and a subjective mental state. Both types of fatigue are usually found to a greater or lesser extent in the same individual. However, there is no direct correspondence between the two phenomena. It is quite possible to feel extremely subjectively fatigued but to perform relatively normally on objective tests of physical or mental functioning.

However, patients’ subjective complaints of physical fatigue relate to changes in the activities of daily living, mobility and the need for daytime naps. Unobtrusive objective monitoring is required to investigate these phenomena and studies have been performed using actigraphy (real-time activity monitoring). Overall, the data from several studies suggest that there is a strong correlation between changes in subjective fatigue and actigraphy data measures. The most consistent correlations occur between fatigue measures and disruption of sleep quality. However, the limitations of and variations in data collection mean these findings need further confirmation. In particular, these data have been recorded in patients on treatment and linked to sleep disturbances and have not adequately assessed the level of daytime fatigue. The exception to this was a study by our group in which, contrary to expectation, we found no significant differences in activity levels in a population of fatigued BCS compared to non-fatigued controls.

Several researchers have investigated cognitive changes in cancer survivors. Recent systematic reviews and a meta-analysis concluded that there is some evidence of objective declines in...
cognitive function (particularly verbal memory and executive function) following chemotherapy, but only one previous study has attempted to relate these objective findings to subjective complaints of fatigue. However, the authors did not use the diagnostic criteria and only employed a limited range of cognitive testing.

The primary aim of this study was to examine differences in objective measures of cognition (specifically focusing on previously identified cognitive domains that were affected) and in physical activity in women who did or did not meet the criteria for CRFS.

### MATERIALS AND METHODS

BCS were recruited from January 2009 to May 2011 from a single centre nurse-led follow-up clinic at St George’s Healthcare NHS Trust. Approval was obtained from Wandsworth ethics committee prior to data collection (ref 08/H0803/182).

All patients who were clinically and radiologically disease-free between 3 months and 2 years after the end of their primary treatment (of any modality) were invited to participate. Concurrent hormone use was allowed.

Those patients with significant cognitive impairment, a psychiatric history or medical co-morbidities on notes review or initial discussion with the researcher (OM) were excluded from entering the study (12 women in total). This was a pragmatic decision as these women were not eligible for the complete study.

Eligible women were identified from the clinic list 14 days before their appointment and received an introductory letter and an information sheet by post. Women who declined to participate in the study were asked if they would be willing to complete a short fatigue questionnaire.

#### Assessment 1

Women who consented to participate were invited to an initial consultation in a designated research facility and completed the following interviews and actigraphy.

**Diagnostic Interview for Cancer-Related Fatigue**

This interview determines whether the participant meets the four criteria for a diagnosis of CRFS: criterion A—the presence of 2 weeks of significant fatigue in the preceding month and the presence of at least five out of nine other fatigue-related symptoms; criterion B—the fatigue has a significant effect on work or self-care; criterion C—the fatigue symptoms are a consequence of cancer or cancer therapy; and criterion D—the symptoms are not primarily a consequence of a co-morbid psychiatric disorder. The final criterion can be assessed clinically, but the most robust method is to use a contemporaneous psychiatric interview. Participants with a significant psychiatric history which was felt to be contributing to fatigue were excluded.

**Structured Clinical Interview for the DSM–IV (SCID)**

The Structured Clinical Interview for the DSM-IV (SCID) provides a method for obtaining Diagnostic and Statistical Manual (DSM)-IV diagnoses. The procedure has been successfully used in previous studies examining CRFS and by our group. All interviews were conducted by the same person (OM). The SCID can be administered by a non-psychiatrist. OM was trained in administration and supervised by a consultant liaison psychiatrist. The average administration time was 30 min.

### Other questionnaires

All women were also asked to complete the following questionnaires:

1. **Functional Assessment of Cancer Therapy (FACT-F).** This is a 13-item questionnaire to measure fatigue in cancer and has been widely used in cancer treatment trials.
2. **The Chalder Fatigue Scale (FS).** This is an 11-item questionnaire to measure fatigue. It was originally developed in non-cancer patients but has been extensively used in a number of studies in cancer.
3. **European Organisation of Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-30).** This is a 30-item instrument with five functional scales, three symptom scales and a global quality of life score.
4. **Hospital Anxiety and Depression Scale (HADS).** This is a 14-item scale with seven items on anxiety and seven items on depression. It is used extensively in clinical trials and has been employed by our group previously in fatigue assessment studies.
5. **European Organisation of Research and Treatment of Cancer Breast Module (BR23).** This is a 23-item scale which is validated for use in breast cancer patients. It includes items on breast and arm symptoms and systemic treatment effects.
6. **The 7-item Insomnia Severity Index (ISI).** This scale has previously been validated in a breast cancer population. The seven items in this scale were combined with two additional sleep related questions to determine if insomnia diagnostic criteria were met:
   - During the past month how many nights per week have you taken more than 30 min to fall asleep?
   - During the past month how many nights per week were you awake for more than 30 min?

A diagnosis of insomnia syndrome was made if one of the above two features was present on more than three nights per week on average, there was significant distress as scored on the ISI and/or fatigue or daytime somnolence was present. It took 20 min on average to administer these questionnaires and conduct the CRFS interview. An initial appointment time of an hour was made and potential participants were made aware of this time requirement.

**Actigraphy**

After completion of the questionnaires and interview, participants were asked to wear an Actiwatch AW4 (CamNtech, Cambridge, UK) for a period of 7 days and nights. The associated software and sleep algorithm allows for the determination of selected measures of activity, sleep and circadian rhythm (over a 7-day average). A predetermined 12 h timeframe is used to define daytime (light) activity: 06:00 to 18:00 h. The night-time activity period (dark) is defined as 18:00 to 06:00 h. The participants used an event marker on the watch to record their own individualised sleep patterns. This was recorded as the time entering and exiting bed overnight and did not include naps.
Assessment 2
Participants underwent objective cognitive testing using a predetermined computerised battery approximately 1 week later (CANTABeclipse, Cambridge Cognition, Cambridge, UK). The procedure uses a touch screen computer (Slimbook P210; PaceBlade, Amersfoort, The Netherlands) and press pad. It consists of seven different tests designed to assess the cognitive domains thought to be affected by previous breast cancer treatment.19 This computerised battery has been previously used in a longitudinal study of cognitive changes after breast cancer treatment.33 The procedure takes 45 min to complete and was administered by one of the authors (OM).

The tests and cognitive domains studied are listed below:
▶ Paired Associates Learning (PAL; visuospatial ability and visual memory)
▶ Rapid Visual Information Processing (RVP; sustained attention and reaction time – motor skills)
▶ Match to Sample Visual Search (MTS; visuospatial ability and motor skills)
▶ Verbal Recognition Memory (VRM; verbal memory)
▶ Delayed Matching to Sample (DMS; attention)
▶ Affective Go No-go (AGN; decision and response and information processing)
▶ Intra-Extra Dimensional Set Shift (IED, executive function/information processing).

Statistical considerations
The power calculation was based on an estimated sample size of 96 women. With 48 cases and 48 controls, the study would have had 80% power to detect a 0.57 (medium) between-group effect size on questionnaire and objective monitoring data at a 5% significance level. Since this was an exploratory and hypothesis generating study, no correction was made for multiple analyses. The between-group analysis was conducted using t tests with comparisons between mean scores.

RESULTS
Due to time and resource constraints, recruitment of fatigued patients terminated slightly early with 45 of an expected 48 patients recruited. However, the number of control subjects was larger than required. A total of 114 women completed the study (69 controls and 45 cases of CRFS). Non-participants (NP=102) were asked to complete the Chalder fatigue questionnaire and ethics approval was obtained to collect anonymised demographic and treatment data from these women. The main reasons for non-participation were cited as work (28%) or the need for extra visits (32%), while 12% mentioned other medical problems and the remainder either had ‘had enough’ or did not want to think about their cancer (28%). The NP had a significantly lower fatigue score (10.7 vs 13.1; p=0.04) and were older (62 years vs 57 years; p=0.005) than the participants. There were no differences on treatment variables, stage at diagnosis or time since diagnosis.

Cases versus controls
The overall prevalence of CRFS was 39% (45/114). A between-group comparison for all data is shown in tables 1–5 (table 1: treatment variables; table 2: questionnaire data; table 3: routine laboratory parameters; table 4: actigraphy data; and table 5: cognitive testing data).

There were no significant differences between groups in mean age (CRFS 56.0 years vs controls 58.6 years; p=0.17), time since treatment (CRFS 12.4 months vs controls 13.0 months; p=0.67) or body mass index (CRFS 27.1 kg/m² vs controls 26.0 kg/m²; p=0.29).

There were no significant differences in treatment variables between groups (table 1).

There was a significantly higher prevalence of oestrogen receptor negative tumours in the control group. There was no difference in the percentage of non-white participants between groups.

There were significant differences in the levels of fatigue, mood disturbance and quality of life. There were also a number of differences in symptom subscales on both the EORTC QLQ-30 and BR23 (table 2).

The prevalence of insomnia syndrome was significantly higher in the CRFS group (44% vs 16%; p=0.001).

The routine laboratory variables (table 3), measured to exclude any gross metabolic disturbance, did not show any significant differences between groups.

The actigraphy data (table 4) which provided a measure of sleep, activity and circadian rhythm, demonstrated some differences. There was a minor difference in sleep with the control group actually having significantly shorter sleep bouts. However, there were no differences in the major sleep parameters (overall time or quality). There were significant differences in average daytime activity and duration of daytime (light) activity.

The cognitive data (table 5) demonstrated subtle but important differences between the groups. Significant differences

| Table 1  | Treatment and pathological variables |
|----------|--------------------------------------|
| Treatment variable                  | CRFS cases | Controls |
|                                     | Frequency | Percentage | Frequency | Percentage | p Value |
| Conserving surgery                  | 31        | 69         | 40        | 58         | 0.24    |
| Non-conserving surgery              | 14        | 31         | 29        | 42         |         |
| Chemotherapy                        | 19        | 42         | 35        | 51         | 0.37    |
| No chemotherapy                     | 26        | 58         | 34        | 49         |         |
| Radiotherapy                        | 39        | 87         | 51        | 74         | 0.10    |
| No radiotherapy                     | 6         | 13         | 18        | 26         |         |
| Hormone therapy                     | 6         | 13         | 11        | 16         | 0.79    |
| No hormone therapy                  | 39        | 87         | 58        | 84         |         |
| Lymph node positive                 | 17        | 38         | 17        | 25         | 0.13    |
| Lymph node negative                 | 28        | 62         | 52        | 75         |         |
| Oestrogen receptor positive         | 42        | 93         | 54        | 76         | 0.03    |
| Oestrogen receptor negative         | 3         | 7          | 15        | 22         |         |
| HER2 receptor positive              | 6         | 13         | 8         | 12         | 0.78    |
| HER2 Receptor negative              | 39        | 87         | 61        | 88         |         |

CRFS, cancer-related fatigue syndrome.
Table 3 Routine laboratory data

| Variable                      | Laboratory reference range | CRFS cases | SD  | Mean | SD  | p Value |
|-------------------------------|----------------------------|------------|-----|------|-----|---------|
| Haemoglobin (g/dl)            | 12–16                      | 12.9       | 0.78| 12.9 | 0.91| <0.001  |
| White cell count (>100/µl)   | 4–11                       | 5.89       | 1.51| 6.12 | 2.1 | 0.26    |
| Neutrophil (×109/l)          | 1.7–8.0                    | 3.54       | 1.08| 4.41 | 4.7 | <0.001  |
| Lymphocyte (×109/l)          | 1.0–4.0                    | 1.84       | 0.71| 1.80 | 0.68| <0.001  |
| Monocyte (×109/l)            | 0.24–1.1                   | 0.36       | 0.16| 0.37 | 0.12| <0.001  |
| Platelet (×109/l)            | 150–450                    | 274        | 55.5| 269  | 53.7| <0.001  |
| Sodium (mmol/l)              | 135–145                    | 139.27     | 2.07| 139.52| 2.22| <0.001  |
| Potassium (mmol/l)           | 3.5–4.7                    | 4.18       | 0.34| 4.28 | 0.23| <0.001  |
| Urea (mmol/l)                | 2.5–8.0                    | 5.48       | 1.19| 5.74 | 1.53| <0.001  |
| Creatinine (µmol/l)          | 60–110                     | 64.10      | 8.29| 66.59| 8.20| <0.001  |
| Uncorrected calcium (mmol/l) | 2.18–2.47                  | 2.36       | 0.099| 2.37 | 0.099|<0.001  |
| Adjusted calcium (mmol/l)    | NA                         | 2.38       | 0.085| 2.40 | 0.085| <0.001  |
| Phosphate (mmol/l)           | 0.75–1.50                  | 1.12       | 0.15| 1.08 | 0.20| <0.001  |
| Alkaline phosphatase (IU/l)  | 30–100                     | 74.07      | 21.86| 67.58| 19.56| <0.001  |
| Alanine transaminase (IU/l)  | 0–40                       | 25.16      | 11.16| 27.72| 14.17| <0.001  |
| Bilirubin (µmol/l)           | 0–17                       | 6.81       | 3.15| 7.35 | 2.98| <0.001  |
| Albumin (g/l)                | 35–48                      | 38.67      | 2.90| 38.56| 2.06| <0.001  |
| GGT (IU/l)                   | 0–30                       | 29.33      | 23.54| 30.49| 24.92|<0.001  |
| TSH (mU/l)                   | 0.4–4.0                    | 2.63       | 3.31| 3.25 | 5.05| <0.001  |
| Free T4 (pmol/l)             | 12–24                      | 13.36      | 4.17| 13.04| 3.14| 0.08    |
| Magnesium (mmol/l)           | 0.74–1.03                  | 0.86       | 0.68| 0.86 | 0.08| <0.001  |

CRFS, cancer-related fatigue syndrome; GGT, gamma-glutamyl transpeptidase; TSH, thyroid stimulating hormone.

were found on the RVP and VRM tests. The AGN test, a sensitive measure of executive function, demonstrated a higher number of commissions (ie, incorrect responses) in the CRFS group. The CRFS group performed worse than the controls in all statistically significantly different tests.

Table 2 Questionnaire data

| Variable          | CRFS cases | SD  | Mean | SD  | Controls | Mean | SD  | p Value |
|-------------------|------------|-----|------|-----|----------|------|-----|---------|
| FS total          | 18.87      | 5.35| 9.22 | 6.35| <0.001   |<0.001|<0.001|<0.001  |
| FACT-F total      | 26.84      | 8.07| 14.54| 6.83| <0.001   |<0.001|<0.001|<0.001  |
| ISI total         | 13.96      | 5.99| 9.01 | 5.98| <0.001   |<0.001|<0.001|<0.001  |
| HADS total        | 14.82      | 6.47| 7.26 | 5.03| <0.001   |<0.001|<0.001|<0.001  |
| VAS-F scale       | 6.44       | 1.53| 4.73 | 2.29| <0.001   |<0.001|<0.001|<0.001  |
| EORTC QLQ-30 subscales |          |     |      |     |          |<0.001|<0.001|<0.001  |
| Physical functioning | 69.19      | 19.45|85.80|14.00|<0.001   |<0.001|<0.001|<0.001  |
| Global health status | 81.09      | 16.80|56.07|22.79|<0.001   |<0.001|<0.001|<0.001  |
| Emotional functioning | 63.70      | 20.73|80.80|17.98|<0.001   |<0.001|<0.001|<0.001  |
| Cognitive functioning | 56.67      | 23.41|79.47|19.63|<0.001   |<0.001|<0.001|<0.001  |
| Social functioning | 59.26      | 27.65|84.81|19.69|<0.001   |<0.001|<0.001|<0.001  |
| Fatigue           | 55.80      | 21.52|25.44|17.68|<0.001   |<0.001|<0.001|<0.001  |
| Nausea/vomiting   | 7.04       | 13.98|2.42 | 6.57| 0.04     |     |     |<0.001  |
| Pain              | 37.04      | 33.88|16.91|21.86|0.01     |     |     |     |
| Dyspnoea          | 22.96      | 27.36|11.59|19.66|0.02     |     |     |     |
| Insomnia          | 48.15      | 32.22|37.68|32.29|0.09     |     |     |     |
| Appetite loss     | 11.85      | 23.74|7.25 | 14.98|0.25     |     |     |     |
| Constipation      | 12.59      | 23.88|6.28 | 14.32|0.15     |     |     |     |
| Diarrhoea         | 2.96       | 9.59 | 3.86|13.45|0.68     |     |     |     |
| Financial difficulties | 31.85      | 34.78|9.18 | 20.52|<0.001   |     |     |     |
| EORTC BR23 subscales |            |     |     |     |          |     |     |<0.001  |
| Breast systemic therapy side effects | 30.37 | 16.22|16.25|11.53|<0.001   |     |     |     |
| Breast symptoms   | 38.89      | 18.63|20.05|16.69|<0.001   |     |     |     |
| Arm symptoms      | 32.59      | 29.24|12.91|16.25|<0.001   |     |     |     |

DISCUSSION

This study is the first to objectively characterise cognitive differences between a rigorously defined group of cases of CRFS and a group of non-fatigued BCS. We found no differences in sleep actigraphy despite a much higher prevalence of insomnia.
syndrome in the CRFS group. However, mean daytime activity was lower in the CRFS group. These findings raise important questions about the nature of CRFS and its relationship to objective deficits in activity and cognition.

The strengths of this study are the tight categorisation of post-treatment fatigue in BCS and the extensive cognitive and activity testing. However, the sample size is small and it is only a single centre study. The multiple analyses may have led to type I errors. This was a hypothesis generating study and was underpowered to detect all the identified differences between the groups, so the discussion and conclusions should be interpreted in that context. However, we feel these are interesting data and are further validated when placed in the context of previous findings.

The domains in which cognitive dysfunction occurs are the same as identified in previous reviews of breast cancer patients. The areas of executive function, processing speed and verbal memory are important for day-to-day tasks and may explain why these are associated with the subjective sensation of mental fatigue. Similar findings were found in a comparative study between subjects with CFS and cancer fatigue but not in a study comparing fatigued and non-fatigued BCS. However, in the latter study it should be noted that the ‘fatigued’ BCS group were defined using a cut-off on a continuous fatigue scale (rather than using a case-based definition) and the cognitive testing only included measures of concentration and reaction time (rather than the more comprehensive battery of tests employed in the current study). The authors failed to find differences between the fatigued and the non-fatigued group on objective cognitive testing. The objective evidence of cognitive impairment that we identified in this study appears to be consistent with the questionnaire data. The Chalder Fatigue Scale and the QLQ-30 both assess perceived cognitive impairment, and the scores on both of these questionnaires were significantly worse in the CRFS group.

One limitation of the cognitive assessments undertaken in this study was that they were only recorded at the end of treatment and were not measured prospectively from baseline. However, we were not specifically examining cognitive change per se following treatment but comparing CRFS and matched controls. The purpose was to identify potential cognitive deficits in the CRFS group. The exclusion of psychiatric co-morbidities reinforces the hypothesis that CRFS is associated with a defined set of cognitive deficits that are unrelated

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### Table 4 Actigraphy data

| Variable                      | CRFS cases | Controls | Mean | SD     | Mean | SD     | p Value |
|-------------------------------|------------|----------|------|--------|------|--------|---------|
| Sleep                         |            |          |      |        |      |        |         |
| Actual sleep time (h)         | 06:04      | 06:07    | 0.74 |        |      |        |         |
| Actual sleep (%)              | 84.40      | 82.49    | 0.27 |        |      |        |         |
| Actual wake time (h)          | 01:07      | 00:11    | 0.48 |        |      |        |         |
| Actual wake (%)               | 17.51      | 15.60    | 0.28 |        |      |        |         |
| Sleep efficiency (%)          | 80.22      | 78.44    | 0.43 |        |      |        |         |
| Sleep latency (min)           | 00:17:32   | 00:17:19 | 0.97 |        |      |        |         |
| Average number of calculated sleep bouts | 23.73 | 24.04 | 0.82 |        |      |        |         |
| Average number of calculated wake bouts | 23.77 | 24.10 | 0.81 |        |      |        |         |
| Mean sleep bout time (min)    | 00:33:03   | 00:19:20 | 0.02 |        |      |        |         |
| Activity                      |            |          |      |        |      |        |         |
| Mean wake bout time (min)     | 00:02:43   | 00:03:25 | 0.19 |        |      |        |         |
| Average value of epoch intensity (24 h period) | 208.48 | 245.82 | 0.04 |        |      |        |         |
| Difference in maximum and minimum activity | 198.85 | 218.55 | 0.45 |        |      |        |         |
| Peak intensity of epoch       | 11.91      | 11.99    | 0.22 |        |      |        |         |
| Average of daytime (light) activity | 299.25 | 342.92 | 0.03 |        |      |        |         |
| Time of night time (dark) activity | 117.70 | 148.72 | 0.14 |        |      |        |         |
| Ratio of light to dark activity | 2.99    | 2.99     | 0.82 |        |      |        |         |
| Circadian rhythm              |            |          |      |        |      |        |         |
| Interdaily stability          | 0.53       | 0.57     | 0.16 |        |      |        |         |
| Interdaily variability        | 0.86       | 0.83     | 0.14 |        |      |        |         |
| Least 5 (L5) active hours     | 1475       | 2348     | 0.50 |        |      |        |         |
| Most 10 (M10) active hours    | 22481      | 24865    | 0.50 |        |      |        |         |
| Relative amplitude            | 0.88       | 0.86     | 0.22 |        |      |        |         |

Sleep efficiency (%) is time asleep (as per algorithm) divided by total time in bed.
Sleep latency is time in bed before algorithm records the subject being asleep.
Average value of epoch intensity (24 h period): the recording is converted to and analysed as a cosine wave around a zero point.
Difference in maximum and minimum activity corresponds to the difference between the peak and trough of the cosine wave.
Interdaily stability is a measure of consistency in daily activity over 7 days.
Interdaily variability is a measure of fragmentation of periods of rest and activity; normal value are <1 and calculated over 7 days.
L5 indicates the 5 h of calculated lowest activity over the 7-day average.
M10 indicates the 10 h of calculated greatest activity over the 7-day average.
Relative amplitude is a measure of the difference between L5 and M10 and thus an indication of overall level of activity over the 7-day period.
CRFS, cancer-related fatigue syndrome.
Research

Table 5  Cognitive testing data

| Variable                                      | CRFS cases | Controls | p Value |
|-----------------------------------------------|------------|----------|---------|
| DMS percentage correct (all delays)           | 81.78      | 11.63    | 84.83   | 11.43   | 0.17    |
| DMS mean correct latency (ms)                 | 3528       | 1151     | 3707    | 1416    | 0.48    |
| IED stages completed                          | 7.40       | 2.40     | 7.33    | 2.40    | 0.89    |
| IED total errors (adjusted)                   | 50.37      | 51.71    | 52.65   | 53.43   | 0.83    |
| MTS mean correct reaction time                | 3515       | 1143     | 3156    | 1137    | 0.10    |
| MTS per cent correct                         | 94.32      | 6.10     | 93.38   | 5.78    | 0.41    |
| PAL stages completed                          | 3.40       | 0.78     | 3.50    | 0.86    | 0.76    |
| PAL total errors (adjusted)                   | 95.60      | 29.67    | 92.90   | 32.05   | 0.65    |
| PAL total trials (adjusted)                   | 20.47      | 6.78     | 20.09   | 7.29    | 0.78    |
| RVP A’ (scores between 0 and 1)               | 0.87       | 0.06     | 0.89    | 0.07    | 0.15    |
| RVP total correct rejections                  | 236.69     | 25.83    | 245.53  | 14.95   | 0.02    |
| RVP mean latency (ms)                         | 533        | 127      | 468     | 126     | 0.009   |
| VRM free recall – total correct               | 7.00       | 1.77     | 7.75    | 1.75    | 0.03    |
| VRM recognition – total correct               | 22.78      | 1.38     | 23.06   | 1.42    | 0.3      |
| AGN mean correct latency (ms)                 | 532        | 71       | 517     | 61      | 0.24    |
| AGN total errors (adjusted)                   | 5.17       | 1.99     | 4.57    | 1.78    | 0.64    |
| AGN total commissions                         | 7.76       | 1.75     | 6.57    | 1.72    | 0.03    |

AGN: Affective Go No-go (information processing and reaction time). There are three outcomes: mean correct latency (time taken for a correct response), total omission which are incorrect responses to a target word (ie, pressing the button inappropriately), and latency of response (time taken to make correct response).

DMS: Delayed Matching to Sample (memory and reaction time). There are two outcomes: overall correct responses (percentage) and latency of response (time taken to make correct response).

IED: Intra-Extra Dimensional Set Shift (rule acquisition and reversal). There are two outcomes: stages complete (number successfully completed and total errors (adjusted for stages) is a measure of the efficiency of completing the test).

MTS: Match To Sample (matching test with speed/accuracy trade off). There are two outcomes: overall correct responses (percentage) and latency of response (time taken to make correct response).

PAL: Paired Associates Learning (visual memory and new learning). There are two outcomes: total errors (adjusted from stages completed) and total trials (number of attempts needed to complete task adjusted for early adoption).

RVP: Rapid Visual Information Processing (sensitive measure of general performance). There are three outcomes: A’ is a probability score of how good a participant is at detecting sequences, correct rejection is the number of times a false sequence is ignored between correct ones and the mean latency is the time of response between the end of a sequence and the participant pressing the button.

VRM: Verbal Recognition Memory (verbal information under free recall and forced choice recognitions). There are two outcomes: free recall number of correct words and a forced choice correct total (yes/no as to whether word was in the original list).

Table 5: Cognitive testing data

The prevalence of insomnia syndrome in the CRFS group was linked to higher scores on the ISI. However, this subjective perception of difficulty with sleeping did not correlate with objective actigraphy measures of sleep. While 44% of CRFS meet the criteria for insomnia syndrome, they are clearly two separate entities and CRFS cannot be explained by sleep disturbances alone. This finding is supported by data from an intervention trial for insomnia that improved sleep but not fatigue.

We found significant differences between groups with respect to objective activity data. This is in keeping with a recent study in breast cancer but in contrast with our earlier findings. The reason for the disparity is unclear but may be due to the different actigraph used and associated analysis algorithm. The differences were seen in the average epoch score (a measure of movement intensity) and in the level of daytime activity. These data confirm that patients who fulfil the criteria for CRFS, as well as being subjectively more fatigued, also have evidence of decreased physical activity. The decreased activity may be a direct consequence of feeling subjectively fatigued, or the decreased activity may arise first (due to a variety of causes) and may be a causative factor in exacerbating or perpetuating the subjective fatigue that these patients experience.

One way to disentangle these phenomena would be to undertake a longitudinal study to assess both subjective and objective manifestations of fatigue and to trace the temporal relationships between them.

The theory that, whatever the cause of the initial fatigue, it is perpetuated by physical deconditioning and decreased activity probably explains why exercise is reported to be an effective treatment for cancer related fatigue. It is likely, however, that the effects of exercise are relatively non-specific (exercise reduces fatigue even in healthy individuals) and this explains the relatively small effect size for exercise interventions in cancer populations.

In a previous study in BCS we found the prevalence of CRFS to be 30% and this general figure was supported by the results of a systematic review. The prevalence of 39% for CRFS that we found in this study although slightly higher than previous...
estimates is broadly in keeping with these figures and may be explained by the finding that the non-participant group were significantly less fatigued than the study sample. A prevalence of 30–39% represents a sizeable percentage of women who have successfully completed treatment for breast cancer and potentially translates into a large absolute number of BCS. This emphasises that it is important to recognise and treat fatigue.

The widespread differences in questionnaire data and levels of other symptoms are in keeping with previous studies.12 We found that the CRFS group had a higher level of mood disturbance despite the exclusion of patients with specific psychiatric diagnoses. It is possible that sub-threshold mood disturbance contributes to CRFS. However fatigue and depression should be regarded as separate entities.43

“Some important negative findings in this study. There were no significant differences in any of the routine laboratory tests. While fatigue may be linked to anaemia during chemotherapy,44 this does not appear to be the case in BCS. There is also no link to thyroid disturbances. We have postulated that serum magnesium levels may be contributory but this was not found to be the case.

There were also no differences in treatment or demographic variables between groups. This is consistent with a critical appraisal in which the authors found very limited associations between fatigue and these variables.

The clinical significance of these findings reinforces the importance of identifying women who have or are at risk of developing CRFS. This should be incorporated into routine practice and might include counselling on potential cognitive and sleep changes. These problems might be diminished with simple information giving at the start of treatment,46 which would in keeping with the Department of Health survivorship strategy.47 However, we are not able to recommend any particular treatment strategy at present in this group.7 In conclusion, we have found that a significant minority of women successfully treated for breast cancer meet the criteria for CRFS. This group is characterised by subjective poly-symptomology. There are important differences between the groups with objectively lower cognitive function and daytime activity in the CRFS group that need further confirmation with a larger sample size. Future work should examine this relationship longitudinally, possibly within a quality of life arm of a treatment trial. Correlation with levels of cytokines and/or functional imaging would be helpful to further characterise this group. The overall aim should be to design more targeted treatments to manage this problematic syndrome.

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