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A systematic review and critical evaluation of the immunology of chronic fatigue syndrome

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Abstract

Objective: Immune dysfunction in patients with chronic fatigue syndrome (CFS) has been widely but inconsistently reported. Traditional reviews of the literature have produced a variety of conclusions. We present the results of the first systematic review of the subject. **Methods:** EMBASE, MEDLINE and PSYCHINFO databases were searched, and leading researchers in the field were contacted. Inclusion criteria were applied, and studies were then divided into groups based on the quality of their methodology. Study results were collated and described. **Results:** Studies ranged widely in quality. There was an inverse association between study quality and finding low levels of natural killer cells, suggesting that the association may be related to study methodology. On the other hand, reports of abnormalities in T cells and cytokine levels were not related to study quality. **Conclusions:** The conclusions of this systematic review differ from a recent traditional narrative review of the immunology of CFS. No consistent pattern of immunological abnormalities is identified.

Keywords: Chronic fatigue syndrome; Immunology; Critical review; Systematic review

Introduction

Chronic fatigue syndrome (CFS) is characterized by disabling physical and mental fatigue, lasting at least 6 months, without an apparent physical cause [1]. The aetiology of CFS is unclear, but many have suggested a role for infection, and for changes in the immune system. Papers reporting immunological changes in CFS are numerous. However, taken as a whole, the body of literature is inconsistent and, in places, contradictory. Few firm conclusions have been drawn.

What are the reasons for this? Strober has suggested several: using groups of patients with differing primary symptoms and differing duration of illness, failing to control for potential confounding factors and using different laboratory procedures when analysing samples [2].

Several reviews of the immunology of CFS have been published. Buchwald and Komaroff [3] found "evidence of diffuse immunological dysfunction... it has not been shown that immunologic findings explain... the symptomatology of CFS." Similarly, Wessely et al. [4] concludes that "there is evidence of some abnormality of immune function, but such changes are inconsistent, nonspecific and rarely correlate with the clinical condition" and Lloyd and Klimas [5] that "no clear conclusions can be drawn from the data." Most recently, Patarca-Montero et al. [6] have written that "CFS is associated with immune abnormalities that can potentially account for physio- and psychopathological symptomatology" and also that "assessment of immune status reveals a heterogeneity among CFS patients."

No systematic review has been completed. The importance of systematic reviews — which can be loosely defined as reviews in which there is a methods section — is established beyond doubt if unbiased conclusions are to be reached [7,8]. Our group has already shown that nonsystematic general reviews in the field of CFS are associated with bias, influenced by professional

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affiliations and country of origin of the authors [9]. The aim of this paper is a systematic review of the immunology of CFS.

Method

EMBASE, MEDLINE and PSYCHINFO databases were searched from 1966 to 2000 using the strategy presented in Fig. 1. Additional checks were made with key investigators and using a personal database of 3000 CFS references maintained by one of the authors in which

1 immu$.mp. [mp=title, abstract, registry number word, mesh subject heading]
2 cytokine$.mp. [mp=title, abstract, registry number word, mesh subject heading]
3 1 and 2
4 1 or 2
5 antibod$.mp. [mp=title, abstract, registry number word mesh subject heading]
6 1 or 4
7 interleukin$.mp. [mp=title, abstract, registry number word, mesh subject heading]
8 4 or 7
9 antigen$.mp. [mp=title, abstract, registry number word mesh subject heading]
10 8 or 9
11 lymphocyte$.mp. [mp=title, abstract, registry number word, mesh subject heading]
12 10 or 11
13 HLA.mp. [mp=title, abstract, registry number word, mesh subject heading]
14 12 or 13
15 MHC.mp. [mp=title, abstract, registry number word, mesh subject heading]

Fig. 1. Search strategy.

- Specific hypothesis (2) ____
- Blinded (2) ____
- Control group ____
  - Age ____
  - Sex ____
  - Inactivity ____
  - Depression ____
  - Therapy ____
  - Diurnal rhythmn ____
- Samples treated appropriately (cells fresh, serum frozen) ____
- Functional study ____
- Recognised immunological markers ____
- Immunologist as author ____

Total (/15)

Fig. 2. Rating proforma.

immunological measures are coded after visual inspection (in contrast to MESH terms). Contact was made with leading researchers in the field to check for missing/unpublished studies.

Certain a priori criteria were set for inclusion in the review: subjects had to have been suffering from medically unexplained, disabling or distressing fatigue as a predominant symptom for longer than 6 months; a sample size of greater than 10 was required; articles had to be written in English. The latter was because of a lack of access to translation facilities. Where it was unclear if two or more papers from the same group represented different samples, authors were asked for clarification.

Studies were rated by ML on a 15-point scale devised after consultation with an immunologist (MP) and a psychiatrist with special experience in CFS (SW). This is shown in Fig. 2. Methodological quality factors were derived from a general knowledge of the literature on bias (for example, the importance of blinding), added to a specific knowledge of the subject under review.

If a clear a prior hypothesis was stated two points were awarded. A statement in the paper indicating that the investigators were blinded to the experimental groups also