Longitudinal study of outcome of chronic fatigue syndrome

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Abstract

***Objective*—To examine the predictors of long term outcome for patients with the chronic fatigue syndrome.**

***Design*—Cohort study.**

***Subjects*—139 subjects previously enrolled in two treatment trials; 103 (74%) were reassessed a mean of 3·2 years after start of the trials.**

***Setting*—University hospital referral centre.**

***Main outcome measures*—Age at onset, duration of illness, psychological and immunological status at initial assessment. Ongoing symptom severity, levels of disability, and immunological function at follow up.**

***Results*—65 subjects had improved but only six reported no current symptoms. An alternative medical diagnosis had been made in two and psychiatric illness diagnosed in 20. The assignment of a primary psychiatric diagnosis at follow up and the strength of the belief that a physical disease process explained all symptoms at entry to the trials both predicted poor outcome. Age at onset of illness, duration of illness, neuroticism, premorbid psychiatric diagnoses, and cell mediated immune function did not predict outcome.**

***Conclusion*—Though most patients with the chronic fatigue syndrome improve, a substantial proportion remain functionally impaired. Psychological factors such as illness attitudes and coping style seem more important predictors of long term outcome than immunological or demographic variables.**

Introduction

The term chronic fatigue syndrome is used to describe a clinical entity characterised by resting and postexertional fatigue and various additional symptoms including impaired memory and concentration, depressed mood, recurrent pharyngitis, and myalgia.[1,2] Much of the debate surrounding the chronic fatigue syndrome has centred on whether the symptoms can be explained by alternative medical or psychiatric conditions. The current diagnostic criteria require exclusion of an extensive list of medical diagnoses.[1] Furthermore, despite high rates of associated physical and psychological morbidity[3,4] its prognosis and the predictors of outcome have not been established.

Various factors have been implicated in determining the outcome of the chronic fatigue syndrome, including ongoing evidence of immune activation,[5] chronic viral infection,[6] current emotional disorder,[7] and strength of attribution of illness to physical causes.[8] We conducted this study to assess the temporal stability of a diagnosis of the chronic fatigue syndrome; evaluate long term physical, psychological, and immunological dysfunction; and determine the extent to which specific immunological or psychological factors predict outcome.

Subjects and methods

We invited 139 patients to participate in the study. All met our clinical and immunological criteria for chronic fatigue syndrome (chronic persisting or relapsing fatigue, neuropsychiatric impairment, and impaired cell mediated immune function)[2] and had participated in the placebo controlled trials of intravenous immunoglobulin[9] or of dialysable leucocyte extract and cognitive-behavioural therapy.[10] The patients were part of a larger cohort with chronic fatigue syndrome assessed by one of four specialist physicians in the departments of immunopathology and infectious diseases at our hospital during 1986-9. No additional criteria were applied to select subjects for inclusion in the trials.

INITIAL ASSESSMENT

All patients had been investigated before entering the trials to exclude alternative medical diagnoses and had had cell mediated immune function measured by T lymphocyte subset analysis and delayed type hypersensitivity skin testing. In addition, a structured psychiatric interview was completed (to determine premorbid and episodic psychiatric diagnoses from the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (DSM-III-R))[10-12] and self reported measures of physical and psychological well-being collected. These measures included the neuroticism subscale of the Eysenck personality inventory,[13] an indicator of trait anxiety and arousal, and the illness behaviour questionnaire.[14] This instrument has been used in primary care and people with chronic pain to describe various aspects of abnormal illness behaviour.[14,15] It generates scores on seven subscales, including hypochondriasis, disease conviction (belief in a physical rather than psychological disease origin), psychological versus somatic focusing, affective (emotional) inhibition, and denial (a measure of "the tendency to regard illness as the sole problem, whose resolution would result in a circumstance devoid of difficulties").[16]

FOLLOW UP

We sent all patients a detailed questionnaire to assess current severity of functional disability, global illness outcome, and residual symptoms. Outcome of illness was rated by patients on a 1-5 point scale from "improved completely" to "worsened to a severe extent." Four point scales were used to measure functional impairment across a range of domains (physical and social activity, current occupational status). Responses were rated from "more [activity] than before your illness" to "no activity." If patients were receiving a government (or similar) disability benefit this was recorded.

Subjects also completed the 30 item version of the general health questionnaire.[17] The Karnofsky performance index was scored at follow up by one of us (AW) after an interview with each subject.[18] This interview was also used to evaluate the possibility of alternative medical or psychiatric diagnoses,[11] with the benefit of details of longitudinal course. Corroborative evidence was also sought from the patient's doctor. Alternative diagnoses were assigned by consensus between two investigators (AW, IH), one of whom (IH) had conducted the psychiatric testing at entry to the trial.

Delayed type hypersensitivity was measured with the CMI Multitest (Merieux, France). The cumulative

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induration diameter was measured at 48 hours and scored in accordance with standards in healthy adults.[19] An induration diameter less than 2 mm was scored as an anergic response. A hypoergic response was defined by a total induration diameter of less than 10 mm for men and less than 5 mm for women.

We obtained informed consent from each patient and the study was approved by our ethics committee.

ANALYSES

Four variables which assessed psychological, functional, and immunological outcome were examined at follow up: self assessed global outcome; psychological caseness identified by the general health questionnaire (score ≥ 5); the investigator rated score on the Karnofsky performance index; and cell mediated immunity (response to the delayed type hypersensitivity skin test). Ratings obtained for patient assessed global outcome were collapsed into dichotomous categories: improved (completely or partially improved) and not improved (not improved at all, worsened to a mild or moderate extent, worsened to a severe extent). Responses to the delayed hypersensitivity skin test were also collapsed into either reduced (anergy, hypoergy) or normal responses. Scores were compared by independent or paired t tests as appropriate. Categorical variables were compared by χ^2 analyses with Yates's correction for small expected values.

The relations between independent predictor variables (measures of immunological and psychological function at entry to the trial, age of onset, and duration of illness) and dependent dichotomous outcome variables (self rated global outcome; presence or absence of caseness on the general health questionnaire at follow up; reduced or normal delayed responses to hypersensitivity skin test) were examined in separate logistic regression analyses. Multiple regression analyses were used to assess the relation between the same independent predictor variables and dimensional outcome measures (Karnofsky performance index). In these analyses predictor variables were entered in three stages: (*a*) age at onset and duration of illness; (*b*) measures of immunological function; and (*c*) measures of psychological function. Stepwise regression analyses were done to allow for the elimination of non-significant variables.

Results

One hundred and three of the 139 subjects (74%) returned completed questionnaires (29 men, 74 women). Five refused to participate and 31 subjects were unable to be contacted. The mean age was 42·2 (range 19-67; median 41) years. Subjects had had symptoms for a mean of 9·2 (range 3-30) years and were followed up for a mean of 3·2 (range 2·4-4·2) years after their initial assessment. Thirty five had participated in the intravenous immunoglobulin trial and 68 in the trial of dialysable leucocyte extract and cognitive behaviour therapy. The 103 subjects who participated in the follow up assessment were significantly older than the 36 who did not participate (mean age at entry to trial 41·4 *v* 33·7, $P<0·001$). There were however, no significant differences in terms of female to male ratio (72% *v* 58%, $P= 0·2$) or duration of illness at initial assessment (5·6 years *v* 4·5 years, $P=0·15$).

Although 65 patients reported improvement, only six had completely recovered. Thirty one reported being unable to perform any form of work, and 26 were receiving disability benefit because of the chronic fatigue syndrome. Twenty one could not perform any significant physical activity, and 41 stated that no social activity was possible. The mean Karnofsky performance score at follow up was 76·3 (SD 8·8, range 60-100), which corresponds to a disability level between "cares for self, unable to carry on normal activity or to do active work" (score=70) and "normal activity with effort" (score=80).

We found no significant differences in global outcome rating between patients in the intravenous immunoglobulin and dialysable leucocyte trials (66% *v* 62% improved; Karnofsky score 77·9 *v* 75·5) at long term follow up.

Patients who had not improved had a significantly higher rate of a primary psychiatric diagnosis at follow up (12/38 (32%) *v* 8/65 (12%), $\chi^2=5·7$, df=1, $P=0·01$, odds ratio=3·3). There were no significant differences, however, between improved and not improved subjects in the proportion with reduced (anergic/hypoergic) delayed hypersensitivity responses (18/37 (49%) *v* 29/65 (45%) at entry; 15/33 (45%) *v* 26/49 (53%) at follow up), or in rates of premorbid psychiatric diagnoses at entry to the trial (14/38 (37%) *v* 17/65 (26%)).

Although all subjects had evidence of impaired cell mediated immune function (either T cell lymphopenia or reduced or absent delayed hypersensitivity responses) at the time of diagnosis,[2] only 45% had an impaired response at entry to the trial (table I). Delayed type hypersensitivity response at entry to the trials was, however, associated with delayed type hypersensitivity response at follow up ($\chi^2=9·6$, df=4, $P<0·05$). In all 51% (42/82) of those subjects who had a delayed hypersensitivity skin test repeated at follow up had had the same response (anergy, hypoergy, or normal) documented at entry to the trials.

Of the 35 subjects who had participated in the placebo controlled trial of intravenous immunoglobulin, 20 had received active treatment during the trial. Of these, eight (40%) had been classed as responders at the end of the trial. There were no significant differences between responders and non-responders to active drug[9] in terms of long term global outcome (75% (6/8) *v* 42% (5/12) improved; $\chi^2=2·15$, df=1, $P=0·14$), Karnofsky scores (76·3 *v* 76·0, $P=0·95$) or delayed hypersensitivity at follow up (75% (6/8) normal response *v* 42% (5/12) $\chi^2=2·2$, df=1, $P=0·13$). We did not analyse the difference in long term outcome in the placebo and treatment arms of the trial of dialysable leucocyte extract and cognitive-behaviour therapy as no treatment effect was seen.[10]

Of the 103 subjects contacted, only two had developed medical conditions that could have accounted for their initial symptoms (one with progressive cognitive impairment in the context of probable small vessel cerebrovascular disease and another who developed systemic lupus erythematosus). Twenty subjects (19%) were thought to have had an alternative primary psychiatric illness at follow up (table II). Of these,

TABLE I—*Responses to delayed type hypersensitivity skin test at entry to trial and follow up*

Response	No (%) of entry (n=103)	No (%) at follow up (n=82)
Anergy*	19 (18%)	23 (28%)
Hypoergy†	28 (27%)	18 (22%)
Normal‡	55 (53%)	41 (50%)

*Total induration: men and women <2 mm.
†Total induration: men 2-9 mm, women 2-4 mm.
‡Total induration: men ≥ 10 mm, women ≥ 5 mm.

TABLE II—*Primary psychiatric diagnoses determined clinically at follow up in patients thought to have chronic fatigue syndrome*

Diagnosis	No of subjects (n=20)
Personality disorder with somatoform disorder	7 (borderline 6, schizotypal 1)
Primary somatisation disorder	3
Recurrent unipolar depressive disorder	6
Anxiety disorder	3 (panic disorder 2, generalised anxiety 1)
Schizophrenia	1

eight had improved at follow up (two completely) and 12 had remained unchanged or deteriorated.

The results of logistic and multiple regression analyses to evaluate trial entry variables as predictors of outcome are shown in tables III and IV respectively. Higher scores on the disease conviction subscale of the illness behaviour questionnaire were predictive of poor outcome on both patient (global outcome rating, P=0·01) and investigator (Karnofsky score, P=0·004) rated outcome measures. A general health questionnaire score of 5 or more (caseness) was predicted by a higher score on the illness behaviour questionnaire affective inhibition subscale (P=0·01). A normal delayed type hypersensitivity skin response at entry to the trials was predictive of a normal response at follow up (P=0·02), although the absence of a premorbid psychiatric diagnosis also approached significance (P=0·05). Stepwise logistic and multiple regression analyses gave the same outcome variable predictors as the one step method: global outcome rating (disease conviction, P=0·04; odds ratio 0·65, 95% confidence interval 0·43 to 0·65); general health questionnaire score 5 or more (affective inhibition P=0·007; 1·46, 1·1 to 1·9); delayed type hypersensitivity skin response (delayed hypersensitivity P=0·005; 1·55, 1·35 to 1·82) and Karnofsky score (disease conviction, P=0·003).

TABLE III—*Logistic regression analyses showing predictive value of immunological, psychological, and demographic variables or entry to trial for self rated global outcome, general health questionnaire score of 5 or more, and delayed type hypersensitivity skin test at follow up*

Independent variables* (predictor)	Parameter (SE)	Significance	Odds ratio (95% confidence interval)
	Global outcome rating†		
Age at onset‡	−0·16 (0·02)	0·49	0·85 (0·82 to 0·89)
Duration of illness‡	−0·19 (0·05)	0·68	0·83 (0·75 to 0·91)
T cell lymphopenia	−0·34 (0·32)	0·27	0·70 (0·38 to 1·33)
Delayed type hypersensitivity	−0·00 (0·32)	0·99	0·99 (0·53 to 1·87)
Premorbid psychiatric diagnosis	0·34 (0·34)	0·32	1·40 (0·72 to 2·74)
Eysenck personality inventory (neuroticism subscale)‡	0·08 (0·06)	0·24	1·08 (0·96 to 1·22)
Illness behaviour questionnaire:			
Hypochondriasis‡	0·11 (0·17)	0·52	1·11 (0·80 to 1·56)
Disease conviction‡§	−0·65 (0·26)	0·01	0·52 (0·31 to 0·87)
Psychological *v* somatic focus‡	−0·18 (0·34)	0·59	0·83 (0·43 to 1·63)
Affective inhibition‡	0·11 (0·16)	0·47	1·12 (0·82 to 1·53)
Denial‡	−0·11 (0·15)	0·49	0·89 (0·67 to 1·20)
	General health questionnaire case‖		
Age at onset‡	−0·01 (0·02)	0·60	0·99 (0·95 to 1·03)
Duration of illness‡	−0·04 (0·05)	0·35	0·96 (0·87 to 1·06)
T cell lymphopenia	0·37 (0·32)	0·24	1·45 (0·77 to 2·71)
Delayed type hypersensitivity	−0·14 (0·32)	0·67	0·87 (0·46 to 1·63)
Premorbid psychiatric diagnosis	0·42 (0·36)	0·25	1·52 (0·75 to 0·66)
Eysenck personality inventory (neuroticism subscale)‡	−0·06 (0·07)	0·37	0·94 (0·82 to 1·08)
Illness behaviour questionnaire:			
Hypochondriasis‡	−0·05 (0·16)	0·76	0·95 (0·70 to 1·30)
Disease conviction‡§	0·34 (0·23)	0·14	1·40 (0·90 to 2·21)
Psychological *v* somatic focus‡	−0·59 (0·41)	0·15	0·55 (0·25 to 1·24)
Affective inhibition‡	0·50 (0·18)	0·01	1·65 (1·16 to 2·35)
Denial‡	−0·25 (0·16)	0·11	0·77 (0·57 to 1·07)
	Delayed hypersensitivity skin test		
Age at onset‡	−0·03 (0·03)	0·29	0·97 (0·92 to 1·03)
Duration of illness‡	0·09 (0·06)	0·13	1·09 (0·97 to 1·23)
T cell lymphopenia	−0·13 (0·36)	0·72	0·88 (0·43 to 1·78)
Delayed type hypersensitivity	0·87 (0·39)	0·02	2·41 (1·11 to 5·13)
Premorbid psychiatric diagnosis	−0·85 (0·44)	0·05	0·42 (0·18 to 1·01)
Eysenck personality inventory (neuroticism subscale)‡	−0·02 (0·07)	0·76	0·98 (0·85 to 1·12)
Illness behaviour questionnaire:			
Hypochondriasis‡	−0·10 (0·20)	0·62	0·91 (0·61 to 1·34)
Disease conviction‡§	−0·16 (0·27)	0·55	0·85 (0·50 to 1·45)
Psychological *v* somatic focus‡	−0·63 (0·44)	0·15	0·53 (0·22 to 1·26)
Affective inhibition‡	0·04 (0·18)	0·81	1·04 (0·73 to 1·48)
Denial‡	0·25 (0·19)	0·18	1·28 (0·88 to 1·86)

*Variables scored as follows: delayed type hypersensitivity skin test responses (0=anergy or hypoergy, 1=normal); T cell (CD4 or CD8, or both) lymphopenia (0=absent, 1=present); premorbid psychiatric diagnosis (0=absent, 1=present), illness behaviour questionnaire subscales (hypochondriasis 0-9, disease conviction 0-6, psychological *v* somatic focusing 0-5, affective inhibition 0-5, denial 0-5).
†Global outcome rating: 0=no change or deterioration, 1=improvement.
‡Analysed as continuous variable.
§Significant at P<0·05.
‖General health questionnaire score ⩾5.

TABLE IV—*Multiple regression analyses showing predictor variables at entry to trial (immunological, psychological, and demographic) and investigator rated Karnofsky performance index scores* at follow up*

Independent (predictor) variables†	B (SE)§	β‖	*t* Value	Significance (*t*)
Age at onset	−0·10 (0·09)	−0·14	−1·04	0·30
Duration of illness	0·06 (0·18)	−0·14	−0·33	0·74
T cell lymphopenia	2·15 (2·38)	0·10	0·91	0·37
Delayed type hypersensitivity	−1·86 (1·20)	−0·16	−1·55	0·12
Premorbid psychiatric diagnosis	−2·99 (2·75)	−0·15	−1·08	0·28
Eysenck personality inventory (neuroticism subscale)	0·24 (0·25)	0·15	0·97	0·33
Illness behaviour questionnaire:				
Hypochondriasis	−0·52 (0·65)	−0·11	−0·90	0·42
Disease conviction‡	−2·63 (0·88)	−0·37	−2·99	0·004
Psychological *v* somatic focus	0·89 (1·43)	0·09	0·62	0·53
Affective inhibition	1·01 (0·62)	0·19	1·62	0·11
Denial	0·13 (0·60)	0·03	0·23	0·82

*R^2=0·24, F=1·97, P=0·04, scored 0-100.
‡P<0·05.
†See table III for continuous or categorical variable scoring.
§B is unstandardised regression weight.
‖β is standardised regression weight.

Discussion

This study indicates that many patients who have chronic fatigue syndrome diagnosed in a tertiary referral setting remain functionally impaired over time. This finding is consistent with previous reports from tertiary referral centres.[4,7]

Alternative medical diagnoses accounted for only two cases in this sample. This probably reflects the initial filtering process before patients present to tertiary centres as well as the stability of the chronic fatigue syndrome complex. By contrast, alternative primary psychiatric diagnoses were eventually made in 19% (20/103) of the sample. These were determined by consensus decision of two psychiatrists (AW, IH) taking into account all available evidence (structured interview, clinical and longitudinal data). The number with a psychiatric illness may still be an underestimate as no diagnosis was made unless sufficient data were available to meet the DSM-III-R diagnostic criteria. Of these 20 subjects, seven had a personality disorder with an associated somatoform disorder. Typically, these were patients with longstanding interpersonal difficulties whose clinical presentation changed greatly during the follow up period and who showed key psychological characteristics such as mood instability, self mutilation, or chaotic eating behaviour over time. Although a primary psychiatric diagnosis seemed to be associated with poor outcome, this was not uniformly the case. Two subjects completely recovered after appropriate psychiatric intervention and three reported improvement. This argues against the proposition that an alternative psychiatric diagnosis was principally determined by the extent of disability at follow up.

We only evaluated patients who had participated in previous clinical trials. These subjects were suitable because they had a detailed medical and psychiatric evaluation at entry to the trials and multiple sources of longitudinal data were available. However, as these subjects had chosen to participate in a clinical trial they may show specific coping styles, attitudes to illness, and aetiological beliefs that are not representative of the whole spectrum of patients with the chronic fatigue syndrome. Participation in the trials may have influenced long term outcome through non-specific treatment factors such as validation of illness and provision of a supportive treatment environment. There was a significant age difference between those who participated in the follow up assessment and non-participants. However, since the two groups were similar in terms of sex ratio and duration of illness this finding probably reflects the geographical mobility of younger subjects rather than a wider bias in the participants in the follow up study. The recovery rate may have been underestimated, however, as patients who remain unwell are perhaps more likely to maintain contact with the referral service (and hence to have been more successfully followed up) than those who recover.

DETERMINANTS OF OUTCOME

We found that psychological factors were important

Clinical implications

- The natural course of the chronic fatigue syndrome has not been clearly established, although both immunological and psychological factors are thought to influence outcome
- This study shows that 37% of subjects assessed in a tertiary centre did not improve and 25% received a disability benefit as a result of the chronic syndrome
- Only 2% developed another medical diagnosis, whereas in 19% an alternative psychiatric diagnosis was thought likely
- More attention should be given to psychological factors when treating patients

determinants of outcome, even though alternative predictor variables (age at onset, duration of illness, and immunological function) were entered before measures of psychological function in the analyses. For both subject rated (global outcome score) and investigator rated (Karnofsky score) measures of improvement, strong conviction in a physical disease process at initial assessment was associated with poor outcome. In addition, emotional inhibition at baseline was predictive of psychological caseness in the general health questionnaire at follow up. Cell mediated immunity, duration of illness, age at onset, trait neuroticism, and premorbid psychiatric diagnosis at entry to the trial did not predict outcome.

These findings suggest that subjects who deal with distress by somatisation (presenting physical rather than psychological symptoms) and who discount the possible modulating role of psychosocial factors are more likely to have an unfavourable outcome. The presence or absence of a specific psychiatric diagnosis may not be as important as a defensive style and attitudes to illness. There are, however, several alternative explanations which need consideration. The initial assessment was carried out at entry to the trials not at onset of illness, and more severe illness course may determine attitudes to illness and influence coping mechanisms. Stronger disease conviction may also have produced higher levels of illness related morbidity, rather than lower levels. Though we obtained the same model using different regression analysis strategies, validation on an independent data set is required to prove the correctness of this model.

Normal response to the delayed type hypersensitivity skin test at follow up was predicted by a normal response at initial assessment, although the absence of a premorbid psychiatric diagnosis approached significance as a predictor ($P=0.05$). Given a significant correlation between the absence of a premorbid psychiatric diagnosis and denial of psychological difficulties (as measured by the denial subscale of the illness behaviour questionnaire; $r=0.45$, $P<0.001$), a relation may exist between psychological factors (such as coping style) and immunological response. This finding would be consistent with the reports that specific coping styles such as suppression of feelings[20] or fighting spirit[21] may modulate the outcome for patients with cancer, perhaps through changes in immune function.[22] Further longitudinal studies are needed to examine the psychobiological relations between psychological distress and coping style, immunological function, and the natural course of chronic fatigue syndrome.

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ONE HUNDRED YEARS AGO

SELF-INFLICTED BULLET WOUND OF THE HEAD.

Dr. Sloan related the salient points of this case. A man with a strong hereditary tendency to insanity placed a revolver close to his forehead, rather to the left of the middle line, and fired. The outer and inner tables of the skull were penetrated, the bullet dropped on the cribriform plate of the ethmoid, and the brain substance was extensively injured. The latter wound discharged substances, which were certainly not aseptic, for several days. There was no blackening, scorching, or singeing of the skin, but the deeper tissues superficial to the bone, as well as the bone itself, were somewhat blackened. The patient made a perfect recovery, and whereas before the attempted suicide, or at all events on the day, or the day after that event, he might have been certified as a person of unsound mind, he was now quite well mentally. Dr. Sloan's remarks were illustrated by the exhibition of the revolver, the extracted bullet, some unfired cartridges, the charge of black gunpowder, the fragments of bone, some of them blackened, photographs, boards of various thicknesses at which the revolver in question had been discharged at various distances. (*BMJ* 1894;i:69.)