A report - chronic fatigue syndrome: guidelines for research

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Report of a consensus meeting held at Green College, Oxford 23 March 1990

Introduction

Patients who present with a principal complaint of disabling fatigue of uncertain cause have received much attention in recent years. Correspondingly there has been an increasing amount of research into this problem. The findings have however often been contradictory. Resolution of these contradictions depends on the ability to compare research studies, but such constructive comparison has rarely been possible. This is largely because research has been carried out by investigators trained in different disciplines, using different criteria to define the condition. Whilst such an eclectic approach is to be welcomed, agreement on case definition, and assessment methods is necessary if progress is to be made.

The principal lack of agreement concerns definition of the clinical syndrome to be studied. A number of clinical syndromes have been described, all apparently referring to similar groups of patients, but differing sufficiently to preclude comparison of published studies. The various names used include epidemic neuromyasthenia[1], idiopathic chronic fatigue and myalgia syndrome[2], benign myalgic encephalomyelitis[3], chronic infectious mononucleosis[4], Royal Free disease[5], postviral fatigue syndrome[6], fibrositis-fibromyalgia[7,8], and chronic fatigue syndrome[9].

An attempt to address the problem of case definition was made by Holmes and colleagues in 1988[9], who chose the name chronic fatigue syndrome (CFS) because it is descriptive and free from unproven aetiological implications. They also proposed an operational definition for the syndrome. Although a welcome advance, this definition proved to be unsatisfactory in practice[10,11]. Other definitions eg by Lloyd and colleagues[12] are also unsatisfactory[13], and have not been widely accepted.

Additional sources of difficulty have arisen from inadequate and poorly described sampling procedures, choice of comparison groups, shortcomings in study design, and measures of poor or unspecified reliability[14].

In an attempt to remove these obstacles to progress, a meeting of research workers with a known interest in the field was convened. The format of the meeting

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was modelled on the MRC workshop on Alzheimer's disease[15].

Aims

The aim of the meeting was to seek agreement amongst research workers on recommendations for the conduct and reporting of future studies of patients with chronic fatigue. Specifically we set out to agree on which patients should be included, how such studies should be approached, and on the minimal data that should be reported.

Procedure

The meeting (attended by all those listed at the beginning of the paper) was held at Green College, Oxford, on 23 March 1990, and chaired by Professor Anthony Clare. It was restricted to invited research workers, all of whom had studied patients with CFS. The disciplines represented included biochemistry, general medicine, general practice, imaging, immunology, infectious diseases, microbiology, neurology, physiology, psychiatry, and psychology.

Before the meeting all participants (and several others who were unable to attend) were circulated with a questionnaire, and their responses used to draw up an initial discussion document which formed the basis of discussion during the meeting. Points on which agreement was reached were recorded and a draft of this paper circulated to participants.

The Guidelines

The following guidelines were agreed.

Symptoms

A preliminary research glossary is appended. This comprises definitions for symptoms and suggestions for their description.

Signs

There are no clinical signs characteristic of the condition, but patients should be fully examined, and the presence or absence of signs reported.

Syndromes

Two broad syndromes can be defined:

Chronic fatigue syndrome (CFS)

(a) A syndrome characterized by fatigue as the principal symptom.
(b) A syndrome of definite onset that is not life long.
(c) The fatigue is severe, disabling, and affects physical and mental functioning.
(d) The symptom of fatigue should have been present for a minimum of 6 months during which it was present for more than 50% of the time.
(e) Other symptoms may be present, particularly myalgia, mood and sleep disturbance.
(f) Certain patients should be excluded from the definition. They include:

(i) Patients with established medical conditions known to produce chronic fatigue (eg severe anaemia). Such patients should be excluded whether the medical condition is diagnosed at presentation or only subsequently. All patients should have a history and physical examination performed by a competent physician.
(ii) Patients with a current diagnosis of schizophrenia, manic depressive illness, substance abuse, eating disorder or proven organic brain disease. Other psychiatric disorders (including depressive illness, anxiety disorders, and hyperventilation syndrome) are not necessarily reasons for exclusion.

Post-infectious fatigue syndrome (PIFS)

This is a subtype of CFS which either follows an infection or is associated with a current infection (although whether such associated infection is of aetiological significance is a topic for research). To meet research criteria for PIFS patients must (i) fulfil criteria for CFS as defined above, and (ii) should also fulfil the following additional criteria:
(a) There is definite evidence of infection at onset or presentation (a patient's self-report is unlikely to be sufficiently reliable).
(b) The syndrome is present for a minimum of 6 months after onset of infection.
(c) The infection has been corroborated by laboratory evidence.

In reporting studies it should be clearly stated which of these two syndromes is being studied. The degree of disability should be measured and stated. The criteria and method used to exclude subjects from study must be clearly described and the degree of examination and investigation specified. All patients should be assessed for associated psychiatric disorder and the results of this assessment reported.

Sampling

The way in which the patient sample was obtained should be clearly described. In particular it is essential to know whether the sample was recruited from primary care or from secondary referral centres. Because of the risk of introducing bias at this stage the use of random samples or consecutive referrals is preferred.

Comparison groups

The term comparison group is preferred to control group. The precise choice of comparison groups should be determined by the hypothesis being tested. In the current state of knowledge multiple comparison groups may be required, as there are pitfalls in the sole use of 'healthy' or 'normal' selected controls.

Suggested comparison groups include patients with neuromuscular disorder, patients with conditions causing inactivity, and patients with depressive disorder. The method used to obtain the comparison group should be clearly specified.

Study design

The design of studies must be chosen with regard to the hypothesis being tested. Both cross-sectional and longitudinal designs may be useful; the former to establish associations; and the latter to demonstrate temporal sequence (eg of infection and symptoms).

Longitudinal single case designs that examine correlations of relevant variables with fluctuations in symptom severity may be useful.

Measurements

All measures (both clinical and laboratory based) should be reliable, valid, and reproducible between centres.

Reliable measures of subjective fatigue and of disability are lacking and require development. When reporting studies the reliability of all measures should be assessed and specified whenever possible.

Glossary

This glossary provides provisional definitions of the principal symptoms and suggests how they may be described. Each symptom is considered as follows:
(i) A description of the symptom (what it is).
(ii) What it is to be distinguished from (what it is not).
(iii) Criteria for rating its presence.
(iv) Additional description.

Fatigue

(i) When used to describe a symptom this is a *subjective* sensation and has a number of synonyms including, tiredness and weariness. A clear description of the relationship of fatigue to activity is preferred to the term fatiguability. Two aspects of fatigue are commonly reported: mental and physical. Mental fatigue is a subjective sensation characterized by lack of motivation and of alertness. Physical fatigue is felt as lack of energy or strength and is often felt in the muscles.

(ii) Fatigue as a symptom should be distinguished from low mood and from lack of interest. The symptom of fatigue should not be confused with impairment of performance as measured by physiological or psychological testing. The physiological definition of fatigue is of a failure to sustain muscle force or power output.

(iii) To be regarded as a symptom, fatigue must:
(a) be complained of;
(b) significantly affect the person's functioning;
(c) should be disproportionate to exertion;
(d) should represent a clear change from a previous state; and
(e) be persistent, or if intermittent should be present more than 50% of the time.

(iv) The symptom should be described as follows:
(a) severity: mild, moderate, or severe;
(b) frequency: continuous or intermittent. If intermittent the proportion of the time present;
(c) relation to activity: it should be stated whether the fatigue is greatly increased by minor exertion and whether it occurs at rest.

Disability

(i) This refers to any restriction or lack (resulting from loss of psychological or physiological function) of ability to perform an activity in the manner or within the range considered normal for a human being (ie things people cannot do in the areas of occupational, social, and leisure activities because of their illness[16]).

(ii) Disability (eg inability to walk) should be distinguished from impairment of function (eg weak legs), and from handicap (eg unable to work).

(iii) There should be a definite and persistent change from a previous level of functioning and it is desirable to seek supportive evidence from an informant.

(iv) The disability should be described as follows:
(a) area of disability (ie occupational, social, leisure, self care);
(b) degree of disability.

Mood disturbance

(i) The term mood disturbance has been used to include depression, loss of interest and loss of pleasure (anhedonia), anxiety, emotional lability and irritability.

(ii) These phenomena should be distinguished from each other.

(iii) To be regarded as a symptom the mood disturbance should be
(a) complained of;
(b) should represent a significant change from a previous state; and
(c) should be relatively persistent or recurrent. Judgements of the appropriateness of mood disturbance are unreliable and should be avoided.

(iv) The symptom should be described as follows:
(a) type: depressed mood, anhedonia, anxious mood, emotional lability, irritability;
(b) severity: standard scales are available to assess the severity of depressed mood and anxiety. In addition it should be determined whether the patient's disorder is sufficient to meet operational diagnostic criteria for major depressive disorder, generalized anxiety disorder or panic disorder according to a recognized psychiatric classification, eg the current edition of the Diagnostic and Statistical Manual of the American Psychiatric Association, DSM-III-R[17];
(c) duration and frequency of the mood disturbance should be reported.

Myalgia

(i) This refers to the symptom of pain or aching, felt in the muscles.

(ii) It should be distinguished from feelings of weakness and from pain felt in other areas such as joints.

(iii) The myalgia should be
(a) complained of;
(b) be disproportionate to exertion;
(c) be a change from a previous state;
(d) should be persistent or recurrent.

(iv) The symptom should be described as follows:
(a) severity: mild, moderate, or severe;
(b) frequency and duration;
(c) relation to exertion: if after exertion the time of onset relative to the exertion, and duration should be described.

Sleep disturbance

(i) The symptom of sleep disturbance refers to a subjective report of a change in the duration or quality of sleep.

(ii) Sleep disturbance should be distinguished from feelings of daytime fatigue or tiredness.
(iii) The sleep disturbance should
(a) be complained of;
(b) not simply be a response to external disturbance;
(c) be a change from the previous state;
(d) be persistent.

(iv) The symptom should be described as follows:
(a) type: hypersomnia or increased sleep; insomnia or reduced sleep (which should be further described as either difficulty getting off to sleep, early waking, or subjectively disturbed or unrefreshing sleep);
(b) severity: the amount of change in duration of sleep should be quantified in hours.

Other symptoms

Many other symptoms may be present and should be recorded as follows:

(i) The definition used.

(ii) Symptoms should be carefully distinguished from one another.

(iii) The criteria for rating its presence.

(iv) Additional information, eg severity.

Conclusions

The contributors hope that these guidelines will provide a basis for fruitful research studies, and for inter-disciplinary collaboration essential to this field of research. The guidelines are preliminary and will undoubtedly require further refinement and revision. The authors would welcome comments and suggestions.

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References

1 Henderson DA, Shelokov A. Epidemic neuromyasthenia - clinical syndrome? *N Engl J Med* 1959;**260**:757-64
2 Byrne E. Idiopathic chronic fatigue and myalgia syndrome (myalgic encephalomyelitis): some thoughts on nomenclature and aetiology. *Med J Aust* 1988;**148**:18-82
3 Galpine JF, Brady C. Benign myalgic encephalomyelitis. *Lancet* 1957;i:757-8
4 Isaacs R. Chronic infectious mononucleosis. *Blood* 1948; 3:858-61
5 The medical staff of the Royal Free Hospital. An outbreak of encephalomyelitis in the Royal Free Hospital Group London, in 1955. *BMJ* 1957;**2**:895-904
6 Behan PO, Behan WMH, Bell EJ. The postviral fatigue syndrome - an analysis of the findings in 50 cases. *J Infect* 1985;**10**:211-22
7 Pritchard C. Fibrositis and the chronic fatigue syndrome. *Ann Intern Med* 1988;**106**:906
8 Yunus MB. Fibromyalgia syndrome: new research on an old malady. *BMJ* 1989;**298**:474-5
9 Holmes GP, Kaplan JE, Gantz NM, *et al.* Chronic fatigue syndrome a working case definition. *Ann Intern Med* 1988;**108**:387-9
10 Manu P, Lane TJ, Matthews DA. The frequency of the chronic fatigue syndrome in patients with symptoms of persistent fatigue. *Ann Intern Med* 1988;**109**:554-6
11 Komaroff A, Geiger A. Does the CDC working case definition of chronic fatigue syndrome (CFS) identify a distinct group? *Clin Res* 1989;**37**:778A
12 Lloyd AR, Wakefield A, Boughton C, Dwyer J. What is myalgic encephalomyelitis? *Lancet* 1988;i:1286-7
13 David A, Wessely S, Pelosi A. Myalgic encephalomyelitis or what? *Lancet* 1988;ii:100-1
14 David A, Wessely S, Pelosi A. Post viral fatigue: time for a new approach. BMJ 1988;**296**:696-8
15 Wilcock GK, Hope RA, Brooks DN, *et al.* Recommended minimum data to be collected in research studies on Alzheimer's disease. *J Neurol Neurosurg Psychiatry* 1989;**52**:693-700
16 World Health Organization. International classification of impairments, disabilities and handicaps. Geneva: WHO, 1980
17 American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, revised 3rd edn. Washington DC: APA, 1987

(Accepted 28 September 1990. A brief report of this meeting was published in the British Medical Journal, *News Section, earlier this year* (Dawson J. Consensus on research into fatigue syndrome. *BMJ* 1990;**300**;832))

Letters to the Editor

Preference is given to letters commenting on contributions published recently in the JRSM. *They should not exceed* **300 words** *and should be* **typed double-spaced.**

The homeopathic conundrum

I read with interest the editorial (September 1990 *JRSM*, p 543) from the Centre for the Study of Complimentary Medicine. It is one of those situations where selecting out the trials gives the best answer. The three trials he quotes: (1) discussing allergy, (2) discussing pollen and (3) discussing the fibromyalgia syndrome are unsatisfactory because of the difficulty of establishing diagnosis and the difficulty in interpreting the treatment regimen and the efficacy. I think it appropriate for me to confine my comments to Fisher's which appeared in the *BMJ* and at the time caused considerable correspondence. There was unease with the trial design and it was difficult to interpret his data, as he did not give pain assessment and all data quoted was changes rather than original, which makes it difficult to interpret his findings.

I do not wish to be dismissive of homeopathic medicine, but I am pressed to find any study to support the view that it has an effect greater than placebo. The fact that it is equal to placebo providing it does not have side effects may be useful in some short limited conditions. Our study which included a placebo group confirmed that a homeopathic remedy was much less effective than a standard non-steroidal anti-inflammatory drug. We too looked at both the patients where the intention was to treat with homeopathy and patients who were going to receive conventional treatment. I note that Dr Lewith has not quoted our study[1].

The case for homeopathy remains unanswered. I am sure the public will continue to support it, but they should be in possession of all the facts not just part of them.

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Reference

1 Shipley M, Berry H, *et al.* Controlled trial of homeopathic treatment for osteoarthritis. *Lancet* 1983;i:97-8