Psychiatric co-morbidity in patients with Chronic Fatigue Syndrome receiving Cognitive Behavioural Therapy - A case control study.

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Abstract

BACKGROUND

Past studies have investigated the association between chronic fatigue syndrome (CFS) and mental disorders. However few studies have investigated this association in CFS patients referred for cognitive behavioural therapy (CBT).

METHODS

286 patients from the Greater London region with CFS were compared to 1693 healthy controls drawn from an epidemiological household survey covering boroughs in South East London. The revised structured clinical interview schedule (CIS-R) was administered to cases/controls and used to measure common mental disorders ('CMDs') by assigning applicable diagnoses from the 10th revision of the International Classification of diseases (ICD-10). SPSS version 21.0 was used to perform statistical analyses on the CIS-R data.

RESULTS

The overall prevalence of CMDs was higher in cases than controls ($p<0.001$). 72% of cases had at least one CMD. The prevalence of the following CMDs was significantly higher in cases than controls: Generalised anxiety disorder ($p<0.001$), Mixed depressive and anxiety disorder ($p<0.001$), Mild, Moderate, and Severe Depressive disorder ($p<0.001$ for these depressive disorders.)

CONCLUSIONS

This study suggests that CFS is frequently associated with CMDs in patients referred for CBT; particularly anxiety and depressive disorders. This co-morbid burden needs to be addressed when these patients are treated with CBT.

Background

Chronic Fatigue Syndrome (CFS) is an illness primarily characterised by sustained, debilitating fatigue lasting for more than 6 months, which is associated with significant functional impairment and has no apparent medical cause. There are various case definitions for CFS which originate from the United States of America (Fukuda et al., 1994; Holmes et al., 1988), Australia (Working Group of the Royal Australasian College of Physicians, 2002), Canada (Meirleir et al., 2003), and the United Kingdom (Sharpe et al., 1991). The most commonly used case definition is the Centre for Disease Control (CDC) criteria (Fukuda et al., 1994) which was originally intended to create a standardised definition of chronic fatigue syndrome for research purposes. The CDC criteria created in 1994 are the revised criteria of those that were formulated in 1988 by Holmes and colleagues (Holmes et al., 1988). The CDC definition requires persistent or relapsing fatigue of a debilitating nature, to be present for at least six months and at least four symptoms from a range of symptoms including memory loss, poor concentration, joint pain and tender glands, to be present. The Oxford criteria (Sharpe et al., 1991) also require fatigue to be present for at least six months although the criteria place less of an emphasis on the presence of somatic symptoms as a requirement for the diagnosis.

The diagnosis of chronic fatigue syndrome is purely clinical, with no distinguishing features on clinical examination or from laboratory tests. The disease process for the disorder is uncertain although research has been conducted with the aim of identifying possible infectious (Ablashi, 1994), genetic (Buchwald et al., 2001), immunological (Landay et al., 1991), endocrinological (Wheatland, 2005) and neuropsychiatric (Wessely, 1993) aetiologies for the disorder. It seems likely that rather than being caused by one distinct pathophysiological process, chronic fatigue syndrome is caused by a combination of such processes to produce the clinical presentation that underlies the diagnosis of the disorder. Indeed, some researchers believe that chronic fatigue syndrome is best described as a functional somatic syndrome alongside fibromyalgia, irritable bowel syndrome, chronic pelvic pain and others (Barsky & Borus, 1999). Other investigators in the field of functional somatic syndromes question the degree to which such syndromes can be viewed as distinct clinical entities (Nimnuan, Rabe-Hesketh, Wessely, & Hotopf, 2001; Wessely, Nimnuan, & Sharpe, 1999).

A significant body of research has been devoted to investigating the association between chronic fatigue syndrome and psychiatric co-morbidity (Fischler, Cluydts, De Gucht, Kaufman, & De Meirleir, 1997; Kruesi, Dale, & Straus, 1989; Nater et al., 2009; Wessely.S Chalder.T Hirsch.S Wallace.P Wright.D, 1996; Wood, Bentall, Göpfert, & Edwards, 1991). These studies have generally found that there is a significant association between CFS and psychiatric co-morbidity, with depression and anxiety disorders being strongly associated with CFS. There has been some debate concerning how inclusion or exclusion of somatic symptoms from the CFS case definition influences the strength of the association between CFS and other psychiatric illnesses. Some research suggests that psychiatric illnesses are associated with the number of somatic symptoms a CFS patient experiences (Katon & Russo, 1992) whilst other research has found that excluding somatic symptoms makes the CFS case definition less specific, thus increasing the likelihood of an association between this disorder and psychiatric illnesses with similar presentations (Skapinakis et al , 2003). A further complication to the interpretation of this body of research is the fact that several of these studies lacked a control group composed of health individuals and were conducted more than a decade ago. Moreover, very few studies recruited CFS patients from the community (Taylor, 2003).

The research outlined in this paper seeks to remedy some of the problems with previous research into CFS and psychiatric co-morbidity, by analysing recent data and by including a control group of healthy individuals from a similar community to the patient cases. All patient cases in this study have been referred for Cognitive Behavioural therapy; which has shown to be effective in reducing fatigue symptoms and increasing functional status in CFS (White et al., 2011). The prevalence of common mental disorders (CMDs) (e.g depression, anxiety disorders etc) in this group of patients will be compared to a healthy control group drawn from the South East London Community Health Study (Hatch

et al., 2011). The overall aim is to compare the prevalence of CMDs and to test for any statistically significant differences between cases and controls.

Methods

Sample

438 patients who had CFS and had been referred for Cognitive Behavioural Therapy were identified (The 'CFS sample'). Data for these patients had been drawn from survey data taken from 2012 to 2013. Socio-demographic data was gathered from these patients by administering a pre-treatment questionnaire. Information on CMDs was gathered through the administration of the Revised Clinical Interview Schedule ('CIS-R') by clinical psychologists and behavioural psychotherapists. All 438 patients had been diagnosed with chronic fatigue syndrome by psychiatrists at The Maudsley Hospital using the Oxford Criteria. Patients came predominantly from London and Greater London (Bromley, Eastern and Coastal Kent, Greenwich, Lambeth, Southwark and Wandsworth). 6% (n=17) of cases came from outside London (Bedford, Sussex,Kent, Surrey, Lincolnshire, Hertfordshire, Northampton and Lincolnshire.)

The following inclusion criteria were applied to these patients:

1. The patient has been referred for CBT
2. The patient has a CFS diagnosis
3. The patient has no other diseases that could produce fatigue/psychiatric co-morbidity e.g cancer, adrenal insufficiency
4. The patient is not pregnant (the pregnancy state could produce fatigue/psychiatric co-morbidity)
5. The patients must have some available pre-treatment data
6. The patient must have completed a CIS-R

286 patients fulfilled the inclusion criteria, meaning 152 patients were excluded from the final sample. The main reasons for exclusion were that baseline data was missing and that excluded patients had not been referred for CBT, or that patients had not completed a CIS-R.

Data for the controls included in this study were taken from the South East London Community Health Study ('The SELCoH Study'). The SELCoH study is a survey conducted between 2008 and 2010 which gathered information relating to psychiatric and physical morbidity. 1698 individuals aged sixteen and over were surveyed of which 1693 were used in this study; the other 5 individuals had missing data and were therefore excluded. The study surveyed individuals from randomly selected households in the boroughs of Southwark and Lambeth (Hatch et al., 2011). Overall therefore, there were 1979 participants in the study - 286 CFS patients and 1693 SELCoH controls.

Measures

Common Mental Disorders

The presence of common mental disorders (CMDs), was measured using the Revised Clinical Interview Schedule (CIS-R), in both the CFS and SELCoH sample. The CIS-R is a structured interview which elicits information concerning 14 symptom domains including fatigue, depression, anxiety and others. A total score of 12 or above (the 'case threshold') indicates the presence of a CMD (Lewis, Pelosi, Araya, & Dunn, 1992)Through the use of algorithms, the total score produced can be converted to ICD-10 diagnoses (generalised anxiety and panic disorders, obsessive compulsive disorder, depressive episode, phobias and mixed depression and anxiety disorder) with mixed depressive and anxiety disorder representing patients who were above the case threshold, but did not fit into any other diagnostic category. In this study, the frequency with which ICD-10 diagnoses occurred in cases and controls was compared.

Socio-Demographic Information

The socio-demographic characteristics of the CFS and SELCoH samples that were explored in this study, were: age, gender, ethnicity, employment and marital status. Unfortunately socio-economic status was not used as a variable in this study, as information on this variable from the SELCoH study and from questionnaire date from the CFS patients, was not sufficiently homogeneous. Age was included as a continuous and categorical variable (the age categories were: 16-24, 25-39, 40-54, 55-64, 65+). The ethnic categories where ' White and White British', ' Black and Black British', 'Asian and Asian British', 'other ethnicity' and 'none specified'. The categories for marital status were: 'single', 'married or cohabiting', 'divorced or separated', 'widowed' and 'other'. Employment status was defined through the following categories: 'full time', 'part time', 'casual', 'student', 'unemployed', 'temporary sick or disabled', 'permanent sick or disabled', 'retired' and 'looking after home or children'. These categories are merged categories which have been created by fusing the categories outlined in the questionnaires administered to individuals in the SELCoH and CFS sample.

Analysis

SPSS statistics version 21.0 was used to conduct analyses. The statistical package was used to compute frequencies for CMDs and the socio-demographic information for the CFS and the SELCoH samples, and to merge categories for socio-demographic variables. SPSS was also used to perform bivariate statistical analyses using the Pearson χ^2 test and Fisher's exact test where appropriate. Odds ratios with 95% confidence intervals, were calculated when the frequency of CMDs in cases and controls was being compared.

Patients that had not completed a CIS-R (n=68) were compared to patients who had completed one (n=286), by socio-demographic variables and a number of other measures. This was done to ensure that there was not a selection bias in selecting the cases. The measures were, the duration of CFS in months, the Chalder Fatigue Scale, the Hospital Anxiety and Depression scale and the Work and Social Adjustment Scale. The independent samples T-test, Mann Witney-U and chi-squared test were used to make statistical comparisons between the CIS-R and non CIS-R groups.

Results

Comparisons between patients who did or did not complete the CIS-R

Tables 1 and 2 show the differences between CIS-R and non-CIS-R patients in terms of different socio-demographic variables. The percentages shown in these tables are valid percentages and reflect the proportion of patients within the 'case' category or 'control' category who fit into a particular category. The main statistically significant differences between these two groups were for the age and employment status variables. For the 65+ age category, a higher proportion of Non-CIS-R patients were in this category compared to CIS-R patients ($p<0.05$). A higher proportion of non-CIS-R patients were also in part time or causal work or were permanently sick or disabled ($p<0.05$).

Table 3 shows comparisons between CIS-R and non CIS-R patients in terms of the duration and severity of their chronic fatigue syndrome as measured by the mean duration of the illness, The Chalder Fatigue Scale, the Work and Social Adjustment Scale (WSAS), and the Hospital and Anxiety Depression scale (HADS). There was no statistically significant difference in the mean total score for any of the scales or for the mean duration of chronic fatigue syndrome. The percentages shown in this table are valid percentages and reflect the proportion of patients within cases and controls.

Tables 1 & 2: Socio-demographic comparisons between CFS patients who did or did not complete a CIS-R 'NS' = **not significant.** Percentages shown are valid percentages.

Table 1	Completed CIS-R (%)	Did not complete CIS-R (%)	P-value of difference
Age			
16-24	36 (13)	5 (7)	NS
25-39	121 (42)	26 (38)	NS
40-54	108 (38)	30 (44)	NS
55-64	21 (7)	5 (7)	NS
65+	0 (0)	2 (3)	p<0.05
Gender			NS
Male	72 (25)	15 (22)	
Female	214 (75)	53 (78)	
Ethnicity			
White or White British	189 (66)	44 (65)	NS
Black or Black British	15 (5)	1 (1.5)	NS
Asian or Asian British	10 (3.5)	1 (1.5)	NS
Mixed	8 (3)	3 (4)	NS
Other	7 (2)	2 (3)	NS
None Specified	20 (7)	8 (12)	NS

Table 2	Completed CIS-R (%)	Did not complete CIS-R (%)	P-value of difference
Employment Status			
Full time	70 (24)	13 (19)	NS
Part Time	52 (18)	6 (9)	p<0.05
Casual	2 (0.7)	4 (6)	p<0.05
student	15 (5)	2 (3)	NS
unemployed	30 (11)	6 (9)	NS
temporary sick/disabled	36 (13)	10 (15)	NS
permanent sick/disabled	31 (11)	15 (22)	p<0.05
retired	10 (3.5)	3 (4)	NS
looking after home/children	14 (5)	5 (7)	NS
Marital Status			
single	111(39)	30(10.5)	NS
married/cohabiting	139(49)	27(9)	NS
divorced/separated	25(9)	6(2)	NS
widowed	2(0.7)	3(1)	NS
other	1(0.4)	0(0)	NS

Tables 3: Comparisons between CIS-R and Non-CIS-R patients according to mean duration of illness and mean total scores for different questionnaire scales

Table 3	Completed CIS-R	Did not complete CIS-R	p-value of difference
Mean Duration of Illness (months)	73.3	92	0.092
Mean Total Score for Chalder Fatigue Scale	28.7	30.2	0.128
Mean Total Score for WSAS*	23.5	23.9	0.524
Mean Total Score for HADS*	18.9	19	0.788

***WSAS** = work and social adjustment scale ***HADS** = Hospital anxiety and depression scale

Comparisons between cases and controls

Table 4 outlines the socio-demographic differences between cases and controls. Percentages given are rounded valid percentages and the missing data column refers to the total number of instances for cases and controls, where there was no available data for each category. The difference between cases and controls was statistically significant ($p<0.05$) for all age categories except the 55-64 category, and for gender ($p<0.001$). A higher percentage of CFS cases were White or White British compared to controls ($p<0.001$); but a lower proportion of such cases were Black or Black British ($p<0.001$). There was not a statistically significant difference in the proportion of Asian or British Asians in either group. A higher proportion of CFS cases worked part time or were permanently sick or disabled ($p<0.001$ for both). The difference in the proportions of cases and controls who were unemployed, single, married or divorced was not statistically significant.

Table 4: Socio-Demographic comparisons between cases and controls. (NS = Not Significant**)**

Table 4	Cases (%)	Controls (%)	P-value of difference	Missing data(cases and controls)
Age				0
16-24	36 (13)	354 (21)	p=0.001	
25-39	121 (42)	572 (34)	p<0.001	
40-54	108 (38)	427 (25)	p<0.001	
55-64	21 (7)	164 (10)	**NS**	
65+	0 (0)	176 (10)	p<0.001	
Gender				0
Male	72 (25)	736 (43)	p<0.001	
Female	214 (75)	957 (57)		
Ethnicity				39
White or White British	189 (76)	1047 (62)	p<0.001	
Black or Black British	15 (6)	406 (24)	p<0.001	
Asian or Asian British	10 (4)	63 (4)	**NS**	
Other	15 (6)	175 (10)	p<0.05	
None Specified	20 (8)	0 (0)	p <0.001	
Employment Status				35
Full time	70 (27)	660 (39)	p<0.001	
Part Time	52 (20)	218 (13)	p<0.005	
Casual	2 (0.8)	79 (5)	p<0.005	
student	15 (6)	207 (12)	p<0.005	
unemployed	30 (12)	169 (10)	**NS**	
temporary sick/disabled	36 (14)	24 (1.4)	p<0.001	
permanent sick/disabled	31 (12)	59 (3.5)	p<0.001	
retired	10 (4)	188 (11)	p<0.001	
looking after home/children	14 (5)	82 (5)	**NS**	
Marital Status				8
single and never married	111 (40)	676 (40)	**NS**	
married/cohabiting	139 (50)	783 (46)	**NS**	
divorced/separated	25 (9)	181 (11)	**NS**	
widowed	2 (0.7)	53 (3)	p<0.05	
other	1 (0.4)	0	**NS**	

Table 5 shows the frequency with which individual CMDs occurred in cases and controls alongside p-values, which were computed using the Chi-squared test and Fisher's Exact test. Unadjusted (crude) odds ratios with 95% confidence intervals were calculated as well. The table is split into primary and secondary diagnoses. For the primary diagnoses, there is a statistically significant difference in the proportion of cases with non-specific neurotic disorder and the depressive and anxiety disorders. This is particularly so for Generalised Anxiety Disorder ($p<0.001$, OR = 7.2). The overall difference in the frequency of primary CMDs in cases versus controls was also highly significant ($p<0.001$). Differences in the frequencies of these diagnoses in the secondary diagnoses category, were very similar to the same for the primary diagnoses category. The main differences were that there was not a statistically significant difference in the proportion of cases and controls that had mild generalised anxiety disorder, whilst there was a significant difference for agoraphobia. The statistical association between total frequencies for common mental disorders in cases and controls, was highly significant ($p<0.001$); as it was for the primary diagnoses.

Table 5: The frequency of individual common mental disorders in cases and controls. (NS = Not Significant**, * =** Fisher's Exact Test used)

Table 5	Frequency in CFS Cases (% within cases)	Frequency in Controls (% within controls)	P-value of difference	Unadjusted Odds ratios Cases/Controls (95% CI)
Common Mental Disorders (Primary)				
Non specific neurotic disorder	40 (14.1)	112 (6.6)	p<0.001	2.324 (1.580 - 3.416)
Mild Generalised Anxiety Disorder	18 (6.4)	60 (3.5)	p<0.05	1.849 (1.075 - 3.180)
Obsessive Compulsive Disorder	1 (0.4)	2 (0.1)	**NS***	2.998 (0.271 - 33.175)
Mixed Anxiety & Depressive Disorder	12 (4.2)	17 (1.0)	p<0.001*	4.366 (2.062 - 9.242)
Specific Phobia	5 (1.8)	30 (1.8)	**NS**	0.997 (0.384 - 2.591)
Social Phobia	1 (0.4)	11 (0.6)	**NS**	0.542 (0.070 - 4.216)
Agoraphobia	2 (0.7)	8 (0.5)	**NS***	1.499 (0.317 - 7.096)
Generalised Anxiety Disorder	16 (5.7)	14 (0.8)	p<0.001	7.187 (3.467 - 14.895)
Panic Disorder	2 (0.7)	8 (0.5)	**NS***	1.499 (0.317 - 7.096)
Mild Depressive Episode	33 (11.7)	73 (4.3)	p<0.001	2.929 (1.901 - 4.513)
Moderate Depressive Episode	61 (21.6)	100 (5.9)	p<0.001	4.377 (3.091 - 6.199)
Severe Depressive Episode	14 (4.9)	18 (1.1)	p<0.001	4.843 (2.381 - 9.853)
Total	205 (72)	453 (27)	p<0.001	
Common Mental Disorders (Secondary)				
Non specific neurotic disorder	46 (16)	104 (6)	p<0.001	2.976 (2.050-4.322)
Mild Generalised Anxiety Disorder	6 (2)	18 (1)	NS	2.022 (0.796 - 5.138)
Obsessive Compulsive Disorder	1 (0.4)	5 (0.3)	NS	1.201 (0.140 - 10.316)
Mixed Anxiety & Depressive Episode	40 (14)	51 (3)	p<0.001	5.318 (3.441 - 8.220)
Specific Phobia	3 (1)	15 (0.9)	NS	1.202 (0.346 -4.179)
Social Phobia	1 (0.4)	2 (0.1)	NS	3.007 (0.272 -33.273)
Agoraphobia	5 (2)	9 (0.5)	p<0.05	3.375 (1.123 - 10.146)
Generalised Anxiety Disorder	47 (17)	70 (4)	p<0.001	4.634 (3.125 - 6.873)
Panic Disorder	4 (1.4)	10 (0.6)	NS	2.420 (0.754 - 7.770)
Total	153	284	p<0.001	

Discussion

Main Findings

A comparison of the occurrence of common mental disorders in a group of CFS patients and a group of controls, addressed the aims of this study to investigate whether there was a statistically significant difference between the two groups in terms of the frequency of CMDs. Overall approximately 72% of cases had a common mental disorder compared to 27% of controls and this difference was statistically significant ($p<0.001$). Most striking about the results, is the marked overrepresentation of the anxiety and depressive disorders in the CFS cases and that such observed differences were so highly significant (the p-values for the majority of significant associations were less than 0.001). The finding that CFS was associated specifically with anxiety and depressive disorders is backed by previous studies in this area (Fischler et al 1997, Skapinakis et al 2003), so this study can be seen as reinforcing the evidence base that suggests there is an association between CFS and these disorders.

On the whole, CFS patients were more likely to be female, young to middle aged (25-39 and 40-54 age categories) and White/White British compared to controls. The overrepresentation of women as cases is supported by the epidemiological literature in this area, which suggests that women are more likely than men to develop CFS (Ranjith, 2005). Gender differences between cases and controls are important since gender has the potential to act as a confounding variable as women are more likely to suffer from CFS and some psychiatric disorders, such as depressive disorder (Kessler, 2003; Nolen-Hoeksema, 2001). In fact, Taylor et al (2003) demonstrated that both gender and socioeconomic status can act as confounding variables as they can both act as predictors for psychiatric disorders in patients in the community with CFS.

CFS patients were also more likely to be in part time work or permanently/temporarily disabled by their illness. This is unsurprising considering that CFS is associated with moderate to severe functional impairment (Lavergne et al, 2010). Interestingly, individuals in the control group, were more likely to be retired; although this may simply be a reflection of the differing age distribution of controls versus cases, where a higher proportion of controls were in the '55-64' and 65+ age brackets. There were no statistically significant differences between cases and controls in terms of marital status except for the widowed category; although the number of individuals who were widowed (n=3) was very small and all the widowed participants were controls.

In terms of comparisons within the CFS sample, the differences between patients who completed the CIS-R and those who did not were minor. Patients who did not complete a CIS-R were more likely to be in the 65+ age bracket, were less likely to be in part time or casual work, and were more likely to be permanently disabled. However it is difficult to come to firm conclusions based on this data due to the very low numbers present within some of the categories such as the 65+ category. The mean duration of CFS and the mean total scores for the Hospital Anxiety and Depression Scale (HADS), the Work and Social Adjustment Scale (WSAS) and the Chalder Fatigue Scales, were similar in these two groups, and were therefore not statistically significant. This provides some evidence to suggest that overall there were no notable differences in the duration, severity or illness associated impairment in patients who did or did not complete a CIS-R. This suggests that patients who completed a CIS-R and were thus included in the main analyses, were broadly representative of the overall CFS sample.

Limitations

Multivariate analyses were not performed, meaning the impact of possible confounding variables such as gender and socioeconomic status was not investigated. This means that the odds ratios given in the results tables above, most likely overestimate the differences between cases and controls. Considering how statistically significant the differences were however, it is unlikely that gender and other variables would have exerted a sufficiently strong confounding effect to render observed associations non-significant. Moreover, the findings of this study cohere with other published studies, meaning they provide supporting

evidence for the hypothesis that there is an independent association between chronic fatigue syndrome and other psychiatric disorders.

The possibility of referral bias occurring in this study is another limitation. The CFS patients in this study were being treated with CBT at the secondary care level. CFS patients being treated at this level may not necessarily adequately represent the CFS population as a whole; not least because patients who accept that CBT may be useful for relieving their symptoms, may differ to those that do not. This means that the observations outlined in the results section, may have been modified by this bias rather than indicating an absolute association between chronic fatigue syndrome and other psychiatric disorders.

Missing data was somewhat problematic in this study, particularly for the socio-demographic variables where the missing data was concentrated in the CFS patient group, rather than in the control group. The missing data may have biased the statistical comparisons made between the two groups. Non-response rates in the households investigated by the SELCoH study (48.1% non-participation rate) may have produced a participation bias meaning data on common mental disorders for the controls in this study, should be approached with caution (Hatch et al., 2011). The exclusion of socioeconomic variables such as educational status from this study, meant that this study was unable to confirm or deny the relationships between CFS, psychiatric co-morbidity and socioeconomic status, found in other studies.

Comparisons with similar published studies

The findings of this study are corroborated by previous studies using CFS samples from primary to tertiary care settings. Wood et al (1991) found that 41% of patients with CFS in a general medical clinic, had a co-morbid psychiatric disorder. Wessely et al (1996) conducted a prospective cohort study of CFS patients in primary care, which discovered that 75% or 78% of patients had a psychiatric disorder, depending on whether the CIS-R or questionnaire data was used. The prevalence of psychiatric disorders identified in this study were significantly higher than in the control group with no CFS patients ($p<0.001$ for both). Hickie et al's study (Hickie et al 1990) in which 48 CFS patients were matched 1:1 with controls who all had major or minor depression, found similar levels of psychiatric co-morbidity to this study, Wessely et al's and Wood et al's studies. Half (n=24) of the CFS patients in this study had a co-morbid psychiatric disorder. All three of these studies had much smaller sample sizes for CFS cases compared to this study, although they affirm the principle that CFS is associated with the presence of other psychiatric disorders.

This study partially confirms the findings of Fischler et al (1997) which found that more CFS patients had generalised anxiety disorder (GAD) and somatisation disorder compared to a healthy control group ($p<0.001$ OR= 8 for GAD and $p=0.002$ for somatisation disorder) Unlike in this study, Fischler et al did not identify a statistically significant association between CFS and any of the depressive disorders; although it is encouraging that Fischler et al identified the preponderance of anxiety disorders in their CFS sample, as this study has.

Using a community sample of CFS patients and patients with a sub-syndromic fatigue-based illness, Nater et al (2009) found that nearly 60% of a CFS sample had at least one current psychiatric diagnosis and 89% had at least one lifetime psychiatric diagnosis. In comparison to the patients with a sub-syndromic fatigue based illness, the lifetime and current prevalence for the affective and anxiety disorders were statistically significant, with GAD being highly significant ($p<0.001$). Current anxiety and affective disorders where moderately represented in the sample with 47.3% and 29.2 % of the CFS patient sample possessing one of these disorders respectively. As was the case in this study, Nater et al did not find that there was a statistically significant difference in the prevalence of the phobias (social, specific and agoraphobia) and panic disorder. The proportion of CFS patients with an affective disorder in Nater et al's study (29.2%) is similar to this study where approximately 36% of CFS patients either had mild, moderate or severe depression. Skapinakis et al (2003) found a relatively higher prevalence of depression in an international sample of CFS patients; with 67% of these patients having depression. Caution should of course be taken when making these comparisons as the CFS samples were not all drawn from like sources.

While some studies found an association between CFS and anxiety disorders, particularly generalised anxiety disorder (Nater et al 2009, Skapinakis et al 2003, Fischler et al 1997), Kruesi et al (1989) did not. In their sample of 28 patients diagnosed with CFS using the CDC criteria, only one patient had co-morbid GAD and another patient had co-morbid panic disorder. The dominant co-morbid psychiatric illness was depression with 21% of the patients currently suffering from the disorder.

Synthesising and interpreting the evidence.

Depressive, anxiety and somatisation disorders seem to feature prominently as psychiatric disorders that are commonly associated with CFS. However the prevalence of these disorders in patients suffering from CFS differ from study to study as well as the statistical significance of any comparison made with non-CFS patient groups. This can be attributed to differing CFS case definitions, clinical settings and sampling methods. Indeed, there is evidence that the interaction between fatigue and psychiatric disorders changes depending on the population that is being investigated, as well as the case definition that is used (Katon & Russo, 1992; Katon&Walker, 1993).

In analysing the interaction between CFS and psychiatric disorders, there is also the issue of temporality. Some studies find that associated psychiatric disorders pre-dated the existence of CFS (Kruesi et al., 1989), while others found that psychiatric co-morbidity and psychological disturbances were more likely a consequence than a cause of the CFS; with the pre-morbid prevalence of psychiatric disorders being similar to community samples (Hickie et al., 1990). This could simply mean that patients already suffering from a psychiatric disorder can suffer from CFS, and that psychiatric co-morbidity is also an important consequence of CFS. This explanation however does not help to clarify the relationship between psychiatric disorders and the pathophysiology of CFS, and heterogeneity in clinical settings and sampling between studies, complicates the abilities to come to firm conclusions about the nature of this relationship.

Conclusion

This study provides good evidence that chronic fatigue syndrome has a substantial degree of psychiatric morbidity and is particularly associated with the anxiety and depressive disorders. The finding that CFS is associated with other psychiatric disorders is broadly supported by previous literature although the magnitude and significance of association between CFS and co-morbid psychiatric disorders differ. Interpretation of the evidence provided by this study is limited by aforementioned methodological weaknesses and future studies in this area should be based on community samples to eliminate referral bias and should use controls that are from similar communities to cases. This study and other like studies in this area, also raise interesting questions about the precise relationship between depression, anxiety and chronic fatigue syndrome. Cognitive behavioural therapists may have to manage cognitions associated with co-morbid psychiatric disorders when delivering CBT to CFS patients. The high co-morbid psychiatric burden associated with CFS also presents a challenge to primary care physicians and psychiatrists to adequately manage fatigue symptoms as well as psychiatric symptoms which may exacerbate the symptoms of chronic fatigue syndrome.

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