The hybridization studies reported here represent the first direct demonstration of the presence of enterovirus RNA within the skeletal muscle of patients with PFS and provides further evidence of the organic nature of this syndrome. However, it is likely that although enteroviruses are major aetiological agents of PFS, other viruses, particularly Epstein-Barr virus[18], may induce the syndrome. We suggest that this disease is a chronic metabolic myopathy induced by persistent virus infection.

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Coxsackie B viruses and myalgic encephalomyelitis

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Summary

Data collected over the past 6 years suggest that Coxsackie B viruses (CBV) play an important role in myalgic encephalomyelitis (ME). Since psychological upset is a feature of this illness, 247 patients, recently admitted to a psychiatric hospital, were tested for neutralizing antibodies to CBV. A total of 12.5% had significantly raised CBV titres compared with 4-5% of 'well' control groups; the percentage positive was greatest (21%) in those aged 30-39 years.

During 1985 and 1986 sera from 290 adults with ME were tested using the newly developed CBV IgM ELISA test; 37% were CBV IgM positive compared with 9% of 500 'well' adult controls. Forty-seven children, with ME were similarly tested during this period; 38% were positive, implying recent or active CBV infection. The combined use of this ELISA test and the virus probe techniques now available should further help to elucidate the exact role of CBV in this disabling illness.

Introduction

Outbreaks and sporadic cases of myalgic encephalomyelitis (ME) have been reported from many parts of the world during the past 50 years. Various terms used to describe this bizarre illness have included epidemic neuromyasthenia, Iceland Disease and Royal Free Disease named after a large outbreak in that London Hospital in 1955. Currently the term ME is regarded as that which best encompasses the multiple symptomatology associated with this illness[1]. Women are more often affected than men and a curious susceptibility is shown by nursing and medical staff. The afflicted patients have a wide variety of complaints but these always include muscle pain, extreme fatigue on exertion and psychological upset. Although most give a history of a preceding viral-like illness investigators have usually failed to identify a virus and the absence of objective abnormalities has led many to propose that the illness is psychogenic.

An outbreak of ME occurred in the West of Scotland in 1980/81. The only positive virological finding was

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the detection of significantly high (≥512) Coxsackie B virus (CBV) neutralizing antibody titres in 59% of the 22 patients[2]. Two further studies of sporadic ME cases again showed a close association with CBV infection[3,4]. Epidemiologically these observations were significant since studies of well adults in the community showed that only 4-5% had similarly elevated titres[5,6].

Because many patients with ME are referred for psychiatric assessment, we examined the prevalence of CBV neutralizing antibodies in patients newly admitted to a psychiatric hospital. This paper also updates previous data on the role of CBV in ME using the recently developed CBV IgM ELISA test[7].

Methods

Patients

Most of the patients studied were from the West of Scotland which has a population of approximately 3 million. Single convalescent phase sera were most commonly submitted for CBV investigations, the majority being from adults. Our clinical classification of patients was based entirely on information provided by hospital clinicians and general practitioners on request cards accompanying specimens to the laboratory. Sera from controls were obtained from apparently healthy adults in the same catchment area, sampled over the same time period.

Neutralization tests (NT)

Neutralizing antibody titres to CBV 1-5 were estimated using the same microtitre method throughout[7] thus permitting comparison of results from year to year. Titres ≥ 512, or less commonly fourfold or greater rising/falling antibody titres, were regarded as evidence of recent CBV infection.

ELISA tests

In 1985 the μ-antibody capture ELISA technique for the detection of CBV 1-5 IgM antibodies was introduced as our routine method for the serological diagnosis of CBV infections[7]. Each serum was tested at a single dilution of 1/400.

Results

Since psychological upset, manifesting as panic attacks, reversal of sleep pattern, emotional lability and poor concentration, is a characteristic feature of ME and many of these patients undergo psychiatric assessment at some stage in their illness, we decided to determine the prevalence of CBV neutralizing antibodies in a group of patients newly admitted to a psychiatric hospital. Serum samples collected between July and September 1981 from 247 patients were available for study; 112 were female and 135 were male and their ages ranged from 18 to 79 years. The results are given in Table 1. A total of 12.5% had significantly high CBV titres compared with 4-5% in 'well' control groups[5,6]. The percentage 'positive' was greatest among the 47 patients (24 male, 23 female) aged 30-39 years. The clinical diagnosis on admission and the CBV results in these 10 positive patients are listed in Table 2. While the detection of elevated titres in groups of patients is epidemiologically useful, the interpretation of elevated titres in individual patients is difficult.

Table 1. Results of CBV neutralization tests in 247 psychiatric patients

Age group (years)	*Number tested*	*CBV titre ≥512*	*(%)*
18-19	1	0	(0)
20-29	42	5	(12)
30-39	47	10	(21)
40-49	60	6	(10)
50-59	43	5	(12)
60-69	31	4	(13)
≥70	23	1	(4)
Total	247	31	(12.5)

Table 2. Details of 10 CBV 'positive' patients aged 30-39 years

Patient	*Age (years)*	*Sex*	*Highest CBV● titre seen*	*Admission diagnosis*
1	30	F	512	anxiety state
2	30	F	512	depressive illness
3	33	F	>1024	schizophrenia
4	33	F	>1024	personality disorder
5	33	M	>1024	depression
6	36	F	512	schizophrenia
7	36	F	>1024	personality disorder
8	37	F	>1024	mixed affected state
9	37	M	512	anxiety depressive state
10	38	F	512	paranoid schizophrenia

● All were CBV 4 serotype

Table 3. CBV IgM results in 290 ME patients and 500 controls tested 1985/86

Group	*Year*	*Number tested*	*CBV IgM positive (%)*
ME	1985	118	36 (31%)
ME	1986	172	72 (42%)
Controls	1985	500	44 (9%)

In 1985 using the ELISA technique, detection of CBV specific IgM, implying recent or persisting infection, became feasible in the context of everyday practice[7]. During 1985 and 1986 sera from 118 and 172 ME patients respectively were submitted for routine CBV IgM tests. The results are shown in Table 3. There was a significant difference in the numbers of CBV IgM positive (31% and 42%) compared with the 'well' control group (9%). The percentages of patients positive in the ELISA test were similar to those positive using conventional NT assays; 35% of 210 ME patients routinely tested in 1984 had titres ≥512[7].

Between January 1985 and December 1986, sera from 47 children with ME were submitted for CBV

Table 4. CBV IgM results in 47 children with ME tested 1985/86

Group	*CBV IgM positive (%)*
23 females	9 (39)
24 males●	9 (37.5)

●One male had proven influenza B infection, another *Mycoplasma pneumoniae*; both were CBV IgM negative

IgM tests. They comprised 23 females and 24 males; all were aged 5-14 years. Most exhibited the extreme fatigue and severe psychological upset described by Fegan *et al.*[2] in the 'family' outbreaks in that practice. Thirty-eight per cent of these children were CBV IgM positive (Table 4). A control group of children was not available for study. However, King *et al.*[8] showed that of 290 children $\leqslant 14$ years tested using the same ELISA technique, only 5.5% were CBV IgM positive.

Discussion

Although other virus infections, e.g. influenza, varicella, rubella, EB may precipitate ME, the data we have accumulated over the past 6 years suggest that the CBVs play an important role in this illness. Coxsackie viruses have a well known muscle tropism as shown in Bornholm disease.

In our study of psychiatric-admission patients three points of interest emerged: (1) 12.5% had titres $\geqslant 512$ compared with 4-5% of controls; (2) elevated titres were most often found in females in the 30-39 year age group. Individuals in the third decade of life are those most frequently affected by ME[2] and female predominance in adults is common[1]; (3) analysis of the admission diagnosis in the 10 positive patients listed in Table 2 showed depression and/or anxiety in at least 4 of them. None of the sera from these 10 patients was CBV IgM positive when tested retrospectively by ELISA, thus indicating that their CBV infection was neither recent (within past 6 months) nor persisting. Alternatively the IgM antibody could have deteriorated during the 5 year storage period at −20 °C.

These observations warrant further evaluation of the hypothesis that some patients admitted to psychiatric hospitals may have experienced a CBV infection causally related to ME.

The introduction in 1985 of the CBV IgM test for the routine serological diagnosis of CBV infections provided a more precise and rapid diagnostic test than was previously possible using conventional NT.

During 1985 and 1986 a total of 290 ME patients were tested routinely by ELISA; 108 (37%) were CBV IgM positive compared with only 9% of 500 controls. Because of the complex nature of their illness, ME patients are not virologically investigated until some months or years after onset of illness which may explain why only about a third were CBV IgM positive. However, these results attain more significance when compared with those of 220 patients with myo/pericarditis tested in 1985. Thirty-three per cent of this group were CBV IgM positive[7]; the role of CBV in this illness is already well established.

It is unclear whether the increased number of children with ME referred to us during 1985 and 1986 for CBV IgM tests reflected a heightened awareness by physicians of this illness or was a direct result of increased CBV activity in the community as evidenced by a larger number of CBV isolations from a variety of illnesses. The reason is unlikely to be the former since most of the children were severely affected and their school attendance interrupted for long periods. Thirty-eight per cent of the 47 children tested were CBV IgM positive. This is again an underestimate since some who were ill for more than 1 year had nevertheless static high CBV neutralizing antibody titres in the absence of CBV IgM antibody.

These results provide further evidence that CBV play a major role in ME, either directly or by triggering immunological responses which result in abnormal muscle metabolism[4].

Detection of CBV-specific RNA sequences in myocardial biopsy samples from patients with myocarditis and dilated cardiomyopathy has recently been described[9]. The combined use of this virus probe technique and CBV IgM tests has convincingly implicated CBV 5 as the cause of fatal meningoencephalitis in a 9-year-old child[10]. The application of these techniques, using muscle biopsy material from ME patients, is the next logical step in the elucidation of the exact role of CBV in this disabling illness.

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