Monospot and VP1 tests in chronic fatigue syndrome and major depression

S P J Lynch MRCPsych[1] **R V Seth** MRCPsych[2] **J Main** MRCP[3] [1]*St James University Hospital, Beckett Street, Leeds LS9 7TF,* [2]*Maudsley Hospital, De Crespigny Park, Denmark Hill, London SE5 8AF and* [3]*St Mary's Hospital Medical School, Norfolk Place, London W2 1PG*

Keywords: Monospot test; VP1 antigen test; chronic fatigue syndrome

Summary

Thirty-four patients with chronic fatigue syndrome (CFS) were compared with controls with DSM-III-R major depression on the Monospot and VP1 antigen tests. There was no significant difference in the numbers initially VP1 positive in the groups (11/34 and 7/34 positive in the chronic fatigue and major depression group respectively). Four CFS but no depressed patients were Monospot positive initially. No patient was both Monospot and VP1 positive. Patients positive on the tests were offered a repeat 6 months later. Eight of the 11 VP1 positive patients in the CFS group were retested and four remained positive, but none of the four depressed patients retested remained positive. No patient retested remained Monospot positive. The Monospot and VP1 tests appear to have little discriminating ability between these groups as screening tests and their predictive validity is unclear.

Introduction

Chronic viral infection by enteroviruses and Epstein-Barr Virus (EBV)[1,2] has been implicated in cases of chronic unexplained fatigue, previously termed 'Chronic mononucleosis syndrome'[2] and 'postviral syndrome'[3,4] but now termed chronic fatigue syndrome (CFS)[5,6]. Two screening tests, the VP1[1] and Monospot[7], have been advocated in diagnosis of 'postviral' forms of CFS and its differentiation from other fatiguing conditions. The Monospot may be positive early in EBV infections and is well-established. The VP1 antigen is common to enteroviruses, a positive test indicating exposure to an enterovirus, which may be useful in initial screening as there are numerous types of enterovirus for all of which it is impractical to screen. It was claimed that the VP1 test may help discriminate patients with the postviral fatigue syndrome (a form of CFS) from other conditions.

Two reports indicated overlap on this test with other fatiguing conditions such as neurological disorders producing peripheral fatigue[8] and depression producing central fatigue[9]. One longitudinal study has cast doubt on the role of chronic EBV infection in producing CFS[2].

Depression is a common condition where overlap of fatigue and psychological symptoms used to define the chronic fatigue syndrome occurs[9], so it would be of interest to assess the utility of the VP1 antigen and Monospot tests in discriminating between these groups initially and on follow-up. To our knowledge there are no longitudinal controlled studies that have addressed this question.

Correspondence to: Dr S P J Lynch, Department of Psychiatry, Clinical Sciences Building, St James University Hospital, Beckett Street, Leeds LS9 7TF

Patients and methods

Chronic fatigue syndrome group

Thirty-four consecutive outpatients (nine general practitioner referrals, 25 from hospital) were assessed in a fatigue clinic at a University teaching hospital by a physician (JM) and psychiatrist (SL or RS). All met consensus criteria for CFS[6] and suffered from persistent, disabling physical and mental fatigue and post-exercise myalgia.

Depressed control group

Controls were consecutive outpatient referrals, mostly in their first episode (19/34), meeting DSM-III-R criteria for major depression[10] and matched for age (within 2 years), sex, depression severity (within 3 points on the Montgomery Asberg Depression Rating Scale[11]) and type of depression (a non-endogenous picture as assessed on the Newcastle Depression Rating Scale[12] by a score less than 5 as previously described in CFS patients[13]). CFS patients who were not cases were matched to depressed controls in remission (seven cases).

Physical assessment

Patients had physical and neurological examinations, haematology (including B_{12} and folate levels), biochemistry screen (including muscle enzymes), Monospot and VP1 antigen. Patients who were initially Monospot or VP1 positive were offered a retest at 6 months.

Psychiatric assessment

DSM-III-R psychiatric diagnoses were generated after standardized psychiatric interview (SCID)[14] by trained raters (SL, RS inter-rater reliability κ 0.8-0.9). The nature of fatigue is controversial in CFS, so diagnosis and depression severity were determined with fatigue excluded and included. Severity of psychological symptoms was assessed by self-report on the GHQ-30[15] at interview by the Montgomery and Asberg Depression Rating Scale (MADRS) for depression[11] and Hamilton Rating Scale (HAS)[16] for anxiety. Physical complaints were assessed by check-list at interview. Fatigue severity was assessed by a new 10 item instrument the Fatigue Rating Scale (FRS)[17].

Statistical analysis

Non-parametric statistics were used for discrete data and parametric statistics for continuous data. They were two-tailed with a 5% level for significance.

0141-0768/92
090537-04/$02.00/0

Results

Sociodemographic characteristics

There were sex-related differences within groups for age: men ($n=11$) were older (mean age 45.2 years, range 21-64 years CFS; 43.1 years, range 23-65 years depressed group) than the women ($n=23$, mean age 33.2 years, range 17-63 years CFS group; 34.9 years, range 19-62 years depressed group, $P<0.05$, t-test).

Proportions in social classes were not significantly different with 11/34 and 7/34 in social class I and II respectively in the CFS group and 9/34 and 6/34 in the major depression group.

Historical data

CFS patients had a longer mean illness (35.8 months, range 14-120 months) than depressed patients (10.3 months, range 3-15 months, $P<0.01$, t-test). More CFS than depressed patients gave a history of a febrile illness before illness onset (Fisher's Exact test, $P<0.001$) or of recent flu-like symptoms (within 2 weeks of testing, Fisher's Exact test $P=0.00041$).

Diagnostic data

With fatigue excluded from diagnostic criteria, seven CFS patients were not psychiatric cases (20.6%), 14 (41.2%) were classified as having major depression (all single episodes, 10 of mild and four of moderate severity) and the remaining diagnoses were dysthymic disorder in 10 cases (29.4%) and generalized anxiety disorder in three patients (8.8%). Including fatigue did not alter the number of cases but meant that two dysthymic patients were then allocated to the major depression category (as cases of mild severity). Major depression patients had the following subclassification by severity - seven (20.6%) were moderate severity cases, 20 (58.8%) were of mild severity and seven (20.6%) cases were in remission (matched to CFS non-cases).

Physical investigations

One depressed woman was diagnosed as having mild hypertension. Four CFS women and one depressed man had marginally raised random glucose levels (normal on repetition). There was a case of iron deficiency anaemia and of folate deficiency (without anaemia) in the major depression group (both women, due to nutritional deficiency).

There was no significant difference in proportions initially VP1 positive in the two samples (Table 1). Although four CFS patients were Monospot positive but no depressed patients, the trend failed to reach significance (Fisher's Exact test $P=0.06$) as so few CFS patients were positive.

At 6 months proportionately more of the 8/11 CFS patients (initially VP1 positive) retested remained positive than the 4/7 depressed patients retested (Fisher's Exact test $P=0.0014$). No CFS patient initially Monospot positive remained so at retest. Decreases in the number of CFS patients VP1 or Monospot positive at retest were significant (Fisher's Exact test $P=0.038$ for VP1 and $P=0.018$ for Monospot).

Patients were divided into those with a remote history of febrile illness and those with recent flu-like symptoms (Table 2). These groups overlapped in membership. Group one with a history of flu-like symptoms before illness onset in the CFS group was not related to being initially VP1 or Monospot positive ($\chi^2=0.42$ d.f. 1 for VP1 NS, Fisher's Exact test $P=0.23$ for Monospot) or remaining positive on either test at 6 months (Fisher's Exact $P=0.89$ for VP1 and 1.00 for Monospot).

Group two patients with recent flu-like symptoms were not related to the chance of being Monospot or VP1 positive initially in the CFS group ($\chi^2=0.35$ d.f. 1 for VP1 NS and Fisher's Exact $P=0.22$ for Monospot) or remaining positive at 6 months (Fisher's Exact test $P=1.00$ for Monospot and $P=0.21$ for VP1).

Table 1. Monospot and VP1 status

	Chronic fatigue syndrome	*Major depression*	
Initial result:			
Monospot +ve	4 (11.8%)	0 (0%)	NS
Monospot −ve	30 (88.2%)	34 (100%)	NS
VP1 +ve	11 (32.4%)	7 (20.6%)	NS
VP1 −ve	23 (67.6%)	27 (79.4%)	NS
Result at 6 month retest:			
No. retested initially VP1 +ve	8/11 (72.7%)	4/7 (57.1%)	NS
No. retested initially Monospot +ve	4/4 (100%)	0	
Still VP1 +ve	4/8 (50%)	0	
Now VP1 −ve	4/8 (50%)	4/4 (100%)	
Still Monospot +ve	0		
Now Monospot −ve	4 (100%)		

Only patients initially VP1 or Monospot positive offered retest at 6 months.
NS, not significant difference between groups

Table 2. Monospot, VP1 results by history

	Chronic fatigue syndrome	*Major depression*
Group 1: with history of febrile illness before onset	24 (70.6%)	None
Initial status		
Monospot +ve	4 (16.7%)	
Monospot −ve	20 (83.3%)	
VP1 +ve	7 (29.2%)	
VP1 −ve	17 (70.8%)	
Result at 6 months		
Still Monospot +ve (All four retested)	0 (0.0%)	
Still VP1 +ve (All seven retested)	1 (14.3%)	
Group 2: with recent flu symptoms	16 (48.5%)	2 (5.9%)
Initial status		
Monospot +ve	3 (18.8%)	0 (0.0%)
Monospot −ve	13 (71.2%)	2 (100%)
VP1 +ve	6 (37.5%)	2 (100%)
VP1 −ve	10 (62.5%)	0 (0.0%)
Result at 6 months		
Still Monospot +ve (All three retested)	0 (0.0%)	0
Still VP1 +ve (All six retested)	2 (33.3%)	0 (0.0%) (Two retested)

(Only patients positive to either test retested at 6 months)

Table 3. Symptom severity by group

	Chronic fatigue syndrome	*Major depression*
Interview ratings (all scales max 60)		
MADRS (depression)		
Including fatigue	21.1 (18.3-24.0)	21.6 (18.7-24.4)
Excluding fatigue	19.4 (17.8-22.1)	22.2 (19.3-25.0)
HAS (anxiety)	15.9 (13.4-18.3)	20.8 (18.1-23.6)***
FRS (fatigue)	24.7 (21.5-27.8)	15.5 (11.6-19.5)***
Self-rating on general health questionnaire GHQ-30 (not all patients completed questionnaire)		
Number	26	29
GHQ 30	10.9 (0-20)	13.8 (3-27)
GHQ cases at 5/6 cut-off	16 (61.5%)	26 (89.7%)**
GHQ cases at 8/9 cut-off	13 (50.0%)	17 (58.6%)
Somatic complaints		
Muscle weakness	34 (100%)	13 (39.4%)***
Muscle pain at rest	21 (63.4%)	4 (12.1%)***
Post-exercise myalgia	34 (100%)	8 (24.2%)***
Mean number of complaints (range)	18.9 (11-20)	15.1 (8-17)

Symptom values are means
Figures in brackets 95% confidence limits unless stated
***$P<0.01$ (2-tailed)
**$P<0.02$

Table 4. Symptom severity by group, VP1 and Monospot status

	Chronic fatigue syndrome			*Major depression*	
	MS +ve (n=4)	*VP1 +ve (n=11)*	*MS/VP1 −ve (n=19)*	*VP1 +ve (n=7)*	*VP1 −ve (n=27)*
MADRS (depression)	20.8 (23.3-18.3)	19.8 (22.1-17.5)	22.0 (27.4-16.6)	28.4*** (33.0-23.8)	19.8 (23.2-16.4)
HAS (anxiety)	22.0 (23.4-20.6)	23.3 (25.3-21.3)	15.6*** (19.5-11.7)	20.9 (24.0-17.8)	22.5*** (25.9-19.1)
FRS (fatigue)	27.0 (28.5-25.5)	24.9 (29.2-20.6)	24.1 (29.2-19.0)	23.2 (25.9-20.5)	13.5*** (18.5-8.5)

Symptom values are means
Figures in brackets 95% confidence limits
***$P<0.01$ (2-tailed)

Only in depressed patients was the chance of being VP1 positive related to history of recent flu-like symptoms ($P=0.037$ Fisher's Exact test). Otherwise there was no significant relationship between recent flu-like symptoms and initial Monospot status and final VP1 status (Fisher's Exact test Monospot 0 months $P=1.0$, VP1 at 6 months $P=1.0$).

CFS patients were less anxious but more fatigued (both $P<0.01$ t-test) than depressed patients (Table 3). Excluding the fatigue (lassitude) item from the MADRS did not significantly alter ratings of depression severity in either group, which retained their matching.

Proportionately fewer CFS patients were GHQ-30 cases at the 5/6 cut-off points ($P<0.02$ $\chi^2=6.15$ d.f. 1) than depressed patients, but not at the higher cut-off 8/9 (used in medically ill populations $\chi^2=0.41$ d.f. 1 NS). Overall CFS patients were significantly less anxious but more fatigued than depressed patients (both $P<0.01$ t-test). Mean numbers of somatic complaints in the groups were not significantly different overall (t-test). More CFS patients had complaints of muscle weakness, muscle pain at rest and post-exercise myalgia (all $P<0.0001$ by χ^2 and Fisher's Exact test for muscle pain).

Table 4 shows symptom severity by diagnostic group and VP1/Monospot status within group. VP1 or Monospot positive CFS patients were more anxious than CFS patients negative for either test ($P<0.01$, t-test). Dividing the CFS group by VP1 or Monospot status, there was no significant difference in mean severity of fatigue or depressive severity within groups on t-test or non-parametric equivalents (Wilcoxon). VP1 positive depressed patients were more depressed and fatigued than those VP1 negative ($P<0.01$, t-test). VP1 negative depressed patients were significantly more anxious and less fatigued than VP1 negative CFS patients ($P<0.01$ for both by t-test).

Discussion

A study in this journal cast doubt on the specificity of the VP1 test[7]. Our study indicates that the VP1 test could not discriminate between depressed and CFS groups. Our CFS sample may be heterogeneous, ie not all cases are due to post-infectious aetiology, but at least 70% had a 'postviral' type fatigue syndrome so selection bias alone cannot explain these results.

The fact that few CFS patients retained VP1 positivity at 6 months does not favour chronic enteroviral infection as a cause of fatigue for the majority of CFS patients and casts doubt on the clinical utility of repeating the test. No depressed patients retested remained VP1 positive which may indicate that VP1 positivity was state-dependent in this group (possibly due to immune changes). However, caution must be taken in interpreting these results as not all patients could be retested and patients may change antigen status in either direction.

We feel that the VP1 test's specificity, sensitivity and predictive validity should be studied longitudinally with larger numbers of CFS patients (preferably community-based) and matched control groups with fatigue, eg neuromuscular disorders, depressed patients and randomly selected normal controls (from the community).

The Monospot was initially positive in only a small number of CFS patients so that although no depressed patients were positive it was not an effective test in discriminating the two groups. The Monospot was negative at retest in all originally positive which casts doubt over the utility of retesting with the Monospot in CFS.

Previous studies reporting an overlap of VP1 positivity in CFS and other fatiguing disorders were cross-sectional and have not controlled for potentially confounding variables such as age, sex, social class and depressive severity. Depressive severity may be important as severely depressed patients have been reported to have non-specific immune abnormalities such as impaired T-cell function[19] possibly via altered corticosteroid metabolism[20]. A greater prevalence of viral antibodies for EBV and herpes simplex virus has been reported in severely depressed patients than normals. These findings are less common in less severely depressed patients and in patients with a non-endogenous pattern of depression[21-23]. Depressed controls in this study were not severely depressed and had a non-endogenous pattern of depression, so it was thought they would be less likely to show the above abnormalities.

In our initial communication[9] we found differences in psychological and fatigue symptoms between diagnostic groups and by VP1 status. Depression severity may have influenced these results as we were not able to control for this; however, this methodological problem was overcome in this study yet many of the original findings were still replicated.

CFS patients were less anxious and had more severe fatigue (both mental and physical) than depressed patients. There was no particular significant difference by VP1 or Monospot status within the CFS group on measures of anxiety, depression or fatigue. However, depressed patients who were VP1 positive, were significantly more fatigued and depressed than other depressed patients and a proportion had similar somatic complaints to the CFS patients.

Acknowledgments: We would like to thank all the consultants at St Mary's and St Charles who referred patients to our clinic and also those colleagues throughout the Parkside district who collaborated with us.

References

1 Youseff GE, Bell EJ, Mann GF, *et al.* Chronic enterovirus infection in patients with postviral fatigue syndrome. *Lancet* 1988;i:146-9
2 Straus SE. The chronic mononucleosis syndrome. *J Infect Dis* 1988;**157**:405-12
3 Behan O, Behan WMH, Bell EJ. The postviral fatigue syndrome - analysis of the findings in 50 cases. *J Infect* 1985;**10**:211-22
4 Ramsay AM. *Postviral fatigue syndrome: the saga of the Royal Free Disease.* London: Gower Medical 1986
5 Holmes GP, Kaplan JE, Gantz NM, *et al.* Chronic fatigue syndrome: a working case definition. *Ann Intern Med* 1988;**108**:387-9
6 Sharpe MC, *et al.* A report - chronic fatigue syndrome: guidelines for research. *J R Soc Med* 1991;**84**:118-21
7 Bowman SJ, Brostoff J, Newman S, Mowbray JF. Postviral syndrome - how can a diagnosis be made? A study of patients undergoing a Monospot test. *J R Soc Med* 1989;**82**:712-16
8 Halpin D, Wessely S. VP-1 antigen in chronic postviral fatigue syndrome. *Lancet* 1989;i:1028-9
9 Lynch S, Seth R. Postviral fatigue syndrome and the VP-1 antigen. *Lancet* 1989;ii:1160-1
10 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*, 3rd edition (revised). Washington, DC: APA, 1987
11 Montgomery SA, Asberg M. A new depression rating scale designed to be sensitive to change. *Br J Psychiatry* 1979;**134**:382-9
12 Carney MWP, Roth M, Garside RF. The diagnosis of depressive syndromes and the prediction of ECT response. *Br J Psychiatry* 1965;**111**:659-74
13 Hickie I, Parker G, Lloyd A, Wakefield D. The psychiatric status of patients with chronic fatigue syndrome. *Br J Psychiatry* 1990;**156**:534-40
14 Spitzer RL, Williams J, Gibbon M. Structured clinical interview for DSM III-R (SCID-II) In: *Biometric research.* New York State Psychiatric Institute, 1987
15 Goldberg DP. *Manual of the General Health Questionnaire.* Windsor: NFER Publishing Co, 1979
16 Hamilton M. The measurement of anxiety states by rating. *Br J Med Psychol* 1959;**32**:50-5
17 Lynch SPJ, Seth RV, Montgomery SA, Priest RG. The Fatigue Rating Scale - An instrument designed to measure the intensity of fatigue and be sensitive to change. Abstracts of Royal College of Psychiatrists Spring Quarterly Meeting, 1990
18 Calbrese JR, King MA, Gold PW. Alterations in immunocompetence during stress, bereavement and depression: focus on neuroendocrine regulation. *Am J Psychiatry* 1987;**144**:1123-34
19 Kronfol Z, House JD, Silva J, Greden J, Carroll BJ. Depression, urinary free cortisol excretion and lymphocyte function. *Br J Psychiatry* 1986;**48**:70-3
20 Maes M, Bosmans E, Suy E, Minner B, Raus J. Immune cell parameters in severely depressed patients: negative findings. *J Affect Disord* 1989;**17**:121-8
21 King DJ, Cooper SJ. Viruses, immunity and mental disorder. *Br J Psychiatry* 1989;**154**:1-7
22 King DJ, Cooper SJ, Earle JAP. A survey of serum antibodies to eight common viruses in psychiatric patients. *Br J Psychiatry* 1988;**147**:137-44
23 De Lisi LE, Nurnberger JI, Simmons-Alling S, *et al.* Epstein-Barr Virus and depression. *Arch Gen Psychiatry* 1986;**43**:815-16

(Accepted 12 November 1991)