

# Sleep Disorders in Chronic Fatigue Syndrome

**Mohankumar Thekkinkattil**

HOD and Senior Consultant Pulmonologist, Chest Clinic, 3F, Cowley Brown Road

Doi : 10.5958/j.0973-340X.7.2.007

Indian J Sleep Med 2012; 7.2, 33-35

From the days when William Osler, published 'The principles and Practice of Medicine' printed by D Appleton and company in 1892, the description of chronic fatigue syndrome (CFS) as neuroasthenia, a condition of weakness or exhaustion of the nervous system, has been popularly known. He described that patients will have sleeplessness, mood changes and weariness on least exertion, the aching in the neck and local tenderness in the spine. This was the first description of CFS.

Most patients with CFS often complain about non-refreshing sleep. When sleep dysfunction disturbs their day-to-day activities, they need to attend a sleep clinic. Improvement in sleep quality in these patients will have positive effects on the sense of well-being<sup>1</sup>.

Patients with CFS having a good night's sleep have less complaints during the day. Disturbances of internal biological clock manifest as fatigue, poor concentration and sleep disturbances, and in CFS patients, a role of circadian pattern abnormality is detected<sup>2</sup>. Daytime fatigue and sleepiness with rapid eye movement REM abnormalities are common in patients with CFS<sup>3</sup>. In this group of patients, there is also increased physiological sleep. To know the prevalence of primary sleep disorders in CFS a study was done on 46 patients who underwent all night polysomnography and Multiple Sleep Latency Test (MSLT). In all, 46% showed apnoea hypopnea index (AHI) >5 and 5% showed evidence of periodic leg movement syndrome (PMLS)<sup>4</sup>.

Address for Correspondence

**Mohankumar Thekkinkattil**

MD, DSC, AB, DPPR, FCCP, FNCCP, FIASM  
HOD and Senior Consultant Pulmonologist,  
Chest Clinic, 3F, Cowley Brown Road  
Coimbatore 6410002, India  
Email: drtmkcb@gmail.com

The diagnosis of CFS is not easy. The criteria for diagnosis are 1. Clinically unexplained persistent or relapsing fatigue of at least 6 months duration results in reduction in levels of occupational, educational, social or personal activities and concurrent occurrence of at least four accompanying symptoms: post-exertional malaise, unrefreshing sleep, significant impairment in memory, concentration, headache, muscle pain, joint pain, sore throat and tender lymph nodes<sup>5</sup>. Unrefreshing sleep is common in all CFS patients. Physical examination must be documented by a physician on at least two occasions at least one month apart who should look for low-grade fever, non-exudative pharyngitis and for palpable or tender anterior cervical posterior cervical or axillary lymph nodes, which should be less than 2 cm in diameter.

The problem with CFS is whether it is a pathologically discrete entity as opposed to a debilitating, but nonspecific condition shared by many different entities. The association between restless leg syndrome (Ekbom syndrome) and CFS is well documented<sup>6</sup>. One of the major complaints the CFS patients have is pain in legs.

The sleep apnoea and CFS co-exist together with mild psychological problems and can be considered as comorbidity. Drugs like sodium oxalate in neurology seems to produce good relief giving the researchers to postulate that good response to CFS suggests a disturbance of sleep similar to narcolepsy in people with CFS or fibromyalgia<sup>7</sup>. Further studies are going on to know the precise cause of CFS.

Study by Spitzer and colleagues<sup>8</sup> also indicate in their CFS sample a very high incidence (58%) of previously undiagnosed primary sleep disorder such as sleep apnoea/hypopnoea syndrome and restless legs/periodic limb movement disorder.

The circadian patterns of activity, sleep and cortisol secretion in patients with CFS show no circadian rhythm

disturbances, but role of automatic activity in the experience of the unrefreshing sleep warrants more studies<sup>9</sup>. Autonomic disturbances during sleep may be one of the reasons for the daytime disturbances during sleep.

Other causes of poor sleep quality may be due to automatic hyper arousal, perceived stress and pain. Vagal induced cardiac changes in heart rate could explain the biological correlate of poor sleep in CFS patients<sup>10,11</sup>.

In some of the CFS patients, the truncated RNase-L fragments act as unregulated cellular components and cut cellular RNA, which increases immune cells suicide rate and opens the door to opportunistic infections. This will also cause dysregulation of ion channels in many cell types, which result in unexplained sweats, transient hypoglycemia, and reduction of pain sensitivity threshold, depression, visual problems, sleep disturbances and hypersensitivity to toxic chemicals. This may be one of the causes for unexplained signs and symptoms in CFS patients. The low-molecular-weight RNase-L will produce channelopathy with low body potassium, metabolic alkalosis and hyperventilation. These people may have polyuria, central fatigue and sleep disturbances.

Patients with CFS often report that exertion makes the symptoms worsen and people thought it may be due to the underlying sleep disorder. CFS patients, as a group, always had sleep disturbance; but after doing exercise<sup>12,13,14,15</sup> they reported less sleepiness. Exercise helps CFS patients to reduce fatigue. It is now advisable to give physician charted exercise programmes for CFS patients in a clinical setting.

In most of the CFS cases, the sleep disturbances are in the following order: periodic movement disorder, excessive daytime sleepiness, apnoea and narcolepsy. The objective sleep disturbance is common in CFS<sup>16</sup>. It is proven beyond doubt that all patients with CFS should undergo polysomnography to rule out sleep disorders so that their treatment and activities of daily living can be scheduled better.

In sleep studies of patients with the 'fibrositis syndrome' and healthy subjects undergoing stage 4 sleep deprivation, it was observed in both groups the anomalous presence of alpha rhythms in the non-rapid eye movement sleep EEG. This phenomenon has been then termed as alpha-delta sleep<sup>18</sup>.

Cyclic alternating pattern (CAP) was found in 65% in fibromyalgia patients versus 45% in controls and

hypothesised that CAP in CFS may be a result of chronic pain, reducing sleep efficiency, and causing more CAP and more arousals and also increases the occurrence of periodic breathing<sup>19</sup>. Upper airway resistance syndrome is now considered the same as CAP<sup>20</sup>. Repetitive increases to airflow within upper airway lead to brief arousals and daytime somnolence. The people do not meet the criteria of sleep apnoea. In this study, manometric and pneumotachographic measurements are the gold standard for the diagnosis of this syndrome. This is mainly seen in women.

Periodic leg movements are due to repetitive cramping or jerking of legs during sleep. It can range from a small movements in the ankles and toes to wild flailing of all limbs. This affects about 60% of CFS patients and is more common in females<sup>21</sup>. Clinicians should routinely query CFS patients regarding RLS symptoms and treatment of RLS can improve sleep and quality of life of these patients.

In patients with CFS, polysomnography is indicated when a sleep-related breathing disorder or periodic limb movement disorder is suspected, initial diagnosis is uncertain treatments fail or precipitous arousals occur with violent or injurious behaviour. Polysomnography is not indicated for the routine evaluation of transient insomnia, chronic insomnia or insomnia associated with fibromyalgia or CFS<sup>22</sup>.

A night of poor sleep is followed by increased pain ratings the following day and the day of increased pain is followed by a night of poor sleep in most of CFS patients. By looking at the polysomnography, wrist actigraphy, sleep and pain diaries and diffuse noxious inhibitory controls, it was shown that CFS patients have dysfunctional sleep and pain<sup>23</sup>. Impaired sleep is associated with reduced activation of the inhibitory pathway and frequent sleep disruptions can cause a reduction in the descending inhibitory control of pain and this is why the CFS patients have high sensitivity to pain<sup>24</sup>. Sleep improvement reduces the pain in these patients.

Disturbances of the internal biological clock manifest as fatigue, poor concentration and sleep disturbance. It is seen that CFS patients do have circadian rhythm disturbances<sup>25</sup>. Daytime sleepiness and abnormal REM regulation are seen in most of the CFS patients. Despite the increased daytime sleepiness most of the CFS patients complain of severe fatigue<sup>26</sup>.

How do we manage sleep issues in CFS patients? You have to explore sleep hygiene and behavioural issues and look for a primary sleep disorder like RLS/PLM, sleep apnoea or UARS, bruxism. Review the current medications for sleep side effects and review all previous treatments. We should assess for nocturnal pain generators and screen for depression and anxiety. You should encourage the patients to have regular sleep schedule and advise to sleep as long as possible (usually 7–8 h for adults). Adjust the room environment to decrease stimuli like sound, light, temperature. Try not to force sleep and resolve worries or concerns before sleep. Avoid caffeine, alcohol and tobacco in the late afternoon. Exercise regularly more than 4 h prior to bedtime and avoid daytime naps longer than 20–30 min. Low-dose or very low-dose cyclobenzaprine (1–4 mg) can be tried. Cognitive behavioural therapy for treatment can also be tried on young and middle-age patients rather than pharmacotherapy.

In conclusion, lot of work has to be done in CFS and sleep disturbances as the problem co-exist in majority of patients.

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