

Chronic Fatigue Syndrome and the Central Nervous System

R CHEN^{1,2*}, FX LIANG^{3*}, J MORIYA¹, J YAMAKAWA¹, H SUMINO⁴, T KANDA¹
AND T TAKAHASHI¹

¹Department of General Medicine, Kanazawa Medical University, Ishikawa, Japan;

²Department of Traditional Chinese Medicine, Union Hospital Affiliated to Huazhong University of Science and Technology, Wuhan, China; ³Department of Acupuncture and Moxibustion, Hubei College of Traditional Chinese Medicine, Wuhan, China; ⁴Department of Nursing, Faculty of Nursing, Takasaki University of Health and Welfare, Gunma, Japan

An increasing amount of neuroimaging evidence supports the hypothesis that chronic fatigue syndrome patients have structural or functional abnormalities within the brain. Moreover, some neurotrophic factors, neurotransmitters and cytokines have also been evaluated

in order to elucidate the mechanism of abnormal neuropsychic findings in chronic fatigue syndrome. In this review, we suggest that the focal point of chronic fatigue syndrome research should be transferred to the central nervous system.

KEY WORDS: CHRONIC FATIGUE SYNDROME; CENTRAL NERVOUS SYSTEM; NEUROIMAGING; HYPOTHALAMIC–PITUITARY–ADRENAL AXIS; CORTICOSTEROIDS; BRAIN-DERIVED NEUROTROPHIC FACTOR; SEROTONIN SYSTEM; CYTOKINES

Introduction

Chronic fatigue syndrome (CFS), as defined by the Centers for Disease Control and Prevention, is mainly characterized by prolonged disabling fatigue lasting at least 6 months.¹ Additional evidence of an underlying psychiatric or neurological disorder requires appropriate psychiatric, psychological or neurological evaluation.¹ Hence, neuroimaging methods, including magnetic resonance imaging (MRI) scans and radionuclide scans, such as single-photon emission computed tomography (SPECT) and positron emission tomography (PET) of the head, have been used for the assessment of structural or functional

abnormalities in CFS.² Moreover, some neurotrophic factors, neurotransmitters and cytokines have also been evaluated to try and elucidate the mechanisms underlying neuropsychic abnormalities.³ In this review, we discuss the connection between CFS and the central nervous system (CNS), and we also look at the current approaches used to understand the neuropathological mechanism of CFS.

Neuroimaging findings

Available neuroimaging data not only show differences in morphology between fatigued patients and normal controls, but also indicate the brain's response to mental fatigue and other complex symptoms of CFS (Table 1).

*These authors contributed equally to this work.

TABLE 1:
Neuroimaging findings in patients with chronic fatigue syndrome (CFS)

Published year	No. of CFS cases	Detection methods	Results in patients with CFS	Reference
1992	60	^{99m}Tc -HMPAO and SPECT	Lower cortical/cerebellar regional cerebral blood flow ratios, mainly in frontal, temporal, parietal and occipital lobes	Ichise <i>et al.</i> ⁴
1995	67	^{99m}Tc -HMPAO and SPET	Confirmed brainstem hypoperfusion	Costa <i>et al.</i> ⁵
1998	18	^{18}F FDG-PET	Hypometabolism in right mediofrontal cortex and brainstem	Tirelli <i>et al.</i> ⁶
1999	39	MRI	Larger number of brain abnormalities on T_2 weighted images in CFS patients without psychiatric symptoms compared with CFS patients with psychiatric symptoms and healthy controls	Lange <i>et al.</i> ⁷
2000	7	Proton MRS	Reduced concentration of <i>N</i> -acetylaspartate in the right hippocampus; no difference between CFS and healthy controls in hippocampal volume	Brooks <i>et al.</i> ⁸
2003	15	SPECT	Less perfusion in the anterior cingulate region	Schmaling <i>et al.</i> ⁹
2004	16	MRI and VBM	Reduced grey-matter volume in the bilateral prefrontal cortex, especially in the right prefrontal cortex	Okada <i>et al.</i> ¹⁰
2005	10	$[^{11}\text{C}]\text{WAY-100635}$ and PET	Widespread reduction in 5-HT_{1A} receptor binding potential, especially in the hippocampus	Cleare <i>et al.</i> ¹¹
2005	28	MRI and VBM	Significant reductions in global grey matter volume	de Lange <i>et al.</i> ¹²
2006	25	Xenon-CT	Reduced absolute cortical blood flow in left and right middle cerebral artery territories	Yoshiuchi <i>et al.</i> ¹³
2007	9	Functional MRI	Greater brain activity in several cortical and subcortical regions such as cerebellar, temporal, cingulate and frontal regions	Cook <i>et al.</i> ¹⁴

CT, computerized tomography; ^{18}F FDG, $[^{18}\text{F}]\text{fluorine-deoxyglucose}$; 5-HT_{1A} , 5-hydroxytryptamine receptor 1A; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PET, positron emission tomography; SPECT, single-photon emission computerized tomography; SPET, single-photon emission tomography; ^{99m}Tc -HMPAO, ^{99m}Tc -hexamethylpropylene amine oxime; VBM, voxel-based morphometry.

REDUCED BRAIN BLOOD FLOW

Previous studies on brain blood flow in CFS patients have found contradictory results. Global hypoperfusion was reported by Ichise *et al.*⁴ and Schwartz *et al.*¹⁵ using SPECT. In addition, hypoperfusion in specific regions has also been detected using SPECT in CFS patients, such as in the anterior cingulate region and brainstem.^{5,9} Yoshiuchi K *et al.*¹³ used xenon-computed tomography as an alternative to SPECT to explore absolute cortical blood flow and found that patients with CFS had reduced flow in the bilateral middle cerebral artery territories. A monozygotic study of twins, however, detected no difference in perfusion between the twin with CFS compared with the healthy twin sibling.¹⁶

Evidence of abnormal perfusion in the brain has led to research on brain metabolism. [¹⁸F]Fluorine deoxyglucose PET was used to measure brain metabolism and found significant hypometabolism in the right mediofrontal cortex and brainstem in CFS patients.⁶ Combined with the results of a perfusion SPECT study,⁵ brainstem hypometabolism seems to be a marker for the *in vivo* diagnosis of CFS.

DECREASED BRAIN VOLUME

Patients with CFS have been found to have significantly abnormal brain volume compared with healthy controls, and these abnormalities occur not only in white matter but also in grey matter according to previous clinical reports involving MRI scans. Natelson *et al.*¹⁷ found increased white matter T₂ signals and ventricular or sulcal enlargement in 52 patients with CFS. While, in a study by de Lange *et al.*,¹² significant reductions were observed in global grey matter volume in 28 patients with CFS. A similar result was also reported by Okada *et al.*¹⁰ with CFS patients having reduced grey

matter volume in their bilateral prefrontal cortex.

Interestingly, hippocampal volume, obtained from MRI using an unbiased method, showed no difference between CFS patients and healthy volunteers, whereas proton magnetic resonance spectroscopy showed a significantly reduced concentration of *N*-acetylaspartate, a putative marker of neuronal density.⁸

SYMPTOM-RELATED NEUROIMAGING CHANGES

It is still uncertain which brain abnormalities dominate in their contribution to the various symptoms of CFS. It has been reported that the decline in grey matter volume was linked to a reduction in physical activity, a core feature of CFS.¹² It has also been reported that a reduction in the volume of grey matter in the right prefrontal cortex was associated with severity of the feeling of fatigue.¹⁰ Research by Cook *et al.*,¹⁴ however, indicated that mental fatigue was significantly related to brain activity, with greater activity detected in several cortical and subcortical regions, such as the parietal, cingulate, inferior frontal and superior temporal cortices, cerebellum and cerebellar vermis during a fatiguing task.

Psychiatric symptoms are often another main complaint reported by CFS patients. Those with no current psychiatric disorders had reduced cortical blood flow in both the right and left middle cerebral arteries, while CFS patients with current psychiatric disorders had reduced blood flow only in the left middle cerebral artery territory.¹³ Additionally, the CFS patients without psychiatric symptoms had a significantly larger number of brain abnormalities on T₂-weighted images compared with those with psychiatric symptoms and healthy controls.

Cerebral changes, consisting mostly of small, punctate, subcortical white matter hyperintensities, were found predominantly in the frontal lobes in CFS patients without psychiatric symptoms, but not in those with psychiatric symptoms.⁷

Pathophysiological mechanisms

HYPOTHALAMIC–PITUITARY–ADRENAL AXIS AND CORTICOSTEROIDS

The first study linking chronic fatigue to hypocortisolism was conducted by Poteliakhoff¹⁸ in 1981. Following this, many studies tested this hypothesis and low concentrations of corticosteroid and enhanced feedback of the hypothalamic–pituitary–adrenal (HPA) axis became an area of intense study in CFS.¹⁹ Contrary evidence for hypofunction of the HPA axis in a proportion of patients with CFS²⁰ has challenged these studies. It is still uncertain whether these disturbances have a primary or secondary role in the pathogenesis of CFS.²¹ Even if the HPA axis dysfunctions are secondary to other factors, they are probably still a relevant factor in symptom propagation in CFS. The indefinable relationship between the HPA axis and CFS has been discussed fairly recently by Cleare,²¹ so will not be repeated in this review.

BRAIN-DERIVED NEUROTROPHIC FACTOR

Brain-derived neurotrophic factor (BDNF) was first purified from the cerebrum of pig by German neuroscientists in 1982²² and is widely expressed in the CNS, including the hippocampus, cerebral cortex and basal forebrain. We recently found that the expression of BDNF mRNA in the hippocampus decreased in a CFS murine

model;²³ hence, we postulated that BDNF might play an important role in the development of CFS.

A decreased BDNF level, especially in the hippocampus, is often associated with the major symptoms of CFS. For example, lack of exercise is one of the main manifestations of CFS and exercise is an important facet of behaviour in enhancing brain health and function. Increased expression of the plasticity molecule BDNF as a response to exercise may be a central factor in exercise-derived benefits to brain function. In humans there is a transient augmentation of serum BDNF concentration immediately after short-term exercise.²⁴ In rodents, daily wheel-running exercise increases the BDNF gene and protein levels in the hippocampus.²⁵

Other symptoms of CFS, such as depression and anxiety, can decrease the expression of BDNF mRNA in the hippocampus.²⁶ Cognitive dysfunction can also influence the level of BDNF not only in rats but also in cellular models.^{27,28} In sleep-deprived rats, the expression of hippocampal BDNF was also found to be reduced.²⁹ In summary, the major symptoms of CFS can lead to a reduction of BDNF mRNA expression in the hippocampus.

The relationship between BDNF in the hippocampus and CFS, or at least the main symptoms of CFS, should be investigated more intensely. BDNF supports the survival and growth of many neuronal subtypes and, as the neurotrophin field has developed, BDNF has emerged as a key mediator of synaptic efficacy, neuronal connectivity and use-dependent plasticity. BDNF signalling is mediated by two different classes of receptors, namely the p75 neurotrophin receptor and the TrkB receptor tyrosine kinase and, so far, virtually all the synaptic effects of BDNF have been attributed to

TrkB.³⁰ BDNF binding to TrkB triggers autophosphorylation of tyrosine residues in its intracellular domain, leading to activation of one of the three major signalling pathways involving mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase (PI-3K) and phospholipase C γ ³¹ or interaction with *N*-methyl-D-aspartate (NMDA) receptors.³² Exercise-induced expression of BDNF in the hippocampus is associated with the increased expression of several key intermediates of MAPK,³³ the PI-3K/Akt pathway³⁴ and NMDA receptors.³⁵ These pathways are also partly involved in sleep disorder,³⁶ long-term potentiation and depression.³⁷ Nevertheless, how these mechanisms contribute to BDNF expression in CFS is still unclear and further studies are necessary.

SEROTONIN SYSTEM

Cleare *et al.*¹¹ provided evidence of decreased 5-hydroxytryptamine 1A (5-HT_{1A}) receptor number or affinity in CFS, which may be an important feature of CFS and related to its underlying pathophysiology, or a finding that is secondary to other processes, such as previous depression, other biological changes or the behavioural consequences of CFS. The serotonergic neurotransmitter system of CFS patients has also been investigated and the results indicated that an alteration of the serotonergic system in the rostral anterior cingulate plays a key role in pathophysiology of CFS.³ In serotonin transporter (5-HTT) gene promoter polymorphism studies, CFS patients had a significant increase in longer allelic variants which retained higher transcriptional activity than the short allele. Additionally, a selective 5-HT reuptake inhibitor, fluvoxamine, was sufficiently effective to enable about one-third of CFS patients to

return to work.³⁸

In a rat model of fatigue induced by polyriboinosinic:polyribocytidylic acid (poly I:C), 5-HTT was shown to be involved in the central mechanisms of fatigue, which suggests that the decrease in 5-HT action on 5-HT_{1A} receptors may, at least partly, contribute to poly I:C-induced fatigue.³⁹

Such clinical and experimental evidence indicates that a defect in serotonergic function is associated with the mechanism of CFS. The serotonin system is also associated with changes to the hippocampus, prefrontal cortex and HPA axis in some neurodegenerative diseases.⁴⁰ It is still uncertain, however, as to whether the serotonin system plays a role in such changes in CFS.

CYTOKINES

It has been reported that most patients with CFS had experienced an infection.⁴¹ In response to a peripheral infection, innate immune cells produce proinflammatory cytokines that act on the brain. When activation of the peripheral immune system continues unabated, the resultant immune signalling to the brain can lead to an exacerbation of feeling unwell.⁴² It is well known that cytokines produced in the brain exert various central actions, including activation of the sympathetic nervous system and HPA axis, impairment of learning memory, etc.;⁴³ this points to the possibility that brain cytokines may play a role in the pathogenesis of CFS.

Natelson *et al.*⁴⁴ detected 11 cytokines in the spinal fluid of CFS patients and found that: (i) levels of granulocyte-macrophage colony-stimulating factor were lower in CFS patients than in healthy controls; (ii) levels of interleukin (IL)-8 were higher in CFS patients who experienced sudden, influenza-like onset compared with controls and patients who

experience gradual onset; and (iii) IL-10 levels were higher in CFS patients with abnormal spinal fluids than in those with normal spinal fluids or healthy controls.

In a poly I:C-induced fatigue rat model, the expression of brain interferon- α (IFN- α) mRNA was significantly increased in the cortex, cerebellum, medial preoptic area, lateral hypothalamic area and paraventricular hypothalamic nucleus, but IL-6 and tumour necrosis factor- α (TNF- α) mRNA expression was not.³⁹ Furthermore, in this model, transforming growth factor- β was increased in the cerebrospinal fluid and this was associated with fever.⁴⁵

Some cytokines have been implicated in the provocation or exacerbation of mood and behavioural disorders in CFS, such as depression, anxiety and fatigue. For example, proinflammatory cytokines such as IL-1 β , IL-6 and TNF- α can elicit or aggravate fatigue and symptoms of anxiety and depression, and IL-2 and IFN- α can

promote depressive symptoms that are attenuated by antidepressant treatment.⁴⁶ The most common sleep disorder in CFS patients is excessive daytime sleepiness and night-time insomnia, which can be exacerbated by IL-6 and/or TNF- α .⁴⁷

Conclusion

In summary, an increasing amount of evidence is becoming available to elucidate the close relationship between CFS and the CNS. Some limitations still exist, however, because some studies have not only discussed the link between CFS and the CNS, but also the link between some of the major symptoms of CFS and the CNS. The focal point of CFS research, therefore, should be transferred to the CNS and exploration of the neuromechanism of CFS.

Conflicts of interest

The authors had no conflicts of interest to declare in relation to this article.

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Author's address for correspondence

Dr T Takahashi

Department of General Medicine, Kanazawa Medical University, 1-1 Daigaku,
Uchinada-machi, Kahoku-gun, Ishikawa 920-0293, Japan.

E-mail: taka2si@kanazawa-med.ac.jp