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The nosology of sub-acute and chronic fatigue syndromes that follow infectious mononucleosis

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ABSTRACT

Background. A previous principal components analysis of symptoms occurring after infectious mononucleosis suggested that a discrete fatigue syndrome occurs, which is independent of psychiatric disorder. This work has not been replicated and no latent class analysis of subjects has been published.

Method. We prospectively examined a cohort of 150 American primary care patients 2 and 6 months after the onset of corroborated infectious mononucleosis. A subset of 50 subjects was studied 4 years after onset. We performed principal components analyses of both psychological and somatic symptoms and latent class analyses of subjects.

Results. Principal components analyses consistently delineated two fatigue factors at 2 and 6 months and one fatigue factor at 4 years. These factors were separate from a mixed anxiety and depressive factor. A four-class solution for the latent class analyses consisted of most subjects with few symptoms, a few with many symptoms, a group with predominantly mood symptoms and some subjects with fatigue symptoms.

Conclusions. The symptoms of the principal factors with fatigue were similar to those previously described. Both the factors and classes were independent of an equally delineated mood factor and class. These results support the existence of two discrete chronic fatigue syndromes after infectious mononucleosis, one of which is still demonstrable 4 years after onset.

INTRODUCTION

Chronic fatigue syndrome (CFS) is a diagnosis of uncertain nosology (Lloyd, 1998; Wessely *et al*. 1998). Several consensus derived, criterion based definitions of CFS exist, which all include the symptoms of fatigue and fatigability (Holmes *et al*. 1988; Lloyd *et al*. 1990; Sharpe *et al*. 1991; Fukuda *et al*. 1994). These definitions have not yet been supported by empirical studies and continue to be refined (Reeves *et al*. 2004).

Retrospective studies have identified fatigue syndromes after various infections, including viral hepatitis (Berelowitz *et al*. 1995), viral meningitis (Hotopf *et al*. 1996), Q fever (Ayres *et al*. 1998) and infectious mononucleosis (IM) (Lambore *et al*. 1991). Recent cohort studies have concentrated on fatigue following IM or glandular fever. White and colleagues (1995*a*) used principal components analyses of physical and psychological symptoms to define an acute fatigue syndrome after IM in primary care that evolved into CFS in 9% of those infected (White *et al*. 1998). The syndrome was found to be essentially independent of psychiatric disorders and consisted of physical and mental fatigue (especially after physical exertion), excessive sleep, poor concentration, anhedonia, retardation, social withdrawal, emotional lability, transient sore throat, and lymph gland

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pain and enlargement. The syndrome was shown to have face validity and was a more reliable diagnosis than depressive disorder (White *et al.* 1995*a*, *b*). Symptoms were consistent with sickness behaviour (Dantzer, 2001).

Buchwald and colleagues have recently reported an American cohort of 150 patients studied after acute IM, also in primary care (Rea *et al.* 2001). They found that 12% had not recovered by 6 months (Buchwald *et al.* 2000). Fatigue and excessive sleep were also the most prominent convalescent symptoms. The present study attempted to replicate and extend the findings that a discrete fatigue syndrome can be defined after IM using data from this American cohort.

METHOD

Clinical setting and subjects

We studied patients in a large health maintenance organization in Seattle, WA (USA) that provides prepaid health care through facilities that include two hospitals, 23 out-patient medical clinics, three speciality centres and a progressive care facility. The plan serves a heterogeneous socio-economic population whose age and gender composition are similar to that of the western region of Washington State.

All subjects who met the following criteria were eligible for the study: (1) were older than 15 years of age; (2) had a positive heterophil antibody test; (3) had no record of a previously positive heterophil antibody; (4) reported the onset of symptoms within 14 days of having the heterophil test performed; (5) were not suffering from a chronic, disabling medical condition; (6) were not being treated with steroids; and (7) demonstrated serological evidence of acute Epstein-Barr virus (EBV) infection with a positive IgM titre to the viral capsid antigen. Using tri-weekly review of laboratory records, we prospectively identified all potential subjects from the out-patient sites who had a positive heterophil test. Subjects were screened for eligibility criteria using a computerized record system followed by a telephone interview. Final determination of eligibility occurred after enrolment and considered information from the chart review, patient interview and EBV serologies performed at the initial evaluation (see below). Thus, we used the initial heterophil antibody test to identify probable cases of IM and a subsequent serological profile to diagnose primary EBV infection. Subjects without serological evidence for acute infection were dropped from the study at this point. The institutional review boards of the University of Washington and the health maintenance organization approved the recruitment and evaluation protocols. All subjects, or their guardians, provided written informed consent.

All subjects were evaluated in person at the initial, 2, and 6 months visits. A postal questionnaire was sent out at a median of 4·1 years (range 1·9–5·5 years) after onset to all 150 subjects, of whom seven were lost to follow-up and 13 refused to participate. The questionnaire included the question 'How much have you recovered compared to the day you had your Monospot test done?'. There were 25 subjects who replied 'worse now than that day', 'about the same', or 'better, but not completely recovered'. These 25 subjects were matched by closest date to initial visit, age and gender to another 25 subjects who had recovered. All 50 of these subjects were sent the amended SCL-90 and these data were included in the present analysis.

Laboratory measures

A physical examination and laboratory evaluation was performed at each visit. A complete blood count, including a manual review of the white cell differential, was performed by the laboratory's pathologist to ensure that atypical lymphocytes, if present, were detected and accurately quantified. Serology for EBV was performed including IgG and IgM antibodies to the viral capsid antigen (VCA-IgG, VCA-IgM) and IgG to the nuclear antigen (EBNA). Indirect immunofluorescence (with induced cells) using serial two-fold dilutions was used to determine antibodies to VCA-IgG (1:10–1:1280) and VCA-IgM (1:10–1:40). The titres for VCA-IgG and VCA-IgM were expressed as the reciprocal of the highest dilution to register a positive reaction. Anti-complement immunofluorescence (MRL, Cypress CA) was used to test for antibodies to EBNA at a single 1:2 dilution. Reactivity above background signal obtained with EBNA-negative cells was considered positive.

Measures of symptoms

The somatization, anxiety, depression and additional vegetative subscales of the Symptom

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Check-List 90 item version (SCL-90) were self-rated at each interview. The SCL-90 is a symptom inventory that assesses the presence and severity of somatic and psychological symptoms (Derogatis, 1977). It has good reliability and validity in medical populations (Peveler & Fairburn, 1990) and correlates highly with data from structured psychiatric interviews. This measure includes an item about energy/tiredness: 'feeling low in energy or slowed down'. Subjects were asked 'how much have you been bothered by each of these symptoms in the last week?'. Possible responses were: 1, not at all; 2, a little bit; 3, moderately; 4, quite a bit; or 5, extremely. Only responses of >2 were used to calculate the frequency of symptoms. The SCL-90 was modified to include 12 IM-associated symptoms most frequently mentioned in previous publications and standard textbooks. These consisted of sore throat, painful lymph nodes, fever, chills, sleeping too much, general muscle weakness, prolonged fatigue or tiredness, eyes sensitive to light, abdominal discomfort, joint aches or pains, cough and rash. At 4 years we were able to add two specific questions that separated fatigue into physical and mental components.

Analyses

A principal components analysis of symptoms was performed at each interview (Chatfield & Collins, 1980). An orthogonal varimax rotation of symptom correlations was used with the SAS computer program (SAS, 1999). Principal components with eigen values <1 were considered non-significant; the eigen value being a measure of significance (Chatfield & Collins, 1980). Each symptom was ranked in descending order of loading; the loading being a measure of the strength of correlation of each symptom with a particular principal component (Chatfield & Collins, 1980). Symptoms that contained all their loadings between $+0{\cdot}25$ and $-0{\cdot}25$ were omitted.

We used categorical symptoms from the modified SCL-90 questionnaire, analysing the symptoms from 2 and 6 months after onset of infection. At 4 years after onset we chose to use only the separate and additional physical and mental fatigue questions, rather than all four fatigue questions, since these were closely correlated to 'prolonged fatigue/tiredness' and 'low energy/slowed down'. Symptoms were excluded from all analyses if they occurred in less than five subjects.

As a further test of the independent syndromes, we also undertook a latent class analysis of subjects at both 2 and 6 months, using the same set of categorical symptoms as defined above. As in previous studies of CFS and fibromyalgia (Sullivan *et al.* 2002), we used a FORTRAN program (Eaves *et al.* 1993) modified to employ an efficient expectation maximization (EM) algorithm (Dempster *et al.* 1977; Buckholz *et al.* 1996). The analysis is detailed in a previous paper (Sullivan *et al.* 2002).

RESULTS

Three hundred and thirty-three subjects were eligible for the study and 150 participated. Eligible persons who declined participation ($N=111$), or could not be contacted despite multiple attempts ($N=72$), were similar in mean (S.D.) age (22 (7) years) and gender (48% women) to the study subjects. Participating subjects had a mean (S.D.) age of 21 (7) years and 80 (53%) of subjects were women. Single subjects made up 93% of subjects, 90% were Caucasian and 64% were students.

We obtained analysable data from 146, 144 and 142 subjects at 1, 2 and 6 months, respectively, and from 50 subjects at 4 years. The final rotated principal components analyses for the interviews are given in Tables 1 to 3. We have shown all factors that contained fatigue with significant loadings since this was the focus of this study. Other non-fatigue factors are available from the authors if required.

Mood factors

Factor 1 was a mood factor, with the greatest variance explained and highest eigen values, which was present at both 2 and 6 months. This contained depressive and anxiety symptoms in equal measure, as well as 'prolonged fatigue' and 'low in energy/slowed down'. At 4 years this factor was split into two separate factors, one made up of depressive symptoms (factor 1) and the other with anxiety symptoms (factor 3).

Fatigue factors

There were either one or two factors that included fatigue at all three interviews, which were

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Table 1. *Rotated principal components at 2 months (with loadings)*

Symptom	Factor 1	Factor 2	Factor 4
Tense or keyed up	**0·67**	−0·12	−0·10
Feeling blue	**0·67**	*−0·26*	−0·15
Everything an effort	**0·66**	*−0·32*	0·05
Worrying too much	**0·65**	*−0·28*	0·18
Crying easily	**0·65**	*−0·41*	−0·13
Feeling trapped	**0·62**	*−0·35*	−0·03
Hopeless about future	**0·62**	*−0·26*	0·10
Low energy/slowed down	**0·61**	**0·41**	0·03
Loss of sexual interest	**0·58**	−0·12	0·02
Self-blame	**0·58**	*−0·38*	−0·02
No interest	**0·57**	−0·10	0·00
Nervous/shaky	**0·53**	−0·04	−0·06
Prolonged fatigue/tiredness	**0·53**	**0·28**	**0·37**
Lonely	**0·53**	−0·24	−0·27
General muscle weakness	**0·52**	0·17	−0·04
Fearful	**0·51**	*−0·35*	−0·11
Trouble falling asleep	**0·51**	0·07	0·15
Sensitive to light	**0·47**	**0·44**	−0·01
Abdominal discomfort	**0·46**	0·20	*−0·30*
Restless sleep	**0·46**	−0·25	**0·35**
Poor appetite	**0·44**	−0·04	0·19
Unable to sit still	**0·39**	0·19	−0·14
Sleeping too much	**0·36**	0·14	**0·29**
Sore muscles	**0·38**	**0·57**	−0·23
Trouble getting breath	**0·28**	**0·53**	−0·02
Stiff neck	**0·42**	**0·48**	−0·11
Weak in parts of body	**0·44**	**0·44**	0·10
Painful lymph nodes	**0·32**	**0·39**	**0·37**
Joint aches/pains	0·23	**0·36**	−0·03
Expecting a bad event	**0·29**	*−0·35*	0·25
Limb heaviness	**0·43**	**0·36**	−0·13
Sore throat	**0·32**	**0·42**	**0·58**
Lower back pain	**0·40**	**0·36**	*−0·44*
Headaches	0·16	**0·27**	*−0·29*
Cough	0·05	0·16	**0·39**
Guilty feeling	**0·39**	*−0·29*	−0·14
Faintness/dizziness	**0·27**	0·15	*−0·44*
Hot or cold spells	**0·27**	0·13	−0·23
Early morning waking	**0·45**	*−0·33*	**0·38**
Eigen values	8·95	3·86	2·18
Variance*	21·8%	9·4%	5·3%

* Percentage of total variance explained by the factor.

Symptoms with all their factor loadings being between ±0·25 were omitted. Bold type signifies those loadings of >0·25. Italics signify negative loadings of more than −0·25.

Table 2. *Rotated principal components at 6 months (with loadings)*

Symptom	Factor 1	Factor 2	Factor 4
Feeling worthless	**0·69**	*−0·33*	0·07
Feelings of guilt	**0·69**	*−0·28*	−0·13
Heart pounding/racing	**0·67**	*−0·44*	0·12
Self-blame	**0·64**	*−0·35*	0·14
Spells of terror or panic	**0·64**	*−0·47*	0·11
Low energy/slowed down	**0·64**	**0·27**	**0·32**
Feeling blue	**0·62**	*−0·34*	−0·11
No interest	**0·60**	0·20	−0·09
Tense or keyed up	**0·60**	−0·12	−0·21
Worrying too much	**0·59**	*−0·27*	−0·12
Nervous or shaky inside	**0·57**	−0·23	0·14
Hopeless about future	**0·57**	−0·18	−0·15
Everything an effort	**0·54**	0·24	0·19
Thoughts of death	**0·54**	−0·25	0·15
Weak in parts of body	**0·52**	**0·48**	0·10
Expecting something bad	**0·51**	*−0·31*	**0·30**
General muscular weakness	**0·51**	**0·44**	−0·06
Feeling trapped	**0·50**	−0·11	−0·04
Poor appetite	**0·48**	0·08	−0·20
Feeling fearful	**0·47**	*−0·42*	−0·07
Prolonged fatigue/tiredness	**0·46**	0·22	**0·38**
Stiff neck	**0·46**	**0·42**	*−0·26*
Lost libido	**0·43**	0·03	**0·29**
Sensitive to light	**0·43**	0·24	0·06
Lonely	**0·40**	−0·22	−0·36
Lower back pain	**0·39**	**0·32**	−0·29
Crying easily	**0·35**	−0·22	−0·22
Abdominal discomfort	**0·43**	**0·57**	0·00
Headaches	**0·27**	**0·46**	0·00
Joint aches/pains	**0·36**	**0·44**	−0·16
Restless sleep	**0·36**	**0·33**	−0·11
Trouble falling asleep	**0·41**	0·04	−0·17
Cough	0·21	−0·03	**0·29**
Heavy arms or legs	**0·36**	**0·36**	−0·13
Unable to sit still	**0·38**	−0·15	*−0·45*
Sore throat	0·14	0·00	**0·46**
Overeating	**0·31**	−0·15	0·24
Painful lymph nodes	**0·31**	**0·27**	0·06
Sore muscles	**0·45**	**0·36**	*−0·27*
Trouble getting breath	**0·32**	−0·08	**0·28**
Nausea/upset stomach	**0·35**	**0·28**	0·20
Numbness/tingling	**0·30**	**0·30**	0·01
Sleeping too much	0·16	**0·26**	**0·35**
Eigen values	9·91	4·05	2·29
Variance*	22·0%	9·0%	5·1%

* Percentage of total variance explained by the factor.

Symptoms with all their factor loadings being between ±0·25 were omitted. Bold type signifies those loadings of >0·25. Italics signify negative loadings of more than −0·25.

separate from the mood factor. At 2 months, factor 2 consisted of low energy with painful muscles, joints, head, back, throat and lymph nodes, sensitivity to light, and trouble getting breath. Factor 3 consisted of prolonged fatigue, with sore throat and lymph nodes, and both disturbed and excessive sleep. At 6 months, factor 2 included more prominent pains in various body parts, with general and specific weakness, and restless and excessive sleep. Factor 4 had more prominent, prolonged fatigue and low energy, with sore throat and sleeping excessively, but no pains or weakness. Lastly, at 4 years, the separation of physical and mental fatigue gave only one factor (factor 2) with prominent physical fatigue. This also included weakness, painful joints, muscles and neck, mental fatigue, irritability and social withdrawal.

Latent classes

At both 2 and 6 months, there was statistical evidence suggesting the approximate equivalence

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Table 3. *Rotated principal components at 4 years (with loadings)*

Symptom	Factor 1	Factor 2	Factor 3
Self-blame	**0·81**	0·00	0·25
Feeling guilty	**0·79**	0·08	0·20
Feeling blue	**0·76**	0·07	**0·32**
Expecting something bad	**0·73**	0·16	0·09
Hopeless future	**0·69**	**0·32**	0·14
General muscle weakness	0·08	**0·91**	0·04
Weak in parts of body	0·23	**0·84**	0·00
Physical fatigue	0·03	**0·75**	**0·29**
Joint aches/pains	−0·03	**0·67**	−0·15
Everything an effort	**0·39**	**0·45**	0·22
Feeling nervous/shaky	**0·31**	−0·10	**0·72**
Poor concentration	0·23	0·23	**0·69**
Irritability	**0·27**	**0·34**	**0·68**
Mood swings	**0·49**	−0·02	**0·63**
Worrying too much	**0·33**	−0·11	**0·52**
Trouble getting breath	**0·32**	−0·06	0·25
Hot or cold spells	−0·14	**0·37**	0·13
Sensitive to light	**0·30**	0·12	0·13
Sore muscles	−0·01	**0·52**	0·08
Crying easily	0·05	0·00	**0·42**
Mental fatigue	0·19	**0·47**	**0·30**
Social withdrawal	**0·31**	**0·43**	**0·40**
Numbness/tingling	−0·02	**0·27**	**0·41**
Lonely	0·21	0·14	**0·31**
Tense/keyed up	**0·40**	0·01	**0·31**
Stiff neck	**0·32**	**0·34**	0·03
Eigen values	10·27	4·33	3·81
Variance*	18·7%	7·9%	6·9%

* Percentage of total variance explained by the factor.
Symptoms with all their factor loadings being between ±0·25 were omitted. Bold type signifies those loadings of >0·25.

of both two and four class solutions. The two-class solution simply divided those subjects (72% at 2 months and 84% at 6 months) with few symptoms from a minority (28% at 2 months and 16% at 6 months) with multiple symptoms. The four-class solution divided the symptomatic class into three further classes.

At 2 months (Table 4), class 1 contained 70% of subjects and was very similar to class 1 in the two-class solution, with few symptoms. Class 2 contained 7% of subjects who had a mixed anxiety/depressive syndrome, but without physical symptoms. Class 3 contained 17% of subjects with fatigue symptoms; sore throat and muscles, stiff neck and initial insomnia with excessive sleep, but no mood symptoms. Class 4 contained 6% of subjects with high endorsements of both mood and somatic symptoms, including both fatigue symptoms.

At 6 months (Table 5), the four-class solution included class 1 containing 5% of subjects with prominent fatigue symptoms, muscle weakness and various pains, and both restless and excessive sleep. Class 2 contained 27% of subjects with some somatic anxiety symptoms of worry, headache and initial insomnia. Class three contained 62% of subjects with few symptoms. Class 4 contained 6% of subjects with multiple somatic and cognitive mood-related symptoms. There were insufficient subjects at 4 years for an analysis.

DISCUSSION

Three fatigue-containing factors occurred at different times after acute IM with reasonably consistent patterns of symptoms. One was consistent with a mixed anxiety/depressive disorder and the other two were independent of mood disorders. One of these mood-independent factors (factor 2 at 2 months and factor 4 at 6 months) contained fatigue, sore throat and lymph gland pain and excessive sleep. The second fatigue-related factor had prominent pain and more disturbed sleep. When fatigue was differentiated into physical and mental aspects, some 4 years after infection, there was only one fatigue factor that was independent of mood, which was characterized by prominent physical fatigue. In addition, the latent class analyses supported the existence of a class of subjects with a fatigue syndrome at both 2 and 6 months after onset. Five per cent of subjects were classified as having this fatigue syndrome 6 months after onset of IM.

How does this compare with the previous literature? The fatigue factor associated with sore throat, lymph gland pain and excessive sleep was similar to that described in the previous study of the nosology of fatigue after IM (White *et al.* 1995*a*, *b*), and is consistent with acute sickness behaviour (Dantzer, 2001). The other fatigue factor, with disturbed sleep and pain, was also found by White and colleagues, but only 6 months after onset. The absence of this second fatigue syndrome at 2 months could be explained by a type 2 error in the previous study, which had fewer cases of EBV infection. Yet, the similarity in the composition of the two independently established fatigue factors is remarkable when one bears in mind both the different populations and measures used in each study. How the use of different questions can alter the results was shown by the slightly

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Table 4. *Latent classes at 2 months*

	Endorsement in total sample	2 class solution		4 class solution			
		Class 1	Class 2	Class 1	Class 2	Class 3	Class 4
Class probability		0·72	0·28	0·70	0·07	0·17	0·06
Sore throat	0·11	0·04	**0·30**	0·02	0·00	**0·54**	0·11
Painful lymph nodes	0·06	0·02	0·18	0·01	0·00	**0·29**	0·11
Muscle weakness	0·08	0·03	0·23	0·03	0·00	0·17	**0·56**
Prolonged tiredness/fatigue	0·20	0·08	**0·53**	0·07	0·10	**0·58**	**0·78**
Joint aches	0·06	0·04	0·13	0·03	0·00	0·21	0·11
Sleeping too much	0·15	0·07	**0·35**	0·07	0·10	**0·33**	**0·56**
Eye sensitivity	0·08	0·00	**0·30**	0·00	0·00	**0·42**	0·22
Trouble getting breath	0·04	0·00	0·15	0·00	0·00	**0·25**	0·00
Cough	0·10	0·09	0·15	0·07	0·10	**0·29**	0·00
Headaches	0·15	0·12	0·23	0·10	0·00	**0·38**	0·22
Faintness/dizziness	0·06	0·01	0·18	0·01	0·10	0·17	**0·22**
Lower back pain	0·13	0·06	**0·30**	0·06	0·00	**0·33**	**0·44**
Abdominal discomfort	0·09	0·03	**0·25**	0·03	0·00	**0·25**	**0·44**
Nausea/upset stomach	0·08	0·05	0·15	0·05	0·00	0·17	0·22
Sore muscles	0·11	0·03	**0·33**	0·03	0·00	**0·42**	**0·33**
Stiff neck	0·18	0·08	**0·45**	0·08	0·10	**0·54**	**0·44**
Hot/cold spells	0·03	0·00	0·13	0·00	0·00	0·13	**0·22**
Numbness/tingling	0·02	0·01	0·05	0·00	0·00	0·13	0·00
Weak parts of body	0·07	0·02	0·20	0·01	0·00	**0·29**	0·22
Heavy feeling in limbs	0·04	0·00	0·15	0·00	0·00	0·17	**0·22**
Nervousness/shakiness	0·04	0·00	0·15	0·00	0·10	0·13	**0·22**
Fearful	0·03	0·00	0·13	0·00	**0·20**	0·04	**0·22**
Loss of sexual interest/pleasure	0·06	0·00	0·20	0·00	0·00	0·13	**0·56**
Low energy/slowed down	0·19	0·06	**0·55**	0·06	**0·00**	**0·58**	**0·89**
Heart pounding/racing	0·01	0·00	0·05	0·00	0·00	0·08	0·00
Tense/keyed up	0·13	0·01	**0·43**	0·01	**0·50**	0·25	**0·67**
Crying easily	0·11	0·02	**0·35**	0·02	**0·60**	0·04	**0·78**
Trapped/caught	0·06	0·00	**0·23**	0·00	**0·30**	0·04	**0·56**
Self-blame	0·07	0·00	**0·25**	0·00	**0·50**	0·08	**0·33**
Lonely	0·15	0·07	**0·35**	0·07	0·30	0·13	**0·89**
Blue	0·14	0·04	**0·40**	0·04	**0·40**	0·13	**1·00**
Worrying too much	0·16	0·02	**0·53**	0·01	**0·80**	0·29	**0·78**
No interest in things	0·07	0·01	**0·23**	0·01	0·10	0·04	**0·78**
Restless/unable to sit still	0·08	0·02	0·23	0·02	0·10	**0·25**	0·22
Everything an effort	0·05	0·00	0·18	0·00	0·10	0·00	**0·67**
Something bad expected	0·05	0·02	0·13	0·01	**0·30**	0·04	**0·22**
Worthlessness	0·03	0·00	0·10	0·00	0·10	0·00	**0·33**
Poor appetite	0·08	0·02	**0·25**	0·02	0·20	0·21	**0·33**
Overeating	0·08	0·03	0·23	0·03	**0·50**	0·13	0·11
Trouble falling asleep	0·15	0·06	**0·40**	0·06	0·30	**0·38**	**0·44**
Early morning waking	0·11	0·03	**0·33**	0·02	**0·60**	0·17	**0·44**
Restless sleep	0·15	0·05	**0·40**	0·04	**0·60**	0·25	**0·56**
Guilt	0·06	0·02	0·18	0·02	**0·40**	0·04	**0·22**

The bold figures differ from the overall endorsement frequency by >15%.

different results at 4 years, brought about by differentiating fatigue in a different way to the previous interviews. Five per cent of subjects had a fatigue syndrome 6 months after IM, which is similar to the 9% of subjects with an empirically defined fatigue syndrome 6 months after the same infection (White *et al.* 1998). This is the second study to find two different non-affective fatigue factors after IM, one consistent with sickness behaviour and the other more related to insomnia and pain (White *et al.* 1995*a*). By 4 years only one fatigue factor was apparent, although this was shown in a smaller sample.

How does this compare with other descriptions of chronic fatigue syndromes in general? Hickie and colleagues' latent trait analyses showed two main syndromes in patients in secondary care diagnosed with CFS (Hickie *et al.* 1995; Wilson *et al.* 2001). He and his colleagues described a condition similar to neurasthenia in three-quarters of patients attending an

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Table 5. *Latent classes at 6 months*

	Endorsement in total sample	2 class solution		4 class solution			
		Class 1	Class 2	Class 1	Class 2	Class 3	Class 4
Class probability		0·84	0·16	0·05	0·27	0·62	0·06
Sore throat	0·11	0·09	0·22	0·00	0·24	0·06	0·22
Painful lymph nodes	0·04	0·01	0·17	0·14	0·05	0·00	**0·22**
Muscle weakness	0·08	0·03	**0·35**	**0·57**	0·08	0·02	**0·33**
Prolonged tiredness/fatigue	0·13	0·07	**0·43**	**0·86**	0·08	0·06	**0·44**
Joint aches	0·09	0·04	**0·35**	**0·57**	0·18	0·01	0·11
Sleeping too much	0·08	0·05	**0·26**	**0·57**	0·11	0·03	0·11
Eye sensitivity	0·10	0·04	**0·39**	**0·43**	0·08	0·03	**0·56**
Trouble getting breath	0·04	0·02	0·17	0·00	0·03	0·02	**0·33**
Cough	0·08	0·05	0·22	0·00	0·21	0·01	0·22
Headaches	0·16	0·10	**0·48**	**0·71**	**0·39**	0·01	0·22
Faintness/dizziness	0·02	0·02	0·04	0·00	0·03	0·01	0·11
Lower back pain	0·13	0·09	**0·35**	**0·29**	0·24	0·05	**0·44**
Abdominal discomfort	0·05	0·01	**0·26**	**0·43**	0·08	0·00	0·11
Nausea/upset stomach	0·06	0·01	**0·30**	**0·43**	0·08	0·00	**0·22**
Sore muscles	0·11	0·07	**0·30**	**0·43**	0·11	0·05	**0·44**
Stiff neck	0·15	0·09	**0·43**	**0·43**	0·24	0·05	**0·56**
Hot/cold spells	0·03	0·00	0·17	0·14	0·00	0·00	**0·33**
Numbness/tingling	0·04	0·03	0·13	0·14	0·05	0·02	0·11
Weak parts of body	0·06	0·01	**0·30**	**0·71**	0·00	0·01	**0·22**
Heavy feeling in limbs	0·04	0·02	0·13	**0·29**	0·00	0·02	0·11
Nervousness/shakiness	0·07	0·02	**0·35**	0·00	0·13	0·00	**0·56**
Fearful	0·04	0·02	0·17	0·00	0·08	0·00	**0·33**
Loss of sexual interest/pleasure	0·05	0·03	0·17	0·14	0·00	0·03	**0·33**
Low energy/slowed down	0·13	0·03	**0·61**	**0·86**	0·08	0·02	**0·78**
Heart pounding/racing	0·06	0·00	**0·35**	0·00	0·05	0·00	**0·67**
Tense/keyed up	0·13	0·05	**0·52**	**0·29**	0·18	0·02	**0·78**
Crying easily	0·10	0·06	**0·30**	0·14	0·16	0·02	**0·56**
Trapped/caught	0·04	0·02	0·17	0·00	0·05	0·00	**0·44**
Self-blame	0·07	0·03	**0·30**	0·00	0·11	0·00	**0·67**
Lonely	0·11	0·05	**0·39**	0·14	0·16	0·03	**0·56**
Blue	0·12	0·05	**0·48**	0·14	0·21	0·00	**0·89**
Worrying too much	0·20	0·12	**0·61**	0·29	**0·47**	**0·00**	**0·89**
No interest in things	0·08	0·03	**0·39**	**0·57**	0·00	0·03	**0·56**
Restless/unable to sit still	0·06	0·04	0·13	0·00	0·11	0·01	**0·33**
Everything an effort	0·04	0·00	**0·26**	**0·43**	0·00	0·00	**0·33**
Something bad expected	0·05	0·02	**0·22**	0·00	0·08	0·00	**0·44**
Worthlessness	0·04	0·00	**0·22**	0·00	0·00	0·00	**0·56**
Poor appetite	0·08	0·03	**0·30**	**0·29**	0·08	0·02	**0·44**
Overeating	0·07	0·03	**0·30**	**0·29**	0·08	0·01	**0·44**
Trouble falling asleep	0·12	0·06	**0·43**	0·14	**0·29**	0·01	**0·44**
Early morning waking	0·07	0·04	0·22	**0·29**	0·18	0·00	0·11
Restless sleep	0·12	0·04	**0·52**	**0·71**	0·24	0·00	**0·33**
Guilt	0·06	0·01	**0·30**	0·00	0·03	0·00	**0·78**

The bold figures differ from the overall endorsement frequency by >15%.

infectious diseases fatigue clinic in secondary care. Seven of the eight most frequent symptoms were the same as in this study (Hickie *et al.* 1995). Other studies have supported the independence and reliability over time of a chronic or persistent fatigue syndrome in primary care or the community, using similar methodologies (Hickie *et al.* 1999; Van der Linden *et al.* 1999; Taylor *et al.* 2001). Jason *et al.* (2002) also differentiated CFS from healthy controls by the occurrence of headaches, lymph node pain, sore throat, joint and muscle pain; all of which were symptoms of one of the fatigue factors found in this study. Jason's sample was followed up and post-exertional fatigue was found to predict longer duration; a reflection of the prominence of post-exertional fatigue after IM (White *et al.* 1995*a*). The empirically defined syndrome in this study shares seven out of nine symptoms in the current international criteria for CFS (Fukuda *et al.* 1994). The two missing symptoms (impaired memory or

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concentration and post-exertion malaise) were not assessed.

Some studies have examined the possible aetiological associations and predictions of the prolonged fatigue syndrome that follows after acute IM. Katon *et al.* (1999) and Buchwald *et al.* (2000) found that reduced activity before onset, life events, and greater family support at onset predicted non-recovery and distress 6 months after IM. White and colleagues (2001) found that a positive Monospot test at onset and physical deconditioning consistently predicted the development of a prolonged fatigue syndrome, depending on the definition used. These authors went on to contrast these aetiological predictions with those that were found with mood disorders in the same cohort. These were quite different and were composed of a previous psychiatric history, an emotional personality trait, and life events or difficulties. Along with the discrete nosological status of a fatigue syndrome, the different aetiological predictions support the syndrome as being separate from psychiatric disorders, especially mood disorders. This provides no support for the suggestion that the fatigue syndrome that occurs after IM is a somatoform disorder, or that it involves the process of somatization.

This study has several limitations. First, compared with previous work, this study used different measures of symptoms, although this fact reinforces the validity of the similarities found. Secondly, the data at 4 years after onset came from non-recovered subjects and their controls, and not from the whole sample, although all non-recovered subjects were included. Thirdly, any definition of an illness based on symptoms alone is at best preliminary, since we do not have either the supportive evidence of outcome or aetiological factors.

In conclusion, this is the first study to empirically define a syndrome of prolonged fatigue many years after onset of a corroborated infection. It is also the first to show a latent class of subjects with a fatigue syndrome after IM. This provides further support for the discrete existence of both acute and chronic fatigue syndromes after IM, and extends the empirical evidence for the reliability of a syndrome up to 4 years after infectious onset. Future research should now address the aetiology, outcome, prevention and management of post-IM CFS (White *et al.* 2001; Candy *et al.* 2002, 2003).

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