

THE AETIOLOGY OF CHRONIC FATIGUE SYNDROME: A REVIEW

Nor Zuraida Zainal

Department of Psychological Medicine, University of Malaya Medical Centre, 50603 Kuala Lumpur, Malaysia

ABSTRACT: Chronic fatigue syndrome (CFS) is a chronic debilitating condition affecting both physical and mental functioning. It was first quoted as a 'new disease' spreading in the developed countries. It became a major issue by doctors, professionals and the media for the past 15 years. CFS was not only affecting the adults but childhood fatigue has also been noted. The CFS patients commonly described themselves to be perfectionists, highly driven, energetic and motivated before the condition started. Studies have been focused on the definition, diagnosis and management of CFS. However, the understanding of CFS and what cause it is still unclear and controversial. Thus the aetiological factors of CFS are reviewed in this article. (*JUMMEC 2000; 2:73-77*)

KEYWORDS: Chronic fatigue syndrome (CFS), Aetiology, Psychiatric disorders, Viral infection, Immunology

Introduction

Broadly defined fatigue appears to be very common in the community, at the primary care level and among the hospital attenders. Doctors, professionals and lay journals started to address fatigue syndrome as a major issue since 15 years ago. An operationalised criteria for chronic fatigue syndrome (CFS) has been developed in the western countries. Chronic fatigue syndrome is a severe chronic fatiguing condition affecting both physical and mental ability. The criteria may include somatic symptoms and require exclusion of serious medical illnesses and a number of psychiatric disorders (1). The current definitions are based on the observation of the symptom constellations rather than detailed knowledge regarding the aetiology or pathophysiology of fatigue syndrome.

Prevalence of CFS

The prevalence estimates for chronic fatigue syndrome varies between 0.07% and 1.8% (2). A population-based study ascertains the point prevalence of chronic fatigue syndrome as 0.37% (3). A survey based on Scottish general practices (4) reported the prevalence of CFS as 1.3%. While they achieved a better response rate, case identification depended largely on individual doctor's perception of CFS. Another study (5) based on the Epidemiologic Catchment Area (ECA) data, found that chronic fatigue syndrome appeared to be quite rare in that only one woman in the entire sample (13538) – 0.07%, fulfilled the criteria.

Aetiology

While there has been a growing consensus regarding the definition, diagnosis and management of CFS, the aetiology remains controversial. To date, studies have focused on a range of biological and psychosocial factors including the role of persistent viral infection, immunology, psychological disorders, neuroendocrine disturbances, structural and functional brain abnormalities, life events, personality traits and genetics.

Relationships between CFS and Psychological disorders

Studies in the community (6), primary care setting (7) and tertiary care fatigue clinics (8,9) have demonstrated a significant relationship between fatigue and psychiatric disorder with reported rates of psychiatric illness in (broadly defined) fatigue patients ranging from 60% to 75%. If one looks at studies relating to chronic fatigue syndrome specifically, reported rates of psychiatric disorder range from 40% - 75%.

Major depression appears to be the most common psychiatric diagnosis in CFS (9,10). Several studies looking at psychiatric features in CFS, and conducted using standardized diagnostic instruments, identified

Corresponding address:
Dr. Nor Zuraida Zainal
Department of Psychological Medicine
University of Malaya Medical Centre,
50603 Kuala Lumpur, Malaysia

between 50% - 70% of CFS patients as suffering from major depressive disorder (11,12).

In addition to depression, it has recently become clear that the incidence of anxiety disorders in CFS was underestimated. For example, one study indicated that 20 per cent of a sample of chronic fatigue patients fulfilled criteria for one or more anxiety disorders (13). Somatization disorder also appears to be relatively common in CFS patients. Most studies find that between 5% and 10% of those seen in specialist CFS clinics fulfill established criteria for somatization disorder (8,14).

Viral infection

There have been many claims linking viral agents with CFS over the years. One reason is the consistent observation made by patients attending specialist units that their illness began with a viral infection, and that the symptoms of their persisting illness resemble those of viral infection (15). However, establishing any link between viral infections and CFS is far from straight forward. Firstly, symptoms of viral infection are not synonymous with evidence of an infective process. Secondly, viral infections are common - the average person has between three and four such infections a year and chance associations are thus hard to exclude. It is also possible that infection may follow, rather than cause fatigue (16).

A controlled, prospective primary care study (17), suggested that common viral infections do not have a causal role in CFS. Another study however, demonstrated a modest increase in chronic fatigue 6 months after presentation with symptomatic common viral infections to a general practitioner (18). In contrast, there is evidence that serious viral infections particularly Epstein-Barr viruses do trigger or precipitate CFS (19).

The link between enteroviruses with ME/CFS started after the Royal Free Hospital (1955) epidemic outbreak as poliomyelitis was seen as the major threat. This led to several studies to look at the association of enteroviruses with CFS. However, the results of the studies were not convincing (20,21). A prospective postal questionnaire follow-up study (22) of patients with viral meningitis and other viral infections found the prevalence of chronic fatigue syndrome was 12.6% which was higher than rates reported from primary care attenders. However, there was no difference in the rates of chronic fatigue between patients infected by enterovirus and the control group (i.e. those who were infected by non-CNS non-enteroviruses). Thus, in conclusion, even though enteroviruses are common, studies have not identified a link between enteroviral infections, persistence of the virus, and the development of chronic fatigue syndrome.

Immunology

The hypothesis that the pathogenesis of chronic fatigue syndrome has an immunologic basis remains tantalizing. Although advanced laboratory techniques have been applied to the study of immunologic function in CFS, no clear conclusions can be drawn from existing data. Some authors have suggested that observed immunological changes are not of pathological significance, but represent a normal immunological response to persistent viral infection (23). However there is frequent occurrence of abnormalities within the cellular and humoral immune system of patients with well-defined chronic fatigue syndrome (24). It was reported that a reduction in the absolute number of peripheral blood lymphocytes; specifically in the total T-cell (CD2), the helper/inducer T-cell (CD4) and the suppressor/cytotoxic T-cell (CD8) subsets which are likely to be associated with the persistence of viral antigens. Other laboratory findings showed depressed natural killer cell function and reduced numbers of natural killer cells; low levels of circulating immune complexes; low levels of several autoantibodies, particularly antinuclear autoantibodies and antithyroid antibodies; altered levels of immunoglobulins; abnormalities in number and function of lymphocytes; and modestly elevated levels of two Epstein-Barr virus-related antibodies, immunoglobulin G to viral capsid antigen and to early antigen (25). The pattern of these findings being typical of that seen in patients during the resolution of acute viral infection (26). However, a case-control study showed that the immunologic abnormalities in CFS patients are in accord with the growing body of evidence suggesting a chronic, low level of the immune system functioning in chronic fatigue syndrome.

As usual, nothing is so simple in CFS. It has not been possible to clarify whether the observed immunological changes are the cause or effect of chronic fatigue. The reported abnormalities are non-specific and similar abnormalities of immune function have also been reported in major depressive illness. In addition, the duration of CFS samples, the use of medications, mood and stress may all be possible confounders.

Hypothalamic-pituitary-adrenal (HPA) axis

Because of its role in the control of sleep, energy, mood and appetite, several authors have suggested a possible role for the hypothalamus as a final common pathway for symptom generation in CFS (27). Demitrack et al (28) studied the normal diurnal variation of cortisol activity and neuroendocrine changes following challenge with corticotrophin releasing hormone (CRF) and adrenocorticotrophic hormone (ACTH). The findings

showed that free plasma cortisol levels and the basal evening cortisol levels were low in CFS patients in contrast to the hypercortisolism in major depression. However it is difficult to interpret these findings as similar effects have been noted in many conditions, some of which overlap with CFS (eg. eating disorders, post-traumatic stress disorder, seasonal affective disorder and fibromyalgia). In addition, sleep disturbance, depression and anxiety are all relevant to CFS and may have an impact on the results of neuroendocrine challenge tests. It is possible therefore that the reported neuroendocrine abnormalities in CFS may be epiphenomena of the clinical condition or, alternatively be related to the confounding effects of psychological distress, sleep deprivation or prolonged inactivity.

Serotonin function

Several studies have investigated central serotonin (5-HT) function in CFS. Results of a study compared central serotonin activity (using the response to buspirone, a 5-hydroxytryptamine (5-HT_{1A}) receptor agonist) in CFS patients, with normal and depressed controls showed a significantly increased sensitivity of central 5-hydroxytryptamine receptors in chronic fatigue syndrome (27). These findings were later supported by a group who used d-fenfluramine, a more selective 5-hydroxytryptamine releasing agent, and showed that CFS may be associated with an increased 5-hydroxytryptamine function (29). However another study found neither significant difference in the prolactin response to d-fenfluramine between CFS patients and controls, nor any significant difference in peak prolactin concentrations achieved (30). This discrepancy in findings could reflect methodological differences in the selection of cases.

Disturbance of brain physiology

There have been several studies using modern neuroimaging techniques to study brain structure and function in CFS. The first MRI study of chronic fatigue was published in 1992 (31). They reported abnormalities in 78% of 144 patients. These abnormalities included foci of high signal intensity on T2-weighted images, typically punctate and occasionally larger patchy areas and which affected the subcortical white matter most often. However, these abnormalities were also found in 21 per cent of the controls and subsequent studies did not replicate these findings (32,33). Both CFS patients and psychiatric controls showed white matters hyperintensities; and no increase in MRI abnormalities.

Given the paucity of abnormal findings on MRI, researchers have begun to explore whether CNS dysfunction can be shown in chronic fatigue syndrome using functional neuroimaging. Single-positron emission

tomography (SPET) has been used to measure cerebral blood flow and regional blood volume. Previous studies suggested a range of abnormalities either in the temporal, frontal or parietal areas, with no visible single pattern. It was reported that brainstem perfusion was significantly reduced in CFS subjects compared with controls, with depressed patients showing intermediate values (34). However, a question arises whether these findings were due to depression and/or anxiety, which also could alter the cerebral blood flow. This is because several studies found that the brain perfusion in CFS was similar to that observed in major psychiatric illness, particularly major depression. In conclusion, the neuroimaging findings are probably neither sufficiently sensitive nor specific to allow its use a diagnostic tool for CFS, although it may have a role in understanding the pathophysiology of the disease.

Life events

Ray et al (35) found, retrospectively, no relation between negative life events and fatigue severity in CFS, although negative life events were associated with more severe anxiety in these patients. Positive events, however, were protective against fatigue, anxiety, depression and general functional impairment. After EBV infection, life events were associated with a 5-fold increase in the risk of developing any psychiatric disorder, and a 10-fold increase in developing depression at 2- and 6-months follow-up. However, there was no association between life events with the development of post-infectious fatigue (36). Finally, the frequency of life events in CFS has been found to be no different from that in healthy controls or those with irritable bowel syndrome (37).

Personality

Study of the relationship between personality and CFS is in its infancy. It is a common perception that CFS patients seen in specialist clinics show characteristic type-A personality traits. The CFS patients would rate themselves as more hard driving prior to illness than the healthy controls (37). In addition, chronic fatigue patients tended to describe themselves as significantly more "action-prone" compared with neurotic or chronic organic patients (38). However, while there was "no unique" set of psychological characteristics which could be considered as necessary antecedents of CFS though high levels of emotionality or neuroticism may act as predisposing factors (39).

Genetic factors

If genetic factors are involved in the transmission of a disorder, the disorder should cluster in the families of affected probands at a higher rate than in the relatives of population controls. However, relatives who share a

number of genes also tend to share common environments, so familial clustering by itself does not necessarily implicate a genetic mechanism; family culture, infectious or other environmental agents may also be involved.

To date, there has been little exploration of genetic influences in the aetiology of chronic fatigue or chronic fatigue syndrome. However, two research groups have recently started to address the issue of genetic factors in chronic fatigue using twin study designs (40,41) and another study on family history of CFS (42).

Prolonged fatigue appeared to have independent genetic and environmental determinants (43). Interestingly, chronic fatigue syndrome was found to be a familial disorder and this similar finding was reported in childhood fatigue as well (41).

Conclusion

Range of aetiological factors have been focused in the reviewed articles. However, it remains controversial and non conclusive. It is still difficult to explain whether depression, viral infection and the observed immunological changes are the cause or effect of CFS. Furthermore, similar study findings in CFS patients have been observed in other psychiatric disorders mainly major depressive disorder. Another area that is interesting to explore in future is whether CFS is a culture bound syndrome since it is more established in the western countries.

References

1. Sharpe M, Archard L, Banatvala J, et al. Chronic fatigue syndrome: guidelines for research. *J.R. Soc. Med.* 1991; 84: 118-121
2. Hotopf M, Wessely S. Depression and chronic fatigue syndrome. In: Robertson M, Katona C, Eds. *Depression and physical illness.* John Wiley & sons. 1997; 499-521
3. Lloyd A, Hickie I, Boughton R, Spencer O, Wakefield D. Prevalence of chronic fatigue syndrome in an Australian population. *Med. J. Aust.* 1990; 153: 522-528
4. Ho-Yen D, Mc Namara I. General practitioners' experience of chronic fatigue syndrome. *Br. J. Gen. Pract.* 1991; 41: 324-326
5. Price R, North C, Fraser V, Wessely S. The prevalence estimates of chronic fatigue syndrome (CFS) and associated symptoms in the community. *Pub. Health Rep.* 1992; 107: 514-522
6. Pawlikoska T, Chalder T, Hirsh S, Wallace P, Wright D, Wessely S. A population based study of fatigue and psychological distress. *Br. Med. J.* 1994; 308: 743-746
7. David A, Pelosi A, McDonald E, et al. Tired, weak, or in need of rest: Fatigue among general practice attenders. *Br. Med. J.* 1990; 301: 1199-1122
8. Manu P, Matthews D. The mental health of patients with a chief complaint of chronic fatigue: a prospective evaluation and follow-up. *Arch. Intern. Med.* 1988; 148: 2213-2217
9. Wessely S, Powell R. Fatigue syndromes: a comparison of chronic "postviral" fatigue with neuromuscular and affective disorder. *J. Neurol. Neurosurg. Psychiatry* 1989; 52: 940-948
10. Wessely S, Chalder T, Hirsh S, Wallace P, Wright D. Psychological symptoms and psychiatric disorder in chronic fatigue syndrome: a prospective study in primary care. *Am. J. Psych.* 1996; 153: 1050-1059
11. Katon W, Buchwald D, Simon G, Russo J, Mease P. Psychiatric illness in patients with chronic fatigue and rheumatoid arthritis. *J. Gen. Intern. Med.* 1991; 6: 277-285
12. Taerk G, Toner B, Salit I, Garfinkel P, Ozersky S. Depression in patients with neuromyasthenia (benign myalgic encephalomyelitis). *Int. J. Psychiat. Med.* 1987; 17: 49-56
13. Farmer A, Jones I, Hillier J, Llewelyn M, Borysiewicz L, Smith A. Neurasthenia revisited: ICD 10 and DSM-III-R psychiatric syndromes in chronic fatigue patients and comparison subjects. *Br. J. Psychiatry* 1995; 167: 503-506
14. Wood G, Bentall R, Gopfert M, Edwards R. A comparative psychiatric assessment of patients with chronic fatigue syndrome and muscle disease. *Psychol. Med.* 1991; 21: 619-628
15. Salit E. Precipitating factors for the chronic fatigue syndrome. *J. Psychiatr. Res.* 1997; 31: 59-65
16. Anonymous. Chronic fatigue syndrome: report of a committee of the Royal Colleges of Physicians, Psychiatrists and General Practitioners. London: Royal Colleges of Physicians, 1996
17. Wessely S, Chalder T, Hirsh S, Pawlikowska T, Wallace P, Wright D. Post infectious fatigue: a prospective study in primary care. *Lancet* 1995; 345: 1333-1338
18. Cope H, Mann A, Pelosi A, David A. Psychological risk factors for chronic fatigue and chronic fatigue syndrome following presumed viral infection: a case control study. *Psychol. Med.* 1996; 26: 907-916
19. White P, Thomas J, Amess J, Grover S, Kangro H, Clare A. The existence of a fatigue syndrome after glandular fever. *Psychol. Med.* 1995; 25: 907-916
20. Chalder B, Warnock P, McCartney R, Bell E, Coxsackie B. Viruses and the post-viral syndrome: a prospective study in general practice. *J.R. Coll. Gen. Pract.* 1987; 37: 11-14
21. Lynch S, Seth R, Main J. Monospot and VP-1 tests in chronic fatigue syndrome and depression. *J.R. Soc. Med.* 1992; 85: 537-540
22. Hotopf M, Noah M, Wessely S. Chronic fatigue and minor psychiatric morbidity after viral meningitis: a controlled study. *J. Neurol. Neurosurg. Psychiatry* 1996; 60: 504-509
23. Mowbray J, Yousef G. Immunology of postviral fatigue syndrome. *Br. Med. Bull.* 1991; 47: 886-894
24. Lloyd A, Wakefield D, Boughton C, Dwyer J. Immunological abnormalities in the chronic fatigue syndrome. *Med. J. Aust.* 1989; 151: 122-124
25. Buchwald D, Komaroff A. Review of laboratory findings for patients with chronic fatigue syndrome. *Rev. Infect. Dis.* 1991; 13(suppl1): S12-S18

26. Lloyd A, Wakefield D, Hickie I. Immunity and the pathophysiology of chronic fatigue syndrome. In: Kleinman A, Straus S, Eds. *Chronic fatigue syndrome*. Chichester, Wiley, 1993 : 176-187
27. Bakheit A, Behan P, Dinan T, Gray C, O'Keave V. Possible upregulation of hypothalamic 5-hydroxytryptamine receptors in patients with postviral fatigue syndrome. *BMJ*. 1992; 304: 1010-1012
28. Demitrack M, Dale J, Straus S, et al. Evidence for impaired activation of the hypothalamic-pituitary- adrenal axis in patients with chronic fatigue syndrome. *J. Clin. Endocrinol. Metab.* 1991; 73: 1224-1234
29. Cleare A, Bearn J, Allain T, McGregor A, Wessely S, Murray R, O'Keave V. Contrasting neuroendocrine responses in depression and chronic fatigue syndrome. *J. Affect. Dis.* 1995 ; 35 : 283-289
30. Bearn J, allain T, Coskeran P, Munro N, butler J, McGregor A, Wessely S. Neuroendocrine responses to d-fenfluramine and insulin-induced hypoglycaemia in chronic fatigue syndrome. *Biol. Psychiatry* 1995; 37: 245-252
31. Buchwald D, Cheney P, Paterson D, et al. A chronic illness characterized by fatigue, neurologic and immunologic disorders, and active human herpes type 6 infection. *Ann. Intern. Med.* 1992; 116: 103-116
32. Cope H, Pernet A, Kendell B, David A. Cognitive functioning and magnetic resonance imaging in chronic fatigue. *Br. J. Psychiatry* 1995; 167: 86-94
33. Greco A, Tannock C, Brotoff J, Costa A. Brain MR in chronic fatigue syndrome. *Am. J. Neuroradiol.* 1997; 18: 1265-1269
34. Costa D, Tannock C, Brotoff J. Brainstem perfusion is impaired in chronic fatigue syndrome. *Q. J. Med.* 1995; 88: 767-773
35. Ray C, Jefferies S, Weir W. Life events and the course of chronic fatigue syndrome. *Br. J. Med. Psychol.* 1995; 68: 323-331
36. Bruce-Jones W, White P, Thomas J, Clare A. The effect of social disadvantage on the fatigue syndrome, psychiatric disorders and physical recovery; following glandular fever. *Psycholo. Med.* 1994; 24: 651-659
37. Lewis S, Cooper C, Bennett D. Psychosocial factors and chronic fatigue syndrome. *Psychol. Med.* 1994; 24: 661-671
38. Van Houdenhove B, Onghena P, Neerinez E, Hellin J. Does high 'action-proneness' make people more vulnerable to chronic fatigue syndrome? A controlled psychometric study. *J. Psychosom. Res.* 1995 ; 39 : 633-640
39. Blakely A, Howard R, Sosich R, Murdoch J, Menkes D, Spears G. Psychiatric symptoms, personality and ways of coping in chronic fatigue syndrome. *Psychol. Med.* 1991; 21: 347-362
40. Hickie I, Kirk K, Martin N. Unique genetic and environmental determinants of prolonged fatigue: a twin study. *Psycho. Med.* 1999; 29: 259-268
41. Farmer A, Scourfield J, Martin N, Cardno A, McGuffin P. Is disabling fatigue in childhood influenced by genes? *Psychol. Med.* 1999; 29: 279-282
42. Zainal N. Family history study of chronic fatigue syndrome (MPhil dissertation) 1999
43. Hickie I, Bennett B, Lloyd A, Heath A, Martin N. Complex genetic and environmental relationships between psychological distress, fatigue and immune functioning: a twin study. *Psychol. Med.* 1999(a); 29: 269-277