For Debate . . .

Postviral fatigue syndrome: time for a new approach

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Abstract

Controversial views on the postviral fatigue syndrome ("myalgic encephalomyelitis") were critically appraised in their historical context and recent advances in research (virology, immunology, neurophysiology, histopathology, and epidemiology) reviewed. Flaws detected in certain aspects of recent research included in particular failure to define fatigue, inadequate assessment of psychological features, and absent or inappropriate control groups. The findings suggest that the fruitless dichotomy of "organic versus functional" should be replaced by a multifactorial approach. Most important, epidemiological studies with explicit operational case definition are essential before progress can be made in the management of this distressing disorder.

Introduction

"Myalgic encephalomyelitis" continues to provoke strong opinions in the medical press[1,2] and intense interest in the lay media, as it has for the past four decades. The condition, variously named epidemic neuromyasthenia, Icelandic disease, benign myalgic encephalomyelitis,[3] Royal Free disease,[4] and epidemic myalgic encephalomyelitis,[5] is more appropriately referred to as the postviral fatigue syndrome. Clinical descriptions include a vast array of symptoms and signs but the two main features that emerge are fatigue and emotional disturbance.[6-8] The condition may be epidemic[4,6] or sporadic.[9,10] In this paper we reconsider some of the arguments surrounding the postviral fatigue syndrome and suggest a starting point from which constructive knowledge may be gained.

The hysteria debate

Published work has been dominated by acrimonious debate between those who view the postviral fatigue syndrome as a narrow "organic" disease—namely, physicians concerned in the Royal Free outbreak[4,8] and current sufferers—and those who follow the lead of McEvedy and Beard in viewing it as "mass hysteria."[11,12] This sterile argument continues to the present day,[2,8,13] serving little purpose, based as it is on fundamental misunderstandings. The "mass hysteria" explanation for institutional outbreaks, even if correct, cannot be extrapolated to the wider problem of patients seen sporadically in primary care presenting with unexplained fatigue and emotional upset.[6,9] Furthermore, using such a pejorative term as mass hysteria was ill advised, as McEvedy and Beard acknowledged in their original article,[11,12] though it does permit an instructive comparison with other epidemics.[14] Unfortunately, it has been inferred in some quarters that the concepts of suggestibility, imitated behaviour, and altered medical perception[15,16] amount to an accusation of fakery and a denial of the plight of those afflicted.[6,8,13] We have personal experience in the care and investigation of patients with the postviral fatigue syndrome and are in no doubt about the genuineness and severity of the condition. We take issue with the notion that if it were not for immunological abnormalities "it would have been easy to concur with McEvedy and Beard that the illness is entirely a manifestation of hysteria."[17] Present controversy rests on a false dualism[18] and an outdated separation of mind and body,[19] and the shortcomings of these approaches are emphasised by increasing knowledge of the biological abnormalities found in psychiatric disorders.

Hysteria itself is an outmoded diagnosis and is being replaced by the concept of "abnormal illness behaviour." This takes account of the interaction between "organic" illnesses and psychiatric symptoms and a more sensitive appreciation of how social factors govern the presentation and outcome of illness. It is a better description of the often fraught interplay between sufferers with the postviral fatigue syndrome and their doctors.[20] Patients may think, sometimes with reason, that their distress is not sufficiently acknowledged by their doctors, who can detect nothing wrong. In a desperate search for recognition patients may resort to what one such sufferer called "unacceptable patterns of behaviour,"[21] which are then taken as further evidence that they are "histrionic" or "manipulative." This is a manifestation of the patient's need for an acceptable diagnosis, often equalled by the pressure on the doctor to provide one, for "the difference between a crazed neurotic and a seriously ill person is simply a test . . . that would allow me to be ill."[21] We review some of these tests below.

Current research

VIROLOGY

A viral aetiology has long been presumed in the condition. If a single virus were to be implicated this would greatly enhance the validity of the syndrome. In our present state of knowledge a great many viruses are potential candidates, including any of the 23 Coxsackie A or six Coxsackie B viruses, herpes viruses, particularly Epstein-Barr virus,[22] and varicella. Diseases caused by herpes viruses are well known to relapse and remit; the myotropic and neurotropic potential of certain enteroviruses, including polioviruses and some of the Coxsackie group,[23] is also established. In reports from general practice 13 out of 17 patients (76%)[9] and 18 out of 22 (82%)[6] with suspected postviral fatigue syndrome had Coxsackie B antibody titres of >256, suggesting past infection. One further group found raised titres in 65 (46%) of 140 patients compared with 25% of controls.[10] These studies, though interesting, remain unconvincing because of methodological flaws such as poor case definition and inadequate control groups (see below). New and more accurate techniques for improved serological diagnosis of Coxsackie B infections[24] in ongoing primary care studies are

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therefore welcome and the results awaited with interest. The number of putative pathogens, however, raises the possibility that they may be non-specific biological or psychobiological stressors.

IMMUNOLOGY

In a study of 50 patients with unexplained acute or chronic fatigue referred to a specialist centre 35 had altered lymphocyte function in vitro.[7] Autoantibodies and abnormalities in complement were found in a minority. Immunoglobulins were normal. Patients with persisting symptoms possibly related to Epstein-Barr virus infection showed similar changes to those of the chronic group in one study[25] but not another,[26] which found different suppressor cell abnormalities. The implications of these findings are unclear.

There has been recent criticism of this type of research, as it disregards the psychological dimension.[27] Increased liability to infection with psychological stress was noted as long ago as 1884.[28] Mechanisms may include cortisol induced alterations in lymphocyte subpopulations and reduction in IgA concentrations, as has been found in students at examination times.[29] Also lymphocyte response to mitogens is altered after sleep deprivation[30]; sleep disturbance is common in the postviral fatigue syndrome.[8] Furthermore, a study in mice showed that infection with Coxsackie B2 occurred only in the presence of environmental stress.[31] The complex and rapidly developing science of psychoneuroimmunology may yet shed light on our understanding of the postviral fatigue syndrome.

NEUROPHYSIOLOGY

Electroencephalography has been useful in excluding encephalitis (as have cerebrospinal fluid examinations) in patients with the postviral fatigue syndrome, showing only modest non-specific abnormalities.[32] Electromyography has produced controversial results with disturbances of volition being interpreted as hysterical.[11] Application of the highly sensitive single fibre electromyography has produced fascinating results.[33] Of 40 patients diagnosed as suffering from the postviral fatigue syndrome, 30 showed signs of disturbed muscle membrane conduction when strict criteria for abnormality were used. These findings are the most persuasive evidence for muscle dysfunction in this syndrome to date.

One patient with fatigue after varicella infection has been investigated by phosphorus nuclear magnetic resonance scanning.[34] This single case report described finding abnormal intracellular acidosis during exercise, and a brief communication reported similar changes in a further five patients. These data remain tantalising as it appears that such features are not found consistently.[8]

HISTOPATHOLOGY

Muscle biopsies have shown minor abnormalities, including necrotic fibres without inflammation, in 15 out of 20 patients selected for biopsy.[7] In that study there was an increase in type II muscle fibres, yet Byrne and Trounce, in a study of 11 patients with chronic fatigue of unknown cause, found mild non-specific atrophy of type II fibres.[35] Electron microscopy has detected increased mitochondria and "bizarre tubular structures."[7] Further details and replication are awaited with interest.

EPIDEMIOLOGY

The postviral fatigue syndrome—sporadic and epidemic—predominantly affects adults, especially women, and, intriguingly, members of the medical professions more than other occupations.[7 8] The preponderance of women and the rarity of the condition in children are difficult to explain on infective grounds. Epidemiological information is inadequate, estimates of yearly incidence ranging from three per 100 000[7] to 140 in a practice population of 10 000.[10] Case reports and uncontrolled hospital series[17 36] have failed to resolve any controversies, and studies using controls[6 9 10 37] are open to severe criticism owing to vague case definition, inadequate control groups, and failure to use validated or reliable questionnaires.[38] The only study (as yet unpublished) which used a matched case-control design apparently showed "serological evidence of the same level of exposure [to Coxsackie B viruses] in both patients and controls."[1]

A new approach

CASE DEFINITION

In the midst of perplexity current research has turned up potentially exciting clues to the understanding of the postviral fatigue syndrome.[1] We, however, believe that perplexity will give way to chaos unless researchers make some attempt at explicit case definition. Other workers have failed to consider in detail the term "postviral fatigue syndrome." If "postviral" is to have any meaning workers must specify what is meant by viral illness. This might be based on a retrospective description by the patient—likely to be least reliable—or, ideally, an illness seen by a doctor accompanied by a fourfold rise in antibody titre to the virus in question or, better still, isolation of the virus itself. A compromise might be an acute, self limiting illness with fever leading to consultation with a doctor at which a clinical diagnosis of viral infection has been made. When does a viral syndrome become a postviral syndrome? Researchers must agree on a reasonable length of time between the acute illness and its sequelae, probably months rather than weeks. This problem has been highlighted by Calder and his colleagues, 65% of whose patients had onset of the "postviral syndrome" within one month of the initial episode and 28% within 24 hours.[10]

TOWARDS A PHENOMENOLOGY OF FATIGUE

A precise definition of "fatigue" is required because of its importance as a central feature of the postviral fatigue syndrome. Malaise, lassitude, tiredness, exhaustion, weakness, and myalgia have all been used to describe this core neuromuscular symptom.[3 5-10] The symptom is made worse by exercise, a single bout of which may produce fatigue lasting weeks,[8] quite unlike the recognised patterns of fatigability.[39] Confusion arises from descriptions of "exhaustion on physical or *mental* effort" (italics added). Plainly such "fatigue" is not simply due to a disorder of muscle metabolism.[34] In 1910 William Osler wrote that there were three basic varieties of fatigue.[40] Firstly, there was "the weakness which is experienced by patients who have paralysis or paresis." This is felt in the body itself—for example, limbs, muscles, and muscle groups. Secondly, there was the "general lassitude felt on slight exercise in states of exhaustion, in which slight movements cause palpitation, dyspnoea, perspiration, tremor and faintness." This variety is more akin to those states seen in systemic illnesses such as brucellosis, tuberculosis, and during acute viral infections.[39] Lastly, there was the "painful weariness" or feeling of being "knocked out, which is associated with slight exercise in many nervous patients." This is experienced primarily in the cognitive domain and has been described more fully by descriptive psychopathologists under the heading "neurasthenia."[41] In 1881 George M Beard, an American neurologist, described people who "without being absolutely sick . . . with acute disorder, are yet very poor in nerve force. . . . If from overtoil, sorrow or injury they overdraw their little surplus, they may find that it will require months . . . to make up the deficiency."[41] As fatigue and its subtle variations, for which there are so many adjectives, are such a crucial symptom an equally subtle descriptive phenomenological framework is required if a new, specific kind of fatigue is advocated.

PSYCHOLOGICAL SYMPTOMS

Most accounts of the postviral fatigue syndrome acknowledge the universal presence of psychological disturbances,[6] ranging from

mild depression or anxiety to severe behavioural abnormalities.[18] These are vividly described in the many first person accounts. There has been little systematic investigation of psychiatric features, and no distinctive pattern of symptoms has emerged. This is unfortunate as severe depression and suicide have been reported,[8] as has a good response to antidepressants.[21 37] Though collaboration among virologists, histopathologists, neurologists, and general practitioners is to be commended,[5] the failure of more psychiatrists (other than those interested in mass hysteria) to contribute leaves a yawning gap in this research. A valuable start has been made by Taerk *et al*, who by using standardised instruments found evidence of severe depression in 16 of 24 patients with the postviral fatigue syndrome.[42]

Future investigations and clinical practice must take into account the similarities between the symptomatology of the postviral fatigue syndrome and that of common psychiatric disorders in the community.[43] When the somatic symptoms of depression are compared with those of the postviral fatigue syndrome not only are they similar (including fatigue, headache, chest pain, dyspnoea, dizziness, dysuria, and gastrointestinal disturbance) but the frequency with which they occur is also remarkably concordant.[44] Also patients seen in primary care with affective disorders often complain of exhaustion and fatigue, the cardinal features of the postviral fatigue syndrome.[43] This does not prove that postviral fatigue is primarily a psychiatric condition but does emphasise the influence that disturbances of affect may have on physical symptoms. Valid and reliable methods of assessing and quantifying psychiatric symptoms have been established—for example, the present state examination and general health questionnaire—which ought now to be applied to patients with the postviral fatigue syndrome.

Why have sufferers and their doctors been so vigorous in rejecting the possibility that these ubiquitous psychological factors may be aetiological in the postviral fatigue syndrome? Firstly, patients have encountered unhelpful and even hostile responses from doctors who believe that psychiatric illnesses are not real illnesses, as is clearly portrayed in first person accounts.[13 21 45] The humiliation perceived in the attachment of a psychiatric "label" reflects poorly not just on these doctors but on psychiatrists, who have failed to influence such attitudes in both their colleagues and the public. This is ironic given that medical professionals are overrepresented among cases of the disorder. Possible explanations include increased awareness of the condition, access to medical specialists, exposure to infection, or features of personality and background which may be manifested by an increased incidence of psychiatric disorder. In addition, we believe that understanding of the postviral fatigue syndrome has been hindered by doctors who suffer from the condition also researching it. Though medical training affords insight into the subjective effects of illness, it is axiomatic that objectivity is not similarly enhanced.

Archer, writing from a general practice viewpoint, has argued convincingly that a balanced approach is required and has warned against the tendency to emphasise the "genuine" nature of the syndrome as opposed to dismissing it as a "functional" disorder.[46] Recent investigators have stated that patients "previously had an excellent personality" or that they "were all known to have good premorbid personalities [which] made us consider an organic cause for their illness."[6] Premorbid personality neither confirms nor refutes an organic aetiology. It is not surprising, given this misguided stance, that patients and doctors have rejected a psychiatric component in the aetiology, as they seem to believe that this implies a "bad" premorbid personality.

It is time for a non-judgmental, eclectic approach which acknowledges the many possible interactions between psychological and physical influences on health, each of which needs further elucidation.

Research strategies

Well designed studies are required with contributions from specialists across disciplines.[5] These must incorporate (*a*) clearly defined operational criteria,[38] perhaps using our suggestions as a framework with emphasis on fatigability and psychological symptoms, onset, and course; (*b*) explicit information on the populations from which cases are drawn—a valuable start has been made with primary care based studies; and (*c*) standardised instruments with proved validity and reliability for assessing symptoms.

Given these basic design requirements, exploratory case-control studies should clarify the postulated risk factors and associations —for example, viral infection, prior psychological state,[15 47] occupation, immune state, and so on. Outcome studies of people with identified risk factors such as Epstein-Barr[27] and Coxsackie virus infection should resolve some of the most important aetiological issues. Also follow up to learn the natural history of diagnosed postviral fatigue syndrome is needed as it is inevitable that a minority of patients will turn out to have known neurological conditions such as multiple sclerosis.[5] The results of these investigations will then permit the proper application of highly specialised tests, such as nuclear magnetic resonance scanning, single fibre electromyography, and electron microscopy.

Conclusions

Partisan viewpoints have contributed little to illuminating the pathogenesis and treatment of the postviral fatigue syndrome and have added to patients' distress. Though we are proposing a "new approach," scientific advances can come only from epidemiological and clinical studies that adhere to well tried, basic methodological principles.

We thank Dr Peter White for helpful advice. AJP is supported by a Wellcome training fellowship in clinical epidemiology.

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(Accepted 16 September 1987)

Lesson of the Week

Crohn's disease presenting as anorexia nervosa

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As there is no diagnostic test for anorexia nervosa other causes of anorexia and weight loss should always be considered before anorexia nervosa is diagnosed. Crohn's disease of the intestine may be mistaken for anorexia nervosa,[1-3] and we report four cases.

Crohn's disease may be mistaken for anorexia nervosa

Case reports

CASE 1

A woman aged 21 was admitted to a psychiatric ward in 1966 with a three year history of anorexia, amenorrhoea, and weight loss. She also, however, complained of intermittent abdominal pain, constipation, and episodes of diarrhoea. She had been investigated in 1964, when her erythrocyte sedimentation rate was raised but barium studies were not performed.

Psychiatric assessment showed her to be conscientious, strong willed, and independent, and her mother was overpossessive. She was thin, weighing 27·2 kg or 53% of her desirable body weight for height. She had a tender mass in the right iliac fossa. The results of clinical investigations were haemoglobin concentration 71 g/l (normal 120-150), erythrocyte sedimentation rate 60 mm in the first hour (normal 0-7), plasma total protein concentration 54 g/l (normal 61-77), serum iron concentration 11 μmol/l (normal 13-32), serum folate concentration 4 μg/l (normal 4-10), and vitamin B_{12} concentration 430 ng/l (normal 150-1000).

She was initially treated with chlorpromazine and modified insulin treatment, but she did not respond and developed overt steatorrhoea. A small bowel meal showed a fistula between the mid-small bowel and sigmoid colon, and laparotomy showed Crohn's disease of the terminal ileum, caecum, and descending and sigmoid colon. A modified right hemicolectomy and resection of the descending and sigmoid colon were performed. Subsequently her symptoms improved appreciably, and she gained 15 kg over 10 months, achieving 80% of her desirable body weight. Later, however, she experienced recurrent relapses and in 1980 required extensive resection of the small bowel. Interestingly, she also developed symptoms of mild schizophrenia, with recurrent psychotic episodes occurring typically during exacerbations of her Crohn's disease, perhaps as a result of treatment with steroids.

CASE 2

A woman aged 37 was admitted to hospital in April 1986 with a three year history of anorexia, weight loss, diarrhoea, amenorrhoea, and Raynaud's phenomenon. She had been previously found to have iron deficiency anaemia (haemoglobin concentration 90 g/l), but the results of a small bowel meal and the histological appearance of a biopsy specimen of the small bowel had been normal. After the death of her father in 1986 she developed a depressive illness and was transferred to psychiatric care, where anorexia nervosa was also diagnosed.

Her psychiatric treatment was interrupted by an abscess in the left groin, which required surgical drainage. She was subsequently unable to tolerate a dietary regimen for anorexia nervosa owing to colicky abdominal pain, diarrhoea, and vomiting. Her weight had fallen to 34 kg (68% of her desirable body weight). The results of clinical investigations were haemoglobin concentration 126 g/l, white cells $12{\cdot}8\times10^9$/l, erythrocyte sedimentation rate 47 mm in the first hour, serum albumin concentration 38 g/l (normal 41-51) serum iron concentration 6·3 μmol/l, iron saturation 10% (normal 18-71), red cell folate concentration 355 μg/l (normal 135-750), and serum vitamin B_{12} concentration 285 ng/l. A small bowel enema showed two strictures in the ileum.

Laparotomy and resection of the ileal strictures were performed, and histological examination confirmed Crohn's disease. The gastrointestinal symptoms rapidly settled, and she gained 7 kg in weight over the next seven months, achieving 82% of her desirable body weight.

CASE 3

A girl aged 13 was admitted to a psychiatric ward in 1986 with a prolonged history of poor food intake, nausea, vomiting, and reduced weight and height for her age. She had been constipated but recently had had loose stools. She had not experienced menarche.

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