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EDITORIAL

Costs, correlates and consequences of fatigue in children and adults[1]

The problems of understanding what causes chronic fatigue, its relationship to psychiatric disorders, and how best to treat it continue to baffle and bemuse clinicians and patients alike (Report to the CMO, 2002; Stanley *et al*. 2002). This edition of the journal carries four original papers that provide much needed knowledge in a subject riddled by polemic and prejudice (White, 2002).

CORRELATES OF ACUTE FATIGUE IN TWINS

There have been several twin studies of both chronic fatigue and CFS (Farmer *et al*. 1999; Hickie *et al*. 1999; Buchwald *et al*. 2001), but no twin study of acute fatigue. Sullivan and colleagues (2003) (this issue, pp. 263–281) undertook a study of American adult twins, asking them the question: 'in the last year, have you had a time lasting at least five days when you felt tired or fatigued most of the time?' Furthermore the fatigue also had to be 'unusual and worse than the subject's baseline energy level'. Thirty-six per cent of the total sample replied affirmatively. Ten per cent also confirmed that the fatigue interfered with their normal life 'completely' or 'a lot'; thus interfering fatigue (IF) was the complaint of interest to these authors.

Because the authors were aware of the likely heterogeneous nature of IF, they sensibly carried out a latent class analysis of independent variables to see if they could describe discrete populations with IF. The best solution provided five classes, which differed by gender, education, poor parenting as children, physical and mental health problems, substance misuse, life adversity and neurotic personality. Hickie and colleagues have previously shown a two class solution to the heterogeneity of chronic fatigue, using symptoms alone (Hickie *et al*. 1995; Wilson *et al*. 2001). The addition of demographic and health related factors would be expected to further delineate the clinical presentations. The intriguing findings in this study were the significant associations with different parental bonding styles, which helped to delineate more than one latent class. These data support the importance of early familial experience in determining ill health in later life (Hotopf *et al*. 2000).

Sullivan and colleagues used three different multivariate analyses in order to allow for the heterogeneous nature of IF. Three independent variables were significant in all three analyses, and these were lifetime major depression or generalized anxiety disorder and high neuroticism. This provides some confidence that these variables are important, even though the best model only explained $<15\%$ of the variance. Six further variables were significant in two out of the three models (a reported major health problem, dissatisfaction with health, $\geqslant 15$ sick days in bed (related to the first variable), the belief that daily activities were limited by health, alcohol misuse and any stressful life event).

With the exception of alcohol misuse, all these variables have been found before to be related to chronic fatigue (Sharpe *et al*. 1992; Wilson *et al*. 1994; Clark *et al*. 1995; Vercoulen *et al*. 1996; Wessely *et al*. 1997), even when following a corroborated virus (White *et al*. 2001). The surprise is that they were also so closely associated with acute fatigue. Perhaps the explanation is that the interviews were not necessarily carried out at the time of the complaint of fatigue. These associations may therefore represent either predisposing and/or maintaining factors for IF. More disabling fatigue is more likely to become persistent than the non-interfering fatigue reported by the other 26% of the sample (Vercoulen *et al*. 1996).

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The one surprisingly missing variable was female gender, which was the most robust demographic association and predictor of fatigue in previous studies (Wessely *et al*. 1997). Sullivan and colleagues suggest that female gender is confounded by more powerful correlations, such as depression, although an alternative explanation is that gender effects are more powerful in chronic rather than acute fatigue (White *et al*. 2001).

As might be expected with such a heterogeneous problem as IF, twin modelling did not produce particularly convincing evidence of genetic or shared environmental effects. Understandably, 73% of the variance was explained by individual environmental influences in both genders. Twin studies of patients with more prolonged fatigue show greater evidence of a genetic influence (Farmer *et al*. 1999; Hickie *et al*. 1999; Buchwald *et al*. 2001).

CFS IN CHILDREN

There is a dearth of good research in children with CFS, which makes the task of helping them more difficult and uncertain. Rangel *et al*. (2003) (this issue, pp. 289–297) have used a case–control study to examine the role of psychiatric disorders and personality in children with CFS. They chose a comparison group of children suffering from juvenile idiopathic arthritis (JIA), in order to control for having a painful and chronic physical illness. Both groups were attending tertiary care clinics in a teaching hospital. They used the K-SADS semi-structured interview to make psychiatric diagnoses and a version of the Personality Assessment Schedule (PAS), which they modified for use in adolescents. Psychiatric (mainly mood) disorders were present in the previous year in approximately twice as many (three-quarters) children with CFS than JIA. Personality difficulties were apparent between twice and four times as often in children with CFS.

What could explain these findings that are in some ways (such as personality) more abnormal than one finds in adult populations with CFS? First, the children with CFS all met the more liberal Oxford criteria as well as the CDC criteria, allowing more chance of co-morbidity. Children with CFS had been ill for a much shorter time than the controls, so perhaps had had less time to adjust to their illnesses. A differential ascertainment bias was likely between children attending a teaching hospital for CFS *versus* JIA, which will further complicate generalization from these data. The authors themselves point out the 'severe' nature of the CFS in their sample. The interviewer was not masked to diagnosis, so there may have been some observer bias, particularly when using an interview. That having been said, the PAS was given to a parent, not the child, and the parent was asked to recall the pre-morbid behaviour of their child. Both groups were reasonably matched in important variables such as education and social class. More children with JIA came from 'broken homes' so one would intuitively expect the opposite findings to those found.

The findings are consistent with other reports of children and adults with CFS attending tertiary care, at least in so far as the psychiatric co-morbidity is concerned (Wilson *et al*. 1994; Clark *et al*. 1995). The high levels of psychopathology are likely to be as related to attendance at a tertiary clinic in a teaching hospital as the diagnosis of CFS itself (Euba *et al*. 1996). Whatever the explanations, these children need treatment that addresses their need for both physical rehabilitation and psychological treatments in the context of their families (Chalder *et al*. 2002).

PREDICTING RECOVERY FROM PERSISTENT FATIGUE

Chalder *et al*. (2003) (this issue, pp. 283–287) have examined the predictors of response to psychological therapy in 160 primary care adult patients attending their general practitioner (GP) because of persistent fatigue. Only 28 per cent of patients met criteria for CFS, suggesting a sample with relatively less severe illness and associated disability than one typically seen in secondary care. Subjects received six sessions of either cognitive behaviour therapy or counselling (Ridsdale *et al*. 2001). Abnormal fatigue 6 months after starting therapy was predicted by poor social adjustment at baseline, a physical illness attribution, a long perceived future illness duration, and the patients' report that they had never seen their GP for an emotional reason.

Surprisingly, baseline psychological distress did not predict non-response, since this is a strong predictor of both natural course and non-response to treatment of CFS in secondary care (Wilson *et al*. 1994; Clark *et al*. 1995; Bentall *et al*. 2002). This finding might be related to illness attributions, in that we know that considerably more primary care patients with chronic fatigue have psychosocial explanations for their fatigue than those in secondary care, even with severity controlled for (Euba *et al*. 1996). Such patients are probably more willing to engage in psychotherapy, which will predict a better response. Studies of CFS in secondary care find other predictors that were not measured in this study, such as membership of a self-help organization, receipt of disability benefits and pervasive inactivity (Prins *et al*. 2001; Bentall *et al*. 2002).

Three of the significant predictions were consistent with studies of CFS in secondary care (Sharpe *et al*. 1992; Wilson *et al*. 1994; Clark *et al*. 1995; Chalder *et al*. 1996; Vercoulen *et al*. 1996). The novel finding was the lack of memory of a previous emotional reason for attending their GP. In contrast, the GP's more objective account of the same variable did not predict poor response, suggesting that such patients may have suppressed the memory of such an attendance. This is consistent with a physical illness attribution and facultative somatizing style of presentation (Bridges *et al*. 1991). The fact that patients who see themselves as physically rather than emotionally unwell respond relatively poorly to a psychotherapy makes intuitive sense. The authors suggest that GPs need to assess the somatizing style of their patients presenting with persistent fatigue before offering psychotherapy. This is probably true of all patients presenting with physical symptoms for which there is no obvious cause.

Fortunately, such patients can be offered a non-psychotherapeutic alternative by means of graded exercise therapy (GET). GET is effective in patients with CFS and the related 'fibromyalgia' attending secondary care (Whiting *et al*. 2001; Richards & Scott, 2002). A randomized controlled trial (RCT) comparing GET to CBT for persistent fatigue in primary care has recently been completed (L. Ridsdale, personal communication). An RCT of group GET for primary care patients with any persistent unexplained physical symptom was no better than a control treatment of stretching at improving symptoms, but was significantly better at reducing primary health-care use and prescriptions (Peters *et al*. 2002). This rather negative result was obtained with patients with more persistent complaints (at least 12 months) in contrast to the 3 months of Chalder and colleagues' sample.

COSTS OF PERSISTENT FATIGUE AND CFS IN PRIMARY CARE

There are few studies of the economic cost of chronic fatigue (CF) and CFS, and none of costs in the UK. Therefore, the study by McCrone and colleagues (2003) (this issue, pp. 253–261) is a welcome addition to the literature on the burden to society of these health problems. McCrone studied 141 primary care patients complaining of 6 or more months of fatigue, albeit at a slightly lower symptomatic level than most other studies (Chalder *et al*. 1993). Thirty-one per cent of their subjects met the CDC criteria for CFS (Fukuda *et al*. 1994). They found that the mean total cost of ill health was £1906 for the previous 3 months, or £7624 extrapolated to the annual cost. The greatest costs were for informal care by friends and family (76%) and lost employment (15%). Only 9% of costs were for health services; mainly attending doctors. The variables most strongly associated with highest costs were having CFS and the severity of functional impairment, as might be expected.

It is difficult to compare these costs with those of other illnesses, since economic analyses are often based on sensitivity analyses and measures are often indirect, requiring sufficient estimation to make one wary of direct comparisons across studies. However, it is interesting to note that 'ill defined disorders' took up more health costs than depression and anxiety combined in the Netherlands in one study (Meerding *et al*. 1998). There are studies that have examined the direct and indirect costs of depressive illness in the UK, with one finding an annual cost of £1217 per patient receiving usual primary medical care (Bower *et al*. 2000). Although great caution should be exercised before concluding that CF and CFS are more costly than depressive illness, it would be surprising if as much as 76% of the costs of depressive illness were related to informal care-giving.

CONCLUSIONS

What can we learn from these studies? Acute fatigue is heterogeneous in its predisposing and maintaining associations. These are mainly environmental factors specific to the individual that may sometimes stem from their parenting during childhood. Children with severe CFS who attend tertiary centres are not only physically ill, but also psychologically distressed and this may have preceded their CFS. CFS in particular costs a lot of money, which is mainly spent caring for the patient. When a patient presents his/her illness with physical attributions, while denying psychological problems, it may be worthwhile considering treatments that respect that style rather than challenge it, so long as there is good evidence for the effectiveness of the alternative therapy.

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