with further studies. One method already mentioned is a cross matching of national birth and death registers, which should become easier once a computer link exists to allow a detailed comparison of information about subjects listed. Another approach is to use regional obstetric registers or national census data to relate death by suicide to childbirth or child age. These methods are currently being pursued.

If the low risk is confirmed, then more exploration of the possible reasons would be valuable. If there is a large protective effect of motherhood based on concern for the welfare of dependants such concern would be an important focus for suicide prevention work, both with postnatal patients and with others at risk.

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Antibody to coxsackie B virus in diagnosing postviral fatigue syndrome

N A Miller, H A Carmichael, B D Calder, P O Behan, E J Bell, R A McCartney, F C Hall

Abstract

***Objective*—To study the association between coxsackie B virus infection and the postviral fatigue syndrome and to assess the immunological abnormalities associated with the syndrome.**

***Design*—Case-control study of patients with the postviral fatigue syndrome referred by local general practitioners over one year.**

***Setting*—General practitioner referrals in Dunbartonshire, Scotland.**

***Patients*—254 Patients referred with the postviral fatigue syndrome (exhaustion, myalgia, and other symptoms referable to postviral fatigue syndrome of fairly recent onset—that is, several months) and age and sex matched controls obtained from same general practitioner; 11 patients were rejected because of wrong diagnoses, resolution of symptoms, and refusal to participate, leaving 243 patients and matched controls.**

***Main outcome measures*—Detailed questionnaire (patients and controls) and clinical examination (patients) and blind analysis of blood sample at entry and after six months for determination of coxsackie B virus IgM and IgG antibodies and other variables (including lymphocyte protein synthesis, lymphocyte subsets, and immune complexes).**

***Results*—Percentage positive rates for coxsackie B virus IgM at entry were 24·4% for patients and 22·6% for controls and for coxsackie B virus IgG 56·2% and 55·3% respectively; there were no significant differences between different categories of patients according to clinical likelihood of the syndrome nor any predictive value in a fourfold rise or fall in the coxsackie B virus IgG titre in patients between entry and review at six months. The rates of positive antibody test results in patients and controls showed a strong seasonal variation. Of the numerous immunological tests performed, only a few detected significant abnormalities; in particular the mean value for immune complex concentration was much higher in 35 patients and 35 controls compared with the normal range and mean value for total IgM was also raised in 227 patients and 35 controls compared with the normal range.**

***Conclusions*—Serological tests available for detecting coxsackie B virus antibodies do not help diagnose the postviral fatigue syndrome. Percentage positive rates of the antibodies in patients simply reflect the background in the population as probably do the raised concentrations of total IgM and immune complexes.**

Vale of Leven Hospital, Alexandria, Dunbartonshire G83 0UA
N A Miller, MRCP, *clinical research assistant*
H A Carmichael, FRCP, *consultant physician*
F C Hall, BSC, *biochemist*

Helensburgh, Dunbartonshire
B D Calder, MRCGP, *general practitioner*

University of Glasgow, Glasgow G12 8QQ
P O Behan, MD, *professor in neurology*

Regional Virus Laboratory, Ruchill Hospital, Glasgow
E J Bell, MRCPATH, *top grade virologist*
R A McCartney, FIMLS, *chief medical laboratory scientific officer*

Correspondence to:
Dr Carmichael.

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Introduction

Since 1934 numerous outbreaks of a curious ill defined illness showing similarities in presentation, clinical picture, and outcome have been reported throughout the world under various synonyms, the most recent being the postviral fatigue syndrome and the chronic fatigue syndrome.[1-4] Outbreaks of the illness have been associated with increased antibody titres to coxsackie B virus.[5-9] One of us (HC) noted that between 1980 and 1984 the annual referral rate of medical outpatients in Dumbarton district thought to have the postviral fatigue syndrome more than quadrupled and seemed to be associated with high positive rates of coxsackie B IgG antibodies (about 40% each year) compared with the previously reported background rate of positive tests.[10] With the advent of a coxsackie B virus IgM antibody test the present prospective trial was set up to assess any association between the postvirual fatigue syndrome and coxsackie B virus infection and to examine immunological abnormalities previously described in this syndrome.[8]

Materials and methods

Patients and controls

During one year starting on 1 May 1985 local general practitioners were asked to refer patients with

the postviral fatigue syndrome, the guidelines being exhaustion for about six months at least with symptoms from the other main groupings (muscle, psychological, cognitive, autonomic, neurological, and cardiological). A matched control was obtained from the referring practitioner's list by taking the next surname after that of the patient and choosing the first subsequent entry for a patient with the same sex and for which the age was within 10% of that of the referred patient.

Clinical assessment

One doctor (NM) completed a detailed questionnaire and examination for each patient and graded the certainty of diagnosis of the postviral fatigue syndrome as follows: category 1, "classic" (acute, viral type onset, other diagnosis very unlikely); category 2, very probable (other diagnosis unlikely); category 3, possible (some doubt); category 4, least likely (non-specific presentation, adverse social or psychological factors).

A total of 243 patients were entered into the study. Eleven were rejected because of wrong diagnoses, resolution of symptoms, refusal to participate, etc. There were 177 (73%) women (mean age 37) and 66 (27%) men (mean age 36). On entry to the study the controls completed the same questionnaire as the patients but without quantifying symptoms.

Laboratory investigations

Blood obtained from patients and matched controls (usually within one month of each other) was tested blind for coxsackie virus IgM antibodies using the mu-antibody-capture enzyme linked immunosorbent assay (ELISA) test[11] and for coxsackie B virus IgG neutralising antibodies with the micrometabolic inhibition method,[12] at entry and after six months. A full blood count, renal and hepatic function tests, and virological screen were done in all patients at entry.

Immunological studies

In vitro peripheral blood lymphocyte protein synthesis, lymphocyte subset analysis, and immune complexes[8] were determined in 35 randomly selected patients and 35 controls as well as immunoglobulin estimations in the 35 controls and 227 study patients.

Statistical methods

The results of coxsackie B virus serological testing in 217 patients and matched controls were analysed with McNemar's test for matched samples and subgroup analysis with the χ^2 test for trend. The immunological results were analysed with the *t* distribution for means for each investigation with the Bonferroni correction for multiple comparisons.

Results

The pattern of symptoms was similar in coxsackie B virus IgM positive and IgM negative patients (table I). There was no significant difference in the clinical outcome at six months' review between patients with a fourfold rise or a fourfold fall in the coxsackie B virus IgG titre between entry and review (table II).

TABLE I—*Clinical picture for patients at entry who were negative and positive for coxsackie B virus IgM*

Symptom	% Negative for IgM	% Positive for IgM	Symptom	% Negative for IgM	% Positive for IgM	Symptom	% Negative for IgM	% Positive for IgM
Exhaustion	100	100	Poor memory	58	41	Disturbed micturition	34	31
Malaise	98	98	Insomnia	57	47	Depersonalisation	34	27
Tiredness	85	85	Cold sensitivity	55	56	Diarrhoea	32	25
Muscle fatigue	62	81	Nausea	45	56	Abdominal pain	30	31
Headache	73	78	Dizziness	55	54	Panic attacks	30	31
Poor concentration	74	64	Palpitations	49	54	Vertigo	27	24
Sweating	72	71	Paraesthesiae	50	51	Numbness	23	25
Flushing	65	68	Sore eyes	49	44	Tinnitus	23	17
Chest pain	66	47	Sore throat	47	42	Muscle cramp	20	19
Anxiety	61	64	Arthralgia	43	46	Sore ears	20	17
Depression	61	63	Tight bands	44	42	Ataxia	14	14
Breathlessness	52	61	Abdominal distension	31	41	Vomiting	11	14
Emotional lability	59	53	Faintness	28	37	Facial pain	12	10
Anomia	59	44	Anorexia	35	34			
Muscle pain	51	58	Blurred vision	35	27			

TABLE II—*Clinical change in patients with fourfold rise or fall in coxsackie B virus IgG titre between entry and six months' review*

Change in titre	No of patients	No (%) clinically improved	No (%) clinically unchanged
Fourfold fall	31	24 (77)	7 (23)
Fourfold rise	26	22 (85)	4 (15)

At entry, although the percentage of positive rates for coxsackie B virus antibodies were high, there were no significant differences between 217 patients and their matched controls with positive results in 53 (24·4%) and 49 (22·6%) respectively for IgM, 122 (56·2%) and 120 (55·3%) respectively for IgG, and 55 (25·4%) and 50 (23·0%) respectively for IgG titre ≥512

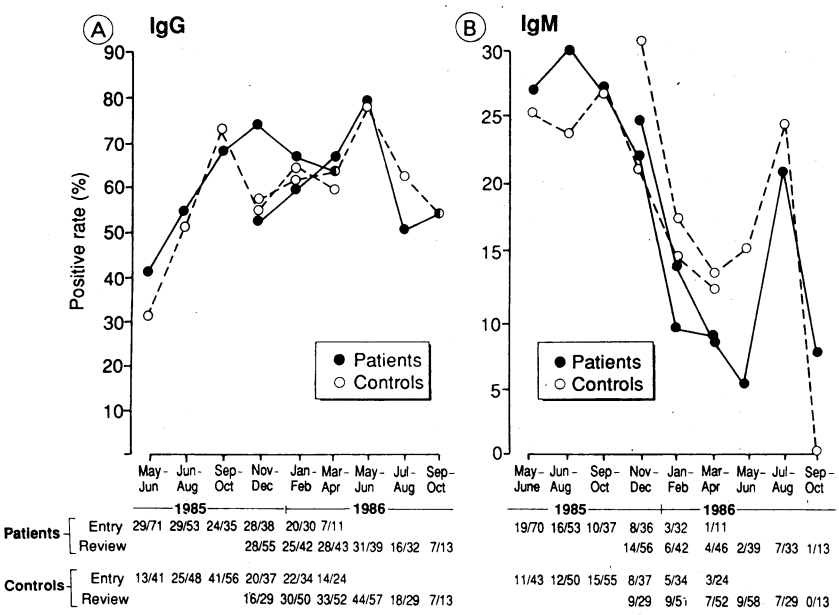
TABLE III—*Analysis of coxsackie B virus IgM and IgG in total sample (217 patients and matched controls at entry and six months and by subgroup at entry visit*

	IgM positive		IgG positive		IgG titre ≥512	
	No	% Positive (95% confidence interval)	No	% Positive (95% confidence interval)	No	% Positive (95% confidence interval)
Total sample (McNemar's test for matched samples)						
At entry: patients	53	24·4* (18·7 to 30·1)	122	56·2 (49·6 to 62·8)	55	25·4 (19·6 to 31·1)
At entry: controls	49	22·6 (17·0 to 28·1)	120	55·3 (48·7 to 61·9)	50	23·0 (17·4 to 28·6)
At review: patients	29	13·4* (8·8 to 17·9)	127	58·5 (52·0 to 65·1)	51	23·5 (17·9 to 29·1)
At review: controls	36	16·6 (11·6 to 21·5)	137	63·1 (56·7 to 69·6)	55	25·4 (19·6 to 31·1)
Subgroup analysis at entry visit (χ^2 for trend)						
Patients:						
Category 1 (n=81)	22	27·2 (17·5 to 36·9)	40	49·4 (38·5 to 60·3)	17	21·0 (12·1 to 29·9)
Category 2 (n=92)	21	22·8 (14·2 to 31·4)	59	64·1 (34·3 to 73·9)	28	30·4 (21·0 to 39·8)
Categories 3 and 4 (n=56)	12	21·4 (10·7 to 32·1)	30	53·6 (40·5 to 66·7)	13	23·2 (12·1 to 34·3)
Controls:						
With 0-1 symptoms (n=74)	18	24·3 (14·5 to 34·1)	41	55·4 (44·1 to 66·7)	23	31·1 (20·6 to 41·6)
With 2-8 symptoms (n=99)	20	20·2 (12·3 to 28·1)	44	44·4 (34·6 to 54·2)	12	12·1 (5·7 to 18·5)
With >8 symptoms (n=70)	17	24·3 (14·3 to 34·3)	46	65·7 (54·6 to 76·8)	22	31·4 (20·5 to 42·3)

*p<0·001.

TABLE IV—*Results of immunological testing in patients and controls compared with normal values. Unless otherwise stated values are means (SD), analysed by the t distribution for means with Bonferroni correction for multiple comparisons and using logarithmic transformation when appropriate**

Variable	Normal value	Controls	Patients: With acute conditions (<6/12 months)	Patients: With chronic conditions (>6/12 months)	Significance
No of patients		35	15	20	
T cells % reactive with monoclonal antibody:					
Tt	71 (6·4)	69·3 (8·3)	74·9 (7·9)	68·5 (9·0)	
Th	48 (3·9)	45·4 (8·7)	49·6 (12·0)	47·5 (9·8)	
Ts	23 (5·4)	23·8 (6·9)	21·3 (7·2)	21·0 (5·8)	
B	11 (3·9)[A]	11·5 (4·9)[B]	7·7 (2·6)[A B]	9·0 (4·4)	A(6)p <0·05 B(6)p <0·01
NK	10 (5·3)	11·0 (6·4)[C]	7·1 (3·6)[C]	11·2 (6·2)	C(6)p <0·05
Th/Ts	2·3 (0·75)	2·2 (1·3)	2·7 (1·5)	2·5 (1·1)	
Lymphocyte protein synthesis (maximum stimulation index)	2·4 (0·36)[D]	2·0 (0·40)[D]	2·1 (0·48)	2·1 (0·45)	D(6) p<0·01
Complement:					
Clq (% of normal human serum)	70-140	107 (21)[E]	92 (24)	90 (21)[E]	E(6)p <0·05
C3c (g/l)	500-1200	1030 (340)	1120 (270)	960 (260)	
C4 (g/l)	220-560	434 (240)	520 (310)	380 (170)	
C3 proactivator (% normal human serum)	80-160	96·4 (24)	91 (24)	84·1 (16)	F(6)p <0·006 G(6)p <0·006
Immune complex (g/l)*	39 (20)[F G H]	114 (112)[F]	126 (108)[G]	114 (98)[H]	H(6)p <0·006
IgM estimation:					
No of women	88	26	168		I(6)p <0·003
Mean IgM (g/l)	160 (62)[I J]	275 (89)[I]	256 (117)[J]		J(6)p <0·003
No of men	62	9	59		K(6)p <0·003
Mean IgM (g/l)	125 (53)[K L]	243 (99)[K]	206 (87)[L]		L(6)p <0·003



Bimonthly percentage positive rates for coxsackie B virus antibody in patients and controls at entry and review, May 1985-October 1986 (A) IgG; (B) IgM

(table III). Similar findings were found by subgroup analysis at entry (table III). The significant fall in the percentage rates for coxsackie B virus IgM in patients between entry and review is probably explained by the strong seasonal variation in rates for both patients and controls, as the figure suggests.

Patients and controls had significantly higher values for immune complex concentration than the normal value (table IV). Although values for lymphocyte protein synthesis were reduced in the patients and controls compared with normal values, the difference only reached significance in the controls. In patients with the acute condition there was a significant reduction in values for B lymphocytes compared with those for controls and normal values and in values for NK lymphocytes in comparison with those for controls. There was a small but significant reduction in the Clq complement component in patients with the chronic condition compared with that in controls. Although there was no difference in total IgM between the patients and controls, there was a highly significant increase in total IgM concentration in patients and controls in comparison with the normal range (among women 256 (SD 117), 275 (89), and 160 (62) respectively and among men 206 (87), 243 (99), and 125 (53) respectively (table IV).

Discussion

The nature, clinical picture, and diagnosis of the postviral fatigue syndrome have been matters of unresolved debate for many decades, made worse by lack of an accepted diagnostic marker. Access to specialist electrophysiology[13] and magnetic resonance imaging[14] may not be available or even appropriate.

Although there has been much interest and discussion regarding the role of immune dysfunction in the aetiology of the postviral fatigue syndrome, few consistent immunological abnormalities have been reported. Reports have included abnormal circulating lymphocytes and depressed lymphocyte function with impaired cytotoxic T cell responses to specific virus epitopes,[15] increased or decreased immunoglobulin concentrations,[16] immune complexes containing coxsackie B virus antigen,[17] and normal and abnormal suppressor and inducer T cell counts.[16 18] Until now, no reports of reduced B and NK cell counts have been published. Discrepancies in lymphocyte subpopulations seen in different studies are also found in other disease states such as multiple sclerosis[19] and may reflect differences in technique, selection of patients, and sampling criteria. Although not specifically designed to investigate the role of immune dysfunction in the aetiology of the postviral fatigue syndrome, our study does throw some doubt on the usefulness of these immunological variables in diagnosing this condition in so far as individual controls often had appreciably abnormal results of one or more of the immunological variables, including T cell subsets, protein synthesis, and complement concentrations. In particular, the raised immune complex and total IgM concentrations found in this study may simply reflect the background exposure of the population to coxsackie B virus. An association between coxsackie B virus infection and the postviral fatigue syndrome has been noted in some studies[5-9] but not others,[20 21] and other causative agents have been incriminated in yet other studies.[15 16 18 22-25]

Newer tests for coxsackie B virus infection are being developed. Yousef *et al* report higher positive results in patients with the postviral fatigue syndrome than in controls with a new method for isolating coxsackie B virus from stool samples and also with a new enterovirus specific antigen test as well as coxsackie B virus IgM antibodies.[26] Evidence of enterovirus specific RNA in skeletal muscle biopsies was shown in 20 out of 96 patients with the postviral fatigue syndrome[27] and Epstein-Barr virus DNA was identified in other cases.[28]

Coxsackie B virus infection is common and asymptomatic in most people. Positive serological results for coxsackie B virus simply reflect exposure to the virus and do not imply ill health or necessarily explain ill health. Our experience shows that the currently available serological tests for coxsackie B virus IgM and IgG do not help to distinguish patients with the postviral fatigue syndrome from the normal population. Future studies using established or newly developed laboratory tests must take account of the need for properly matched controls from the same geographical area studied at the same time. Such studies must also try to deal with the question of whether a positive result simply implies exposure to the virus or a cause of chronic continuing ill health.

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Serum sialic acid concentration and cardiovascular mortality

Gunnar Lindberg, Gunnar A Eklund, Bo Gullberg, Lennart Råstam

Centre for Public Health Research, S-65182 Karlstad, Sweden
Gunnar Lindberg, MD, *senior physician*

Department of Cancer Epidemiology, Radiumhemmet, Karolinska Hospital, Stockholm, Sweden
Gunnar A Eklund, PHD, *professor of epidemiology*

Department of Community Health Sciences, University of Lund, Malmö, Sweden
Bo Gullberg, MA, *senior lecturer in medical statistics*
Lennart Råstam, MD, *senior lecturer in family medicine*

Correspondence and requests for reprints to: Dr Lindberg.

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Abstract

***Objective*—To determine whether serum sialic acid concentration may be used to predict short and long term cardiovascular mortality.**

***Design*—Prospective study on all men and women who had their serum sialic acid concentration measured as part of a general health survey in 1964 or in 1965. All were followed up for an average of 20·5 years.**

***Setting*—Geographical part of the county of Värmland, Sweden.**

***Subjects*—Residents in the area participating in a health check up in 1964-5 (27 065 men and 28 037 women), of whom 372 men (169 with incomplete data and 203 lost to follow up) and 345 women (143 and 202 respectively) were excluded; thus 26 693 men and 27 692 women entered the study. The study sample was restricted to subjects aged 40-74 during any of the 20 years' follow up.**

***Main outcome measures*—Serum sialic acid concentration, serum cholesterol concentration, diastolic blood pressure, body mass index at the general health survey visit; cardiovascular and non-cardiovascular deaths during three periods of follow up (0-6 years, 7-13 years, and 14-20 years), according to the Swedish mortality register, in subjects aged 45-74.**

***Results*—Mean serum sialic acid concentration (mg/100 ml) was 68·8 (SD 8·0) for men and 69·2 (8·0) for women; the average concentration increasing with age in both sexes. A total of 5639 (21%) men and 3307 (12%) women died during the follow up period, in whom death in 3052 (54%) men and 1368 (41%) women was from cardiovascular causes. During short (0-6 years), medium (7-13 years), and long (14-20 years) term follow up the relative risk of death from cardiovascular disease increased with increasing serum sialic acid concentration. The relative risk (95% confidence interval) associated with the highest quartile of sialic acid concentration compared with the lowest quartile was 2·38 (2·01 to 2·83) in men and 2·62 (1·93 to 3·57) in women. Similar results were found for deaths from non-cardiovascular disease with relative risks of 1·50 (1·34 to 2·68) in men and 1·89 (1·57 to 2·28) in women, but these relative risks were significantly lower than those for deaths from cardiovascular disease ($p<0·001$ and $p<0·005$ respectively). In multivariate analysis of total mortality and of cardiovascular mortality with sialic acid concentration, serum cholesterol concentration, diastolic blood pressure, and body mass index as independent variables the impact of sialic acid concentration was virtually the same as in univariate analysis.**

***Conclusion*—Serum sialic acid concentration is a strong predictor of cardiovascular mortality. A possible explanation of these findings is that the serum sialic acid concentration may reflect the existence or the activity of an atherosclerotic process, and this may warrant further investigation.**

Introduction

Sialic acid, a family of acetylated derivatives of neuraminic acid, is widely distributed in mammals. It usually occurs as a terminal component at the non-reducing end of carbohydrate chains of glycoproteins