The postviral fatigue syndrome – an analysis of the findings in 50 cases

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Summary

The clinical, pathological, electrophysiological, immunological and virological abnormalities in 50 patients with the postviral fatigue syndrome are recorded. These findings confirm the organic nature of the disease. A metabolic disorder, caused by persistent virus infection and associated with defective immunoregulation, is suggested as the pathogenetic mechanism.

Introduction

The postviral fatigue syndrome has been observed in epidemics and sporadically throughout the world during the past 50 years.1,2 Various names have been used to describe it. They have included epidemic neuromyasthenia, epidemic myalgic encephalomyelitis, Iceland disease and Royal Free disease, to name the most common.3 Investigators have failed to incriminate a virus or toxin and the absence of objective abnormalities has led others to propose that the illness is psychogenic.4 We have studied a large group of patients and have delineated the syndrome. Its principal symptom is severe muscle fatiguability but there may be a range of secondary symptoms, such as aching of muscles, dysequilibrium and psychiatric manifestations. Our data confirm the organic nature of the illness. They suggest that it is associated with disordered regulation of the immune system and persistent viral infection. Different viruses may be involved, particularly the Coxsackie B viruses, as shown in two recent outbreaks.2,5,6 Study of the pathogenetic mechanisms in this disorder may be relevant to the investigation of other postviral neurological illnesses.2

Materials and Methods

Patients

Fifty patients were studied. Of these 18 were males and 32 were females. They ranged in age from 17 to 55 years, with a mean age of 37 years. They included five medical practitioners, eight nurses, the wives of four doctors, two medical social workers, one medical student and one hospital laboratory technician. The duration of the illness ranged from 3 months to 22 years with a mean duration of 5 years. Cases were termed acute when seen within the first 6 months (11 patients). All subjects gave a clear-cut history of a viral or viral-like illness
as the initial event. In 45 cases a non-specific disorder with sore throat, fever, muscle aches and diarrhoea was described, while in three the onset was associated with varicella and in two, with rubella. Six patients were affected initially during a recent local epidemic of Coxsackie B infection and another nine were derived from a past local epidemic of unknown aetiology; the remainder were isolated cases. Three patients reported that one or more members of their families had originally had the same viral illness as themselves, but did not go on to develop the fatigue syndrome. The wife and daughter (not included here) of a senior hospital laboratory technician did, however, develop the illness.

All 50 patients had the same primary symptom, that of gross fatigue made worse by exercise. This fatigue was so conspicuous that one could see why the illness had been termed 'epidemic neuromyasthenia'. It was present at rest and quite different from that found in myasthenia or the myasthenic syndromes. The nearest clinical equivalent is the exhaustion reported by middle-aged males with multiple sclerosis affecting the spinal cord. Most of them also complained of depression, difficulty in concentration, varying degrees of tinnitus and feeling of disturbed equilibrium as well as hot and cold flushes. The illness was severe, with a high morbidity and a disastrous effect on their lives. Four of the five medical practitioners and all the eight nurses were unable to continue work; the medical student withdrew from his course for a year. The illness was chronic in 37 patients but had a relapsing and remitting course in 13.

**Investigations**

All the patients except the medical student were admitted to hospital. Each had a full clinical evaluation and underwent routine laboratory tests. These included urinalysis, full blood count, estimation of erythrocyte sedimentation rate (ESR) and of urea and electrolytes, liver function tests, muscle enzyme studies, chest X-ray and electrocardiograph (ECG). Anti-acetylcholine receptor antibodies were also sought. A muscle biopsy was performed in 20 patients. The material was examined by routine histological, histochemical and electron microscopical methods.

Conventional electromyographic (EMG) and nerve conduction studies were done on all patients, followed by single-fibre EMG studies, as previously described. These studies were done entirely by Dr Goran Jamal. Complete details of them are being published separately. Single fibre EMG was performed on the right extensor digitorum communis muscle because this muscle shows minimum age-related changes in persons below 60 years of age. Its jitter values reveal only a small standard variation, and we have a great deal of data on it from other controlled studies. In each patient five recordings of paired potentials were studied. We used a very strict definition of abnormality as follows: two pairs of the five studies were required to be greater than 55 μs or one pair was required to be greater than 55 μs while the mean overall jitter of the remaining pairs were required to be more than 34 μs. The normal jitter for this muscle is 23.4 μm with a standard deviation of 8.5 μs. Electrophysiological testing under regional curarisation was done in the five most severely affected patients.
Nuclear magnetic resonance (NMR) studies of muscle were performed in six cases in the Clinical Magnetic Resonance Laboratory located in Oxford and directed by Dr George Radda.

**Immunological studies**

*In vitro lymphocyte protein synthesis*

Protein synthesis by peripheral blood lymphocytes was measured by a whole blood technique in 50 cases. This test estimates the uptake of tritiated leucine by peripheral blood lymphocytes, on stimulation by phytohaemagglutinin (PHA), over a period of 22 h. A dose-response curve for various concentrations of PHA was plotted for each subject, and compared with the results obtained in 50 healthy age and sex-matched controls.

*Estimation of lymphocyte subpopulations*

Mononuclear cells were isolated from heparinised venous blood samples by Ficoll-Hypaque density-gradient centrifugation as previously described. Orthomune monoclonal antibodies (OK) \( T_3, T_4, T_8 \) and Ial (Ortho Diagnostic Systems Ltd., Buckinghamshire) together with Leu 7 (Becton Dickinson, Laboratory Impex Ltd., Twickenham, Middlesex) were employed to enumerate the total T lymphocyte population, the helper and suppressor/cytotoxic subpopulations, the B lymphocytes and activated T lymphocytes, as well as the natural killer cells, respectively. Cyttofluorographic analysis was done by means of indirect immunofluorescence with fluorescein-conjugated anti-mouse IgG (sheep F(ab)2 anti-mouse Ig-fluorescein-conjugated. New England Nuclear, Boston, Mass.) and the fluorescence-activated cell sorter (FACS IV) (Becton Dickinson, Mountain View, California) according to the method of Reinherz and colleagues. Two modifications were made, however, in order to facilitate and standardise the analysis as well as to achieve a high degree of accuracy. These were (1) the use of 90° scatter in order to eliminate all contaminating monocytes, so that the Ial subset consisted of B cells and activated T cells only and (2) logarithmic amplification of the fluorescent signals so as to give a better curve display. Altogether 40 patients were tested. They were divided into two groups: Group A, 11 patients who had had the disease for up to 6 months, and Group B, 29 patients who had been ill for periods ranging from 1-20 years. Two control populations were included: Group C, 30 patients with various neurological and muscular disorders including motor neurone disease (2), myasthenia gravis (3), alcoholic and diabetic myopathy (2), meningitis (1), Guillain-Barré syndrome (2), migraine (10) and lumbar disc problems (10); and Group D, 20 healthy age- and sex-matched controls. A two-stage functional assay was done at the same time. This included preparation of supernatants containing suppressor-cell activity from each patient followed by use of the whole blood technique to assess the activity.

*Immunoglobulin (Ig) concentrations*

IgG, IgA and IgM serum concentrations were determined in all cases by single radial immunodiffusion with the aid of commercially available monospecific antisera (Hoechst Pharmaceuticals, Hounslow, Middlesex).
Complement studies

In all cases CH50 units were measured as an index of classical pathway function and a haemolytic plate assay was used to estimate the integrity of the alternative pathway\textsuperscript{15}. C1q, C3, C4 and Factor B plasma concentrations were measured by single radial immunodiffusion with the aid of commercially available monospecific antisera (Hoechst Pharmaceuticals, Hounslow, Middlesex).

Immune complex assays

1. Staphylococcus aureus binding assay\textsuperscript{16}

Complexes were precipitated from serum with polyethylene glycol 6000 at a final concentration of 5\%. The precipitants were washed and redissolved in phosphate buffered saline and then incubated with a 1\% suspension of S. aureus. After washing, the bound complexes were detected by means of radio-labelled protein A. The lower limit of sensitivity of the assay is 3–6 mg/l aggregated IgG in serum. For this assay and the one following, the results were obtained by comparing the sera from these patients with another group of sera processed simultaneously. The latter were from an equal number of age- and sex-matched healthy donors attending the Blood Transfusion Centre. Samples classed as positive yielded values greater than the mean plus two standard deviations of results derived from the control group.

2. Solid-phase C1q assay

This was performed with radiolabelled anti-human IgG antibodies as described,\textsuperscript{17} 16 mg/l aggregated IgG in serum being the lower limit sensitivity.

3. Anticomplementary assays

These were also performed as previously described.\textsuperscript{18}

Detection of autoantibodies

Rheumatoid factor (with the aid of Rheumaton reagent, Denver Laboratories) and the following autoantibodies (by means of standard indirect immunofluorescence techniques) to nuclear, smooth muscle, mitochondrial, thyroid microsomal, gastric parietal cell and salivary duct constituents were sought. Autoantibodies to insulin and to insulin receptors were also determined in 12 sera, through the kindness of Dr C. R. Kahn of the Joslin Research Laboratory, Harvard University, Boston, Massachusetts, U.S.A.

Virological studies

Routine tests for viral antibodies were done in all cases. The 50 sera were tested for neutralising antibodies to the six Group B Coxsackie viruses by a modified micro-metabolic inhibition test.\textsuperscript{19} Coxsackie IgM antibodies were investigated by means of an ELISA technique.\textsuperscript{20}

Results

On clinical examination, we found, as others have reported, that no muscle weakness could be demonstrated in any of the different muscle groups examined. If, however, the subjects were exercised (e.g. in the arm muscles,
by squeezing the rubber ball of an ergometer for 1 min) the ensuing
weakness lasted for up to 1 h. Similarly, 10 patients were exercised by making
them go up 40 steps. These patients developed symmetrical proximal weakness
of the legs. The weakness was of grade 3/5-4/5, and lasted for up to 3 h in
each case. Routine laboratory investigations were entirely normal, except for
a mild degree of eosinophilia of from 7–10% in eight patients. Large circulating
lymphocytes with conspicuous nucleoli and basophilic cytoplasm, considered
to be immunoblasts, were found in another seven cases.

Muscle biopsies were abnormal in all 20 patients examined by this technique.
In 15, single, widely scattered, necrotic muscle fibres were identified but there
was no inflammatory infiltrate associated with the necrosis. Histochemical
stains showed moderately increased size and numbers of Type II fibres in all.
By electron microscopy, mitochondria were conspicuously increased at the
periphery of the fibres and occasional tubular inclusions were present.

Routine electrophysiological testing was normal, but 30 of the 40 patients
showed conspicuously abnormal jitter, indicating subtle but definite primary
muscle lesions. The topical nuclear magnetic resonance investigation revealed
abnormal muscle metabolism in each of the six patients studied. This varied
in degree from mild to severe. There was abnormally early intracellular acidosis
during exercise. This finding was interpreted as being consistent with increased
lactic acid formation and denoting a disorder of metabolic regulation in the
muscle.

Immunological results

*In vitro* lymphocyte function was highly abnormal in 35 of the 50 patients and
less but significantly abnormal in the group as a whole (Fig. 1). Six of the 35
patients with severe lymphocyte dysfunction were examined serially. This
revealed the same changes for periods of up to 2 years.

**Lymphocyte subsets**
The results are summarised in Table I. Significant changes were found in
patients with both the acute and chronic postviral fatigue syndrome. All 11
Table I. Lymphocyte subsets in 40 cases of the postviral fatigue syndrome

<table>
<thead>
<tr>
<th>Group</th>
<th>T₃</th>
<th>T₄</th>
<th>T₈</th>
<th>Ia1</th>
<th>Leu 7</th>
<th>T₄/T₈</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (n = 11)</td>
<td>62 (2)</td>
<td>45 (2)</td>
<td>17 (0.6)</td>
<td>14 (2)</td>
<td>12 (2)</td>
<td>2.7 (0.2)</td>
</tr>
<tr>
<td>P =</td>
<td>&lt; 0.01</td>
<td>N.S.</td>
<td>0.001</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Chronic (n = 29)</td>
<td>70 (2)</td>
<td>40 (1)</td>
<td>27 (1)</td>
<td>15 (1)</td>
<td>15 (2)</td>
<td>1.6 (0.1)</td>
</tr>
<tr>
<td>P =</td>
<td>N.S.</td>
<td>0.001</td>
<td>N.S.</td>
<td>0.01</td>
<td>N.S.</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>OND</td>
<td>67 (2.1)</td>
<td>46 (1.9)</td>
<td>24 (1.1)</td>
<td>15 (1.6)</td>
<td>9 (0.9)</td>
<td>2.4 (0.2)</td>
</tr>
<tr>
<td>P =</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>Normal controls (n = 20)</td>
<td>73 (3)</td>
<td>48 (2)</td>
<td>24 (2)</td>
<td>11 (1)</td>
<td>14 (3)</td>
<td>2.2 (0.3)</td>
</tr>
</tbody>
</table>

Standard errors of the means are shown in brackets.
OND = other neurological diseases.

Patients in the 'acute' group showed a reduction in the numbers of suppressor/cytotoxic (T₈) lymphocytes. In just over half the patients, the loss amounted to nearly 50% of the expected value and in the group as a whole the results are highly significant (P = 0.001), with only 17% of T₈ cells being detected, instead of the normal proportion of 24%. A lesser but still significant decrease in the total number of T lymphocytes was also identified in the 'acute' group, while percentages of the helper, Ia and natural killer cells as well as the T₄/T₈ ratios were within normal limits.

Among the patients with chronic illness, it was the helper/inducer (T₄) lymphocytes which were significantly decreased (P = 0.001). Again, the group as a whole showed loss of the subset, with only four of the 29 patients having the normal percentage of T₄ lymphocytes. In seven patients, there was a gross decrease in the circulating helper cells with from 30-35% of T₄ cells only being identified, compared with the normal value of 48%. The T₄/T₈ ratio was significantly reduced in this group of patients and a moderate increase in the Ia population was found. The percentages of T₈ and natural killer cells fell into the normal ranges.

Assay of suppressor cell activity correlated well with the absolute subset counts, indicating that the changes detected were in the suppressor, rather than the cytotoxic, T₈ lymphocytes.

Five patients were examined at intervals over periods of up to 2 years; the decrease in helper (T₄) cells was found to persist.

Immunoglobulin concentrations

These were normal.
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Table II Results of immune complex assays in 50 patients with postviral fatigue syndrome (100 samples)

<table>
<thead>
<tr>
<th>Assay</th>
<th>No. of positive samples*</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. aureus</em></td>
<td>30</td>
</tr>
<tr>
<td>CIq</td>
<td>18</td>
</tr>
<tr>
<td>ACA</td>
<td>10</td>
</tr>
<tr>
<td>One or more assays</td>
<td>58</td>
</tr>
</tbody>
</table>

* Samples classed as positive by the criteria outlined in the methods section.

Table III Neutralising and specific IgM Coxsackie antibody titres in 50 patients with the postviral fatigue syndrome

<table>
<thead>
<tr>
<th>Stage of disease</th>
<th>Neutralising titre ( \geq 512 )</th>
<th>IgM titre positive</th>
<th>Neutralising titre ( \leq 512 )</th>
<th>IgM titre positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute ( n = 11 )</td>
<td>11</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chronic ( n = 39 )</td>
<td>24</td>
<td>4</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

Complement studies

Four patients had reduced CH50 values ranging from 93 to 118 units (normal range 150–250 units/ml) and in nine patients the C4 concentrations were decreased to values ranging from 11–16 μg/dl (normal range 20–48 μg/dl). All other values were normal.

Immune complex assays

All three assays were done when the patients were first seen and were repeated approximately 1 month later. The results are shown in Table II.

Autoantibodies

The serum of 18 patients had high titres of autoantibodies to smooth muscle, 13 to thyroglobulin, six to nuclear constituents and four to gastric parietal cells.

Virological tests

Tests for antibodies to viruses other than Coxsackie viruses were negative. Thirty-five of the 50 patients had antibody titres of 512 or greater to Coxsackie B viruses, while in six of them specific IgM antibodies were detected (Table III). Results in these six were undoubtedly positive but an additional 11 patients had borderline values which we elected to discount.
Discussion

The postviral fatigue syndrome is not rare although its true incidence in unknown. Our experience is that, when general practitioners are aware of the disease, it is diagnosed more commonly than motor neurone disease (1 per 100,000) and as commonly as multiple sclerosis (3 per 100,000). An extraordinary feature which has been noted previously in several epidemics is the number of medical personnel affected. The reason for this is unknown but a determination to explain the prolonged ill-health in these persons may play a part.

We found no abnormal clinical signs in our 50 patients. If they were exercised, however, they did exhibit gross weakness. It is clear that, although the main symptoms are related to muscle, i.e. fatigue, aches and pains, there is also involvement of the central nervous system e.g. emotional lability, difficulty in concentration, dysequilibrium, and a change in sleep pattern all of which may reflect metabolic abnormalities in the nervous system. Viral infections have long been known to be followed by severe depression or other psychiatric abnormalities.

The histological changes of scattered muscle fibre necrosis, while subtle, were definite, being found in 75% of the biopsies while there was predominance of Type II fibres in all. Bizarre tubular structures and increased peripheral mitochondria were detected by electron microscopy. Similar tubular structures, shown to be derived from sarcoplasmic reticulum, have recently been demonstrated in cases of severe myalgia. That muscle appeared to bear the brunt of the disease is also confirmed by the findings of conspicuously increased jitter on single-fibre EMG, and by the metabolic changes noted during NMR studies.

The NMR findings in one of the patients studied by us, have recently been reported in great detail. During exercise, abnormally early intracellular acidosis of muscle was found. Since intracellular acidosis may be associated with muscle fatigue, it is possible to ascribe the patient’s symptoms to this early and excessive production of lactic acid. The reason for the abnormality could not be identified with certainty but increased formation of lactic acid or a decreased ability to metabolise the normal amounts produced during exercise are possible explanations. From the results obtained, the authors suggested that the defect was in regulation of the respective effects of the glycolytic and oxidative pathways during muscle metabolism. Excessive glycolytic activity seemed more likely than increased oxidative processes and this hypothesis was supported by the increased numbers of Type II muscle fibres present.

Of our patients, 70% had impaired T cell function in vitro as estimated by lymphocyte protein synthesis. This impairment was detectable in patients examined serially for up to 2 years. Similar depression of lymphocyte function has been demonstrated in patients with viral illnesses, autoimmune disorders and neoplasia. When the patients were grouped into those acutely or chronically affected, estimation of lymphocyte populations revealed distinct abnormalities (Table I). In the acute cases, the total percentage of T lymphocytes was significantly reduced together with a conspicuous fall in the percentage of suppressor cells. The helper to suppressor ratio, however,
The post viral fatigue syndrome was in the normal range. By contrast, in the chronic cases it was the helper cells which were significantly reduced. Furthermore, the helper-suppressor ratio approached inversion.

The results seen in patients early in their illness are similar to those we have obtained in patients with polymyositis, about half of them showing a severe decrease in suppressor lymphocytes during the acute phase with T₈ lymphocytes being significantly reduced in the group as a whole. The OKT8 subset of lymphocytes contains both cytotoxic and suppressor cells but the demonstration of decreased suppressor activity in a functional assay performed at the same time, suggests that the loss is of suppressor T lymphocytes. In polymyositis, it is not yet known whether the cells are sequestered in the tissues, destroyed or undergo modulation of the cell surface receptor for OKT8, so that they are no longer identifiable. A similar loss of immunoregulatory cells has been described in certain patients with multiple sclerosis, being on occasion closely associated with clinical activity, as well as in other immunologically-mediated disorders such as systemic lupus erythematosus, graft versus host disease, acute graft rejection and haemolytic anaemia.

Later in the course of this postviral syndrome, the percentages of suppressor cells returned to normal, but a significant reduction in the helper T lymphocytes was observed, together with an obvious decrease in the helper-suppressor ratio. This combination of depressed lymphocyte response to mitogens with a particular pattern of lymphocyte subsets, is typical of the Acquired Immune-Deficiency Syndrome (AIDS). Other features of this syndrome, i.e. generalised lymphadenopathy, opportunistic infections or Kaposi’s sarcoma, were not present in our groups but four of the patients with the chronic form of the illness were practising homosexuals so that there may be a relationship between AIDS and postviral fatigue syndrome.

Immunodeficiency is well described in viral illnesses, e.g. cytomegalovirus and Epstein-Barr virus infections. In the latter, specific activation of the suppressor lymphocyte subset is thought to act as a protective mechanism that inhibits activation and proliferation of the B cells which are the target for the virus. Failure of the suppressor cells to return to their normal degree of function, may be the reason why acquired agammaglobulinaemia develops in certain persons and suggests a mechanism whereby other viral infections may lead to immunodeficiency syndromes. It is important to examine the lymphocyte subpopulations at different stages of the illness; indeed, other workers have reported an imbalance of regulatory lymphocytes in patients who have persistent ill-health after infectious mononucleosis.

Serum immunoglobulins G, A and M were present in all our patients in normal concentrations. We have not yet measured their IgE concentrations. Our clinical impression, however, is that there is a high incidence of atopic illness in patients with this syndrome but this has not been evaluated critically. Immune complexes were present in nearly two-thirds of the patients. Their detection, however, does not of itself indicate a pathogenetic role, although the finding of complement activation also in nine of the 50 patients does provide some supportive evidence. If persistent viral infection is present, then chronic antigenic stimulation may play a pathogenetic role. An interesting finding was the presence of antibodies to smooth muscle in 18 patients. Although usually
associated with liver disease; these antibodies have been reported in patients with various viral infections, including cytomegalovirus infection and infectious mononucleosis.\textsuperscript{35,36} None of our patients had diabetes and none had antibodies to insulin or insulin receptors.

Previous studies of two outbreaks of the postviral fatigue syndrome have shown a relationship with Coxsackie B virus infections.\textsuperscript{5,6} In addition, we have performed detailed virological investigations in sporadic cases presenting over the past few years and have noticed an increased incidence of high antibody titres to Coxsackie B viruses. The Enterovirus Laboratory for Scotland has a wide experience of these infections in the local population so that, compared with those obtained from controls, the results reported here are highly significant, titres of 512 or more being found in 70% of the patients. Such increased titres have been detected in only 4% of the general population on random sampling.\textsuperscript{37} No single Coxsackie group B virus could be implicated, although most of the increased titres were related to either Coxsackie B\textsubscript{1} or B\textsubscript{4} viruses. There is considerable cross-reactivity between the six Coxsackie B viruses. Only in children at the time of their first exposure, does detection of the corresponding IgM antibody identify the infecting virus. Nonetheless, the results obtained suggest there is recent or continuing infection in these patients.

This investigation suggests a major role for Coxsackie viruses in the postviral fatigue syndrome but there is no doubt that other viruses may cause a similar disease. We have observed the same features in patients who have had varicella or cytomegalovirus infections while others have implicated the Epstein-Barr virus, infectious hepatitis and influenza viruses.\textsuperscript{22,33,38} In patients with a prolonged illness which resembled the postviral fatigue syndrome, increased IgM antibodies against the viral capsid antigen of the Epstein-Barr virus were found.\textsuperscript{38} In another group, an acute attack of typical infectious mononucleosis was followed by persistent ill-health with an imbalance in the regulatory lymphocyte subsets.\textsuperscript{33} Nonetheless, it is involvement of Coxsackie virus which is supported by most data. Indeed, in one report this virus was isolated from two patients.\textsuperscript{39} Furthermore it does have well-known muscle tropism, as shown in Bornholm disease.

We did consider the possibility that a particular subgroup of the population might be predisposed to develop the postviral fatigue syndrome. The patients were therefore typed for histocompatibility antigens. A mild increase in the HLA-B\textsubscript{8} haplotype was found but the numbers are too small for this to be regarded as significant.

The results reported here suggest that the syndrome is due to the interaction of viral infection and immunological processes which produce damage to intracellular enzymes and result in abnormal muscle metabolism, especially on exercise. Viral infections have already been shown to cause such enzyme abnormalities, e.g. depletion of adenylate deaminase.\textsuperscript{40} Another possibility is that an autoantibody, such as the anti-mitochondrial antibody recently identified in patients with viral myocarditis, might be involved.\textsuperscript{51} We conclude that further study of the postviral fatigue syndrome and elucidation of the pathogenetic mechanisms involved will have important implications not only for patients with this syndrome but also for those with other postviral neurological illnesses.
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References