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Der Pharmacia Sinica, 2011, 2 (2): 212-219



ISSN: 0976-8688 CODEN (USA): PSHIBD

## **Chronic Fatigue Syndrome: A Review**

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## ABSTRACT

Chronic fatigue syndrome (CFS) is an illness characterized by disabling fatigue of atleast 6 months accompanied by several other secondary symptoms. Till date there is no approved treatment available in the market. The diagnosis is based on symptoms and no specific diagnostic tests are yet exist. CFS is a heterogeneous condition with multifactorial etiology. Immunological, Infectious, Sleep, Neuroendocrine, oxidative stress and Central nervous system mechanisms have been investigated but still etiology of CFS is not clear. Our review will summarize a current status of Pathophysiology and treatment of chronic fatigue syndrome.

Keywords: Chronic fatigue syndrome, Pathophysiology, Treatment.

## INTRODUCTION

Chronic Fatigue Syndrome which is also known as Myalegic Encephalitis is a debilitating, multicausative syndrome whose etiology is still unclear and for which there as yet no reliable treatment are available. CFS symptoms overlap with many other illnesses viz. Inflammatory Bowel Syndrome, Fibromyalgia, Multiple Chemical Sensitivities, Temporal Mandibular Joint disorder which makes it difficult to diagnose [1]. CFS is an illness that came into picture in mid 1980. It was firstly defined by United States Centre for Disease Control and Prevention (CDC) in 1988. Later on this definition was revised by Fukuda which sets a new criterion (table 1) for diagnosis of CFS [2].

The high prevalence and direct and indirect health cost of CFS patients is a matter of great concern for both developed and developing nations. Our review will throw a light on current status of CFS with special emphasis on treatment and cause behind this incapacitating syndrome.

#### Table 1: Fukuda's diagnostic criteria

Presence of prolonged fatigue (6 or more consecutive months) not substantially alleviated by rest, not the result of ongoing exertion and that produces significant reductions in occupational, social or personal activities.
Concurrent occurrence of at least 4 or more of the following symptoms, which must have persisted or recurred during 6 or more consecutive months:
Recently impaired memory or concentration

- Sore throat
- Tender cervical or axillary lymph nodes
- Muscle pain
- Multijoint pain without joint swelling or redness
- Headaches of a new type, pattern, or severity
- Unrefreshing sleep
- Discomfort post effort lasting more than 24 hours

## PATHOPHYSIOLOGY

There are many putative theories suggesting the cause of CFS but still pathogenesis of CFS is unclear and there is a strong need to explore hidden domains demonstrating the exact pathogenesis of CFS.

## Genetic

In one family history study it is found that relatives of patients with Chronic Fatigue Syndrome had significantly higher rate of occurrence of CFS [3]. In one twin study of CFS, it is found that concordance rates were higher between monozygotic twins than dizygotic twins [4]. The genetic evaluation of the serotonergic system in CFS identifies the association of HTR2A - 1438G/A with CFS and reveals allele-specific binding of a transcription factor at that locus. Interestingly, the strength of the association of the HTR2A - 1438G/A allele was significantly decreased when CFS patients were compared with non fatigued subjects. Future studies will be needed to replicate the association of HTR2A - 1438G/A with CFS [5].

## **HPA-axis dysfunction**

Enhanced feedback of HPA axis was found to be associated with CFS. The first study linking CFS to hypocortisolism was conducted by Poteliakhoff [6]. Low cortisol level has also been reported by Parker in CFS patients. [7]. Study by Torpy found low protein globulin level in CFS patients which is required for transportation of cortisol in blood [8]. Genetic mutations are suspected to be the causative factor behind low globulin level. Contrary to evidence for hypofunction of HPA- axis in a proportion of patients diagnosed with CFS has challenged these studies. It is still uncertain whether these abnormalities play a primary or secondary role in pathogenesis of CFS [9].

## Immune system abnormalities

There are many studies of immune system in patients with CFS and various abnormalities have been put forwarded but only few have been consistently reported by different scientists. The most robust findings are: NK cell function deficiencies and increased level of CD 8 and cytotoxic T cell [10,11,12,13,14]. High level of autoantibodies, reduced responses of T cells to mitogens and other specific antigens and alteration in cytokine profile are the other immunological aspects of CFS [15].

## **Sleep disruption**

Role of sleep disruption in CFS is conflicting as polysomnographic studies did not yield consistent outcomes. Some studies shown a characteristic alpha intrusion during Non-REM sleep and decrease in stage 4 sleep [16] while other do not [17]. Further sleep apnea was reported so

overall association of sleep disorders with CFS patients cannot be ignored [18]. One most descriptive and consistent polysomnographic finding was high level of MAI (Micro Arousal Index) in CFS patients [19,20]. Sleep disturbances associated with CFS has encouraged the scientists to study whether there is abnormal excretion of GABA and/or its structural analogue  $\beta$ -Alanine associated with CFS patients. In one study no statistically significant difference is found in excretion of neither GABA nor  $\beta$ -Alanine in CFS patients when compared to healthy controls. However increased excretion of  $\beta$ -Alanine has been seen in some CFS patients that point out towards linkage between CFS and  $\beta$ -Alanine [21].

## **Exercise studies**

CFS patients have reduced physical activity as compared to control subjects [22]. They are most intolerant to exercise and require longer rest periods after activity peaks. Even some evidence suggests that CFS patients cope with their illness by resting or avoiding physical activity [23]. Other studies have demonstrated increased lactic acid production [24] and reduction in muscle mitochondric and oxygen transport capacity [25]. CFS patients displayed a greater reduction in Electromyographic activity during physical exercise which suggests the inability to recruit normal amount of muscle, underlining a failure of central activation.

## **Infectious agents**

Many patients believe that CFS began with flu like illness. The state of immune activation in CFS also suggests the possibility of chronic infection process. Nevertheless, except in few cases, there is no convincing evidence that CFS results from an infection. Many scientists believe that infectious agents may trigger or perpetuate the symptoms of CFS. There is evidence that chronic active infection with various viruses may be present in some cases of CFS. Some researchers believe that Epstein-Barr virus (EBV) plays a central role in CFS [26]. Several studies have found that human herpes virus-6 (HHV-6) is activated more often in patients with CFS, but a casual role of HHV-6 has not yet been established. More circumstantial evidence of chronic viral infection in many CFS patients comes from report of an abnormality in antiviral lymphocyte enzyme system called the 2-5A pathway. This antiviral pathway appears to be chronically activated in patients with CFS [27]. All this provide strong evidence that CFS can be triggered by an acute infection but no evidence supports the direct link between chronic fatigue syndrome and infection.

## Serotonin system abnormalities

Decreased 5- hydroxytryptamine 1A (5HT1-A) receptor affinity was reported in CFS patients. [28]. The serotonergic transmission system is found to be altered in CFS patients and the results indicate hyperserotonergic state but the question that whether these alterations are a cause or consequences of CFS still to be answered [29].

## Brain derived neurotrophic factor (BDNF)

BDNF is a neurotrophic factor which plays a significant role in stimulating and controlling neurogenesis and is also capable of preventing programmed cell death of some groups of neuron. In the brain it is widely present in hippocampus, cortex and basal forebrain. A recent study has shown a decreased expression of Bcl-2 and BDNF mRNA which is believed to be induced by major symptoms of CFS viz. stress and depression. [30]. Bcl-2 is a crucial regulator of programmed cell death in CNS and its decreased expression can result in neuron apoptosis. It has been estimated that decrease in Bcl-2 mRNA expression is perhaps due to decreased expression of BDNF mRNA in hippocampus. Hence there is a relationship between CFS and BDNF but still further studies are required to link that how the mechanism contributes to BDNF expression in chronic fatigue syndrome [9].

## **Oxidative stress**

Oxidative stress and imbalance in antioxidant pool was considered as one of the major contributor of CFS [**31**]. Although it is uncertain that whether oxidative stress is a cause or a result of this illness, recent studies demonstrated that oxidative stress contributes to pathology and clinical symptoms of CFS. Fulle observed evidence of oxidative damage to DNA and lipids in Vastus Lateralis muscle sample of CFS patients. In addition they also found increase in activity of antioxidant enzyme system which is actually a compensatory measure in response to oxidative stress [**32**]. However Pall contends that it was elevated peroxinitrite which causes mitochondrial dysfunction and lipid peroxidation in CFS. He also suggested that increase cytokine level cause the formation of nitric oxide (NO) that combines with superoxide to form a potent oxidant viz. peroxynitrite. [**33**]. Further it was found CFS patients had elevated levels of methemoglobin (MetHb), which is one of the marker of oxidative stress [**34**]. Hence both oxidative and nitrosative stress plays a role in pathogenesis of CFS.

## **Co-conditioning Theory**

Fatigue in a body triggers an inhibitory system that prevents an organism to do further overwork. But due to impaired homeostasis and functional disturbances, the threshold triggering the inhibitory system (alarm signal) and fatigue sensation is lowered which is a specific feature of chronic fatigue syndrome. This may also contribute to mental and physical inactivity [**35**]. There are two evidences supporting the co-conditioning theory. Firstly, Central nervous system appears to have an inhibitory system which maintains the homeostasis by preventing overwork [**36**]. Secondly, an animal model of conditioned fatigue sensation has already been developed which implies that fatigue sensation can be conditioned [**37**]. Further research is required in this field to explore the neural mechanism behind co– conditioning theory and to study re-conditioning approach as a futuristic treatment strategy for CFS patients.

## TREATMENT

Till date there is no recommended treatment available for CFS patients. The pharmacological and non-pharmacological treatments that are available provide symptomatic relief only.

## **Pharmacological treatment**

**Immunotherapy**: Immunoglobulin has shown promising effect in treating CFS in placebo controlled trial studies [**38**]. A randomized controlled trial (RCT) on Ampligen shows positive effect on cognitive functions [**39**]. Another immunological substance alpha interferon shows improvement in quality of life (QOL) in one RCT [**40**]. Only one vaccine, Staphylococcus toxoid has been tested and shows positive effect in terms of QOL and physical health [**41**].

Antiviral: Acyclovir when tested in one clinical trial shows no change in Epstein-Barr virus titer value but Valacyclovir did [42]. In one pilot study Inosine pranobex demonstrates significant improvement in immune functions but no improvement in QOL and cognitive functions [43].

**Antidepressant:** MAO inhibitor Selegiline results in improving state of CFS patient but fluoxitine, a SSRI has shown a minimal effect in combating CFS. However these antidepressants checks specific symptom viz. muscle pain, sleep disturbance and mood swings associated with CFS. Other antidepressant medications viz. moclobemide, sertraline resulted in no significant improvement in state of chronic fatigue syndrome. [44]. Bupropion, a SNRI (Serotonin-Norepnephrine reuptake inhibitor) has offered some improvement in CFS patients but further rigorous trials will be needed to prove its effectiveness in CFS patients [45].

**Steroidal Therapy:** Hydrocortisone, in one study found to decrease fatigue [**46**] but in another trial did not prove effective [**47**]. Also in another steroid study of fludrocortisone, shows no significant results in CFS trial subjects [**48**]. Blockmann compared combination of hydrocortisone and fludrocortisone verses placebo but came with no difference in alleviation of fatigue [**49**]. Dehydroepiandrosterone (DHEA) reported to improve fatigue, pain and mood in one study [**50**].

Anticholinergic: Mental fatigue, cognitive disorder and sleep disturbances in CFS may be attributed to cholinergic deficit. Galantamine Hydrobromide, a selective acetylcholinesterase inhibitor was studied for its therapeutic effect. In a RCT it was found that Galantamine did not have any therapeutic effect in CFS patients [51]. But in another uncontrolled study it was found that fatigue, sleep disorders have improved significantly [52]. Studies showing effect of Galantamine on cortisol level yields inconsistent results. Although a study showed increased level of cortisol by Galantamine [53], in a recent study no effect of Galantamine on cortisol level was demonstrated [54].

**CNS stimulants:** CNS stimulants have been studied for their effectiveness in CFS patients. Out of them Dexamphetamine, Modefinil and pyridostigmine have showed improvement in one RCT and three case studies [55]. However, long term and more robust RCT are required to further investigate the efficacy and safety of drug as a treatment option for chronic fatigue syndrome.

Antiemetic: A pilot study on Granisetron, a 5HT3 antagonist has shown positive results which suggest that larger controlled studies may be justified. Other 5HT3 antagonist, Tropisetron and Ondansetron have shown improvement in fatigue in a small clinical trial [56].

**Hormones:** As sleep disturbances are associated with CFS hence Melatonin, a hormone which regulates sleep/wake cycle had been studied. In one clinical study, improvement quality of life and physical functioning was noticed [**57**]. But in a randomized controlled trial, it failed to show any effect [**58**]. Earlier also a RCT of growth hormone shows no significant improvement in quality of life on patients with CFS [**59**].

Diet and supplements: A double blind placebo controlled study of magnesium sulphate positively affects the health and function of CFS patients. The latter shows improved pain and scores on emotional reaction subscale [60]. However, still no evidence of magnesium deficiency has been reported in case of CFS patients [61]. Low serum zinc level was reported in CFS patients. So Zinc supplement has been suggested as a treatment option for CFS [62]. An alteration in intestinal microbial flora has been reported in CFS patients. Further it was postulated that these alterations are actually stress induced and augment the domination of Th2 cytokines so it is contend that administration of lactic acid bacillus can regulate composition of internal flora and have a significant impact on shifting cytokine level back towards Th1 driven cellular immunity [63]. A RCT of Acetyl-L-Carnitine and Propionyl-L-Carnitine shows significant improvement in fatigue and cognitive functions associated with treatment [64]. One RCT of essential fatty acids shows no beneficial effect [65] and one found an overall beneficial effect of the intervention [66]. Food intolerance is implicated in presentation of symptoms of CFS and dietary medication results in alleviation of these symptoms. In a pilot study which includes wheat free diet with nutritional supplements, about 70 % of enrolled patients showed improvement in physical symptoms and mental outlook [67]. Oral NADH shows improvement in symptoms of CFS patients when compared to control group but no significant difference in symptoms in another RCT [68].

## **Complementary and Alternative [CAM] Treatment**

Treatments of CFS with pharmacological therapies have given disappointing results and are also associated with adverse effects especially immunological and viral treatment. A triple blind RCT was done to check efficacy of homeopathic treatment on CFS which yields equivocal evidence of superiority of homeopathic medicine as compared to placebo. But still it is unclear that whether effects of homeopathy are due to action of medicine or of non specific effects of consultation [69]. Acupuncture was reported as one of the best among various complementary and alternative medicine treatment in treating symptoms associated with chronic fatigue syndrome. Future research will be needed to study the effectiveness of acupuncture interventions on large samples [70]. Recently, distant healing, an another form of CAM was studied for its effectiveness in CFS patients but the outcomes revealed non-significant effect on mental and physical health of patients [71].

## Non pharmacological treatment

Non pharmacological treatment has proven much effective in treating outcomes of CFS as compared to pharmacological treatment. Various non pharmacological approaches are mentioned as below.

## **Cognitive behavioral therapy (CBT)**

Studies of CBT have mixed results but overall CBT proves to be effective in treating depression and pain conditions [72]. In a randomized controlled trial study of people diagnosed with CFS who received CBT, it is found that 70 % of cognitive behavior group patients show substantial improvement in physical functioning. One RCT of CBT in children reported significant improvement in symptoms and quality of life [73]. A RCT of modified CBT resulted in positive effect on physical health and quality of life [74]

## Graded aerobic exercise

Graded aerobic exercise studies shown positive effect on physical functioning of many CFS patients. The latter showed reduced fatigue and increased functional capability with proper graded aerobic exercise programme and results are more promising as compared to relaxation and flexibility exercises [75]. Even awareness about benefits of exercising in CFS patients yields fruitful results [76]. The educational awareness resulted in improved physical functioning, sleep, mood and fatigue as compared to control group.

## **Prolonged rest**

Some evidence suggests that many CFS patients can cope with their illness by resting or just avoiding any physical activity. But many scientists does not believe in this concept as prolonged rest in case of viral illness or in case of healthy subjects leads to perpetuation of fatigue [77].

## CONCLUSION

CFS is a complex illness that remains elusive and is poorly understood. There is no management regime and no treatment can be considered as cure. It is useful to differentiate among predisposing, perpetuating and precipitating factors to understand etiology and treatment of CFS. Among all pathophysiological theories, a great emphasis is given to link between central nervous system and CFS which appears to be the major contributor behind pathogenesis of CFS followed by immunological dysfunction and oxidative stress. There are considerable number of studies evaluating intervention for treatment and management of CFS. But most of the mentioned RCT and controlled trials are of low quality because of unavailability of long term data on effectiveness and adverse event, less sample size, scantily reported reasons for withdrawals.

Future clinical trials should use more robust research methodology to achieve high validity score. Further, much pragmatic treatment approach is required which should include tailoring of treatment according to individual patient needs.

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