ORIGINAL ARTICLE

A Retrospective Review of the Sleep Characteristics in Patients with Chronic Fatigue Syndrome and Fibromyalgia

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■ **Abstract:** This study characterizes findings on sleep testing and Human Leukocyte Antigen (HLA) markers in a group of patients with fibromyalgia (FM) and chronic fatigue syndrome (CFS). One hundred eighteen patients seen in a general neurology practice over 5 years meeting standard clinical criteria for FM or CFS were analyzed retrospectively. Cases of untreated sleep apnea or restless legs syndrome were excluded prior to inclusion in this study. Ninety-two patients had multiple sleep latency testing (MSLT). Seventy-three (80%) were abnormal by standard criteria. Of 57 females having positive MSLTs, 22 (39%) had one or more periods of sleep onset rapid eye movement (SOREM), and 5 of 16 (31%) males with positive MSLTs had one or more SOREM. Highly fragmented sleep, as previously described in FM, was seen but not analyzed quantitatively. HLA DQB1*0602 was obtained in 74 patients, and positive in 32 (43%), $P < 0.0001$ compared with published values in 228 populations. In our patients, who presented with neuromuscular fatigue or generalized pain, we found a sleep disorder characterized by objective hypersomnia. Some patients had characteristics of narcolepsy. Objective assessment by sleep studies can assist the diagnostic process, aid future research, and provide rationale for treatment. ■

Key Words: fibromyalgia, chronic fatigue syndrome, sleep disorder, narcolepsy, HLA marker, hypersomnia

INTRODUCTION

The diagnoses of chronic fatigue syndrome (CFS) and fibromyalgia (FM) are based on clinical criteria. In 1990, The American College of Rheumatology presented the criteria for FM,[1] primarily comprising the "presence of widespread pain (at least 3 months duration) and tenderness on 11 of 18 pressure points." The Centers for Disease Control and Prevention (CDC) incorporated these recommendations and added "Fibromyalgia is a disorder of unknown etiology characterized by widespread pain, abnormal pain processing, sleep disturbance, fatigue and often psychological distress."[2] The CDC defines CFS as a collection of symptoms that include "chronic, debilitating fatigue" and other vague complaints that may include pain.[2]

The descriptions and definitions of these disorders have substantial overlap, and there is controversy about the distinction between them. Previously, it has been difficult to clearly or objectively identify any abnormality in patients carrying clinical diagnoses of CFS or FM. Various mechanisms have been proposed, including viral infections, immunological causes, dysfunction of the hypothalamic-pituitary-adrenal axis, neurally mediated hypotension, and nutritional deficiencies,[3,4] but despite extensive research, no exact mechanism has been

proven, nor has treatment aimed at these mechanisms proven overly successful. The pathophysiology of CFS and FM is unknown, and these disorders are characterized as rather refractory to treatment.

Although the presence of abnormal nocturnal sleep in FM is recognized, its significance with respect to the pathophysiology of the disorder is debated. Neither FM nor CFS has been classified as a disorder of sleep. Complete sleep testing is not part of the routine evaluation for either, and sleep disturbance is often considered a secondary phenomenon. The role of excessive daytime sleepiness has not been investigated systematically in either condition.

In the course of routine care, a large number of patients meeting established clinical definitions of CFS, FM, or both were identified and treated in a neurology practice. Recurring patterns of sleep disturbance, excessive sleepiness, and fatigue in these patients were noted frequently, and a large number of sleep studies and HLA markers were obtained in these patients.

A retrospective analysis of the data was undertaken because these patients seemed to present fairly stereotypical clinical patterns and results on diagnostic testing. In particular, it was noted that clear hypersomnia was seen in patients complaining of fatigue. The analysis was performed to estimate the frequency of daytime hypersomnia in these groups of patients. Certain features that occur in patients with narcolepsy were also noted in many patients, and this review analyzed some of those features as well. In view of difficulty distinguishing CFS and FM, we reviewed our cases to see if the patients with pain had different sleep findings than the ones with fatigue only. This review was also undertaken to determine the consistency of objective sleep-related findings in these patients and to explore the possibility that sleep studies could help clinicians in the challenging diagnostic process in these cases.

METHODS

This study comprises a retrospective review of sleep study and HLA results in 118 patients with CFS and FM that had all been seen as part of routine care in a general neurology practice over 5 years, from 2003 to 2008. Clinical diagnoses of CFS or FM followed standard published guidelines.[1,2,5] In the course of routine care, sleep studies were recommended to all patients in the practice clinically identified with excessive sleepiness, disrupted sleep, or extreme fatigue. These included patients who presented with generalized pain but who also had fatigue or sleepiness. While most patients agreed to the sleep studies, a few patients declined to have them done. These patients were treated without the results of the sleep studies if the clinical evidence alone was strong enough to be deemed sufficient for diagnosis. While the Epworth Sleepiness Scale (ESS) had been frequently used to judge the sleepiness in making the recommendations for the sleep studies, the numerical values were not often recorded, and so were not available for retrospective analysis. An elevated ESS was frequently the reason for recommending a sleep study during clinical treatment. This retrospective study was approved by the University of Michigan Institutional Review Board.

Routine polysomnography (PSG) and multiple sleep latency testing (MSLT) were performed with standard methodology.[6] If other obvious causes of fatigue, such as sleep apnea or restless legs syndrome, were found on PSG, those cases were not included in this series. An MSLT was graded as positive if the latency to sleep on 4 or 5 consecutive naps averaged less than or equal to 8 minutes. Sleep onset rapid eye movement (SOREM) during these daytime naps of 20 minutes or less was noted.

Prior to the sleep study, any recently added or adjusted medications were withdrawn over several weeks, as were stimulants. However, medications that the patients had been taking 6 months or longer (in many cases, for many years) were not withdrawn, so as not to create sudden changes in their established chronic physiological state. Typically, these medications would have included pain medications including opiates, antidepressants, medications for control of migraines, and other long-standing medications. In patients on antidepressants and several pain medications, stimulants, and medications for other chronic conditions, all having been taken for many years, withdrawal of all of these over 2 to 4 weeks would cause very significant changes in physiology and would make assessment of an equilibrium state impossible. These patients were being assessed for problems persisting while on (and despite) these stable medications, and this condition was considered their steady state.

HLA testing for HLA DQB1*0602 was obtained in the majority of cases, at 1 laboratory at a major teaching hospital. The testing was not predicated on sleep study results and was ordered independently on clinical grounds. Thus, these markers were not obtained selectively only in patients with positive sleep studies.

Diagnoses of narcolepsy were eventually established in many of these patients, after the results of complete evaluation. The diagnosis of narcolepsy followed stan-

dard clinical practice, which involves the assessment of multiple criteria to determine the diagnosis. No single criterion by itself is diagnostic nor exclusive. Criteria including excessive daytime sleepiness, sleep attacks, sleep paralysis, and hypnagogic or hypnopompic hallucinations, cataplexy, disrupted nocturnal sleep, abnormal MSLT, and presence and number of SOREM were all considered.[7] The preponderance of evidence, with emphasis on cardinal features, was used to make the diagnosis, consistent with good clinical practice. However, this does not mean every case had exactly the same exact set of features. The HLA marker itself was never used to make a diagnosis of narcolepsy. In some cases where other strongly suggestive pieces of evidence were present, it was considered as a possible supporting evidence.

In considering the multiple criteria for narcolepsy, in the presence of sufficient other pieces of evidence, a single SOREM was considered supportive of the diagnosis of narcolepsy. Thus, in retrospectively reviewing these cases, we counted the cases with one or more SOREM, when it had also been determined there were other multiple, adequate combined features of narcolepsy.

RESULTS

A total of 118 charts were identified for retrospective review. Patients had been treated over the course of approximately 5 years, from 2003 to 2008. Only a minority of cases were originally referred for a diagnosis of CFS (3/118, 2%) or FM (33/118, 28%). Cases were referred for typical diagnoses that would be seen in a neurology practice, such as low-back pain, migraine, or suspected epilepsy. Because of complaints of weakness or myalgia, many of the cases were referred for consideration of neuromuscular disorders, such as myopathies or neuromuscular junction disease, or consideration of multiple sclerosis. None of the cases were originally referred for a primary sleep disorder. Most of the patients had been seen previously by rheumatologists or psychiatrists, as is typical in this group of patients. In many of the cases, symptoms of CFS or FM were discovered during review of systems while a patient was being treated for an unrelated disorder such as migraine or epilepsy, while in some cases, a diagnosis of CFS or FM had been previously suggested by another physician but was not the reason for the neurological consultation.

Twenty-five of the patients were male (21%) and 93 were female (79%), in keeping with the accepted female preponderance of CFS and FM. The mean age was 53 ± 12. These demographics are very similar to pub-

lished demographics of these disorders. Of the 118 patients, 117 (99%) had long-standing fatigue consistent with CFS, and 82 (69%) had generalized pains and muscle aches in a pattern consistent with FM. Of the 25 male patients, 14 had pain (56%), and of the 92 female patients, 68 had pain (74%). Thus, while there are more female than male patients, once the disorder is present, the clinical characteristics appear fairly similar in males and females, with males having somewhat less tendency to pain. The pain was most typically described as "all over," as considered characteristic of FM, and as considered diagnostic of the disorder by standard criteria. Persisting chronic pain "all over" has been found to be a strong clinical feature of FM.[1] The fatigue was chronic and long standing, and without other cause, meeting standard criteria for CFS.[2]

Any patients having another cause of excessive sleepiness discovered on PSG, such as obstructive sleep apnea or restless legs syndrome, were excluded from this study, unless it could be shown on PSG that the condition had been successfully, completely corrected. Thus, none of these 118 patients had untreated sleep apnea or restless legs syndrome.

Of the 118 patients, 92 patients underwent MSLT (Table 1). Of these 92, 73 (80%) had a positive study by standard criteria, with a mean sleep onset of less than or equal to 8 minutes. Among 74 females who had MSLTs, 57 (77%) were positive, whereas among 18 males having MSLTs, 16 (89%) were positive. Of the 82 patients with generalized pain, 61 had MSLT. Of those 61, 45 had positive MSLTs (74%), while the remaining 16 had negative results. Thus, the majority of patients with a symptom of generalized body pain who had

Table 1. MSLT Results Obtained in 92 of 118 Patients who had MSLT Testing. Positive Results Comprise Average Sleep Latency less than or equal to 8 minutes. Other Causes of Excessive Sleepiness, including OSA and RLS, had been Excluded Clinically and by PSG in all Patients. All Patients had Varying Degrees of Fatigue. The Group with Pain was Most Consistent with the Clinical Syndrome of Fibromyalgia. The Remainder had Little or No Pain, More Consistent with Chronic Fatigue Syndrome

MSLT	Total	Positive (%)
Total	92	73 (80)
Male	18	16 (89)
Female	74	57 (77)
Pain	61	45 (74)

MSLT, multiple sleep latency testing; OSA, obstructive sleep apnea; PSG, polysomnography; RLS, restless legs syndrome.

Table 2. Presence of SOREM. The First Column Identifies Patients who had Positive MSLTs (See Table 1). The Second Column Identifies those who had Positive MSLTs who also had One or more SOREM during Daytime Naps. The Third Column Identifies those who had one or more SOREM but who had a Normal MSLT (were not among the Group in Column 1). Because of the Small Numbers, a Percentage was not Calculated for this Group. A more Detailed Discussion is Provided in the Text

SOREM	Positive MSLT	Positive MSLT and SOREM (%)	Negative MSLT and SOREM
Male	16	5 (31)	0
Female	57	22 (39)	6

MSLT, multiple sleep latency testing; SOREM, sleep onset REM.

MSLT done had significant objective abnormal results indicating excessive sleepiness. Notably, the values for patients with pain (74% positive) are similar to the results for those with fatigue. Objective hypersomnia is a recurring finding in our patients.

Of the 57 females with positive MSLTs, 22 (39%) had one or more periods of SOREM, and among the 16 males with positive MSLTs, 5 (31%) had SOREM (Table 2). Of the patients with negative MSLTs, 6 female patients had one or more SOREM. Thus, altogether, of the 92 patients having MSLTs, 33 (36%) had at least 1 period of SOREM. Thus, given the appropriate clinical symptoms being presented, nearly 40% of patients were having at least 1 SOREM period, and this was used as a supportive feature toward the diagnosis of narcolepsy in the overall context. Other supportive criteria of definite narcolepsy, such as sleep attacks, cataplexy, sleep paralysis, or an HLA marker, were also present in these patients, but an analysis of these criteria separately and together was not performed.

Subgroup analysis was performed, including, for example, those with pain and SOREM, or "with pain and SOREM and positive HLA markers," however, many of the subgroups in the analysis became too small for meaningful results. Data on the individual features of the clinical characteristics to make the diagnosis, such as sleep paralysis, nocturnal hallucinations, or cataplexy, had not been recorded separately in every case. The aggregate was often referred to broadly in the clinical diagnosis. Therefore, further subgroup analysis was not pursued.

Patients used various terms to describe their fatigue. The numbers of patients using each descriptor were not recorded quantitatively or consistently in every

Table 3. Presence of HLA DQB1*0602

HLA	Tested	Positive (%)
Male	15	6 (40)
Female	59	26 (44)
Total	74	32 (43)

chart. Terms used by patients included sleepiness, a desire to sleep, a desire to sleep but inability to fall asleep, muscular fatigue, fatigue worsened by physical exertion or exercise, unrefreshing sleep, light and fitful sleep, myalgias, unexplained falling episodes without loss of consciousness, difficulty getting started for the day or performing routine chores, or difficulty "getting off the couch." Initially, it was thought that these terms would have predictive value, and, as typical in a clinical neurology practice, great emphasis was placed on the accurate description of the symptoms. Ultimately, none of the clinical terms served to differentiate or predict sleep study results, nor eventual response to treatment. Interestingly, they did not predict neuromuscular vs. sleep findings, as originally expected. The data had not been recorded in a quantitative manner that allowed numerical analysis in this retrospective review.

A total of 74 patients out of the 118 were tested for the HLA DQB1*0602 marker (Table 3). Selection for testing was not based on sleep study results, and generally, the tests were ordered in parallel on clinical grounds. Twenty-six of 59 females tested (44%), and 6 of 15 males (40%), were positive. Altogether, 32 of 74 (43%) were found to be positive.

In this retrospective study, formal grading of the nocturnal sleep pattern had not been employed during treatment, beyond routine standard measures. The initial intent of the nocturnal PSG, performed the night before the MSLT, was to exclude other causes of fatigue, and in fact, if such were found, those patients were not included in the study. However, one author (A.R.S.) did qualitatively assess all PSGs, and all of them showed inability to achieve deep stage III/IV sleep, inability to sustain sleep, or most typically, a highly fragmented pattern of the nocturnal sleep stages. This pattern has been described in FM by other authors[8] and was not reanalyzed for this study.

DISCUSSION

Disrupted nocturnal sleep has been reported and recognized in patients with FM. The pathophysiological sig-

nificance has been debated, but recent treatment studies aimed at this nocturnal sleep pattern raise the question whether the sleep disturbance is a primary, rather than a secondary, component of the disorder. Our data show that these patients have clear, substantial, objective daytime hypersomnia in the face of, and simultaneous with, this disrupted nocturnal sleep pattern. Patients with sleep deprivation and sleep apnea will not have inability to sleep at night, and those with idiopathic hypersomnia are described as having "longer and more consolidated nocturnal sleep than do other patients with daytime sleepiness."[9] Deprivation of deep sleep will lead to a rebound of increased nocturnal deep sleep during the recovery phase. Our finding supports the theory that, in these cases, the inability to sleep at night is primary rather than secondary. Patients with this degree of hypersomnia should be attempting to recover with increased sleep at night. Rather, the pattern is closer to that of patients with narcolepsy, who have poor nocturnal sleep in the face of significant daytime hypersomnia, and in whom the sleep disorder is primary.

There is debate about the distinction of FM and CFS. Our results in the subgroups with pain and fatigue, and fatigue alone, were similar. The lack of a difference in the sleep data suggests the need for prospective studies to look at underlying sleep in both groups of patients. Sleep has not been studied in CFS, and treatment of CFS has been considered distinctly from FM. Our observation provides a basis for considering treatments aimed at sleep in both conditions, CFS included. Our preliminary data suggest that treatment aimed at the sleep disorder in CFS may be helpful.

We compared our frequency of the HLA DQB1*0602 marker with published population prevalences of the marker. The allele frequency of HLA DQB1*0602 was noted to be 0.128 (12.8%) in Olmstead County Minnesota.[10] Mignot et al. have found an approximate prevalence of 24% in their population.[11] This marker varies in different population groups. Therefore, we took all reported frequencies of HLA DQB1*0602 in 228 surveyed populations[12] and computed the mean value of these reported frequencies. The mean value was 0.0798 (7.98%). When our data are compared with this population prevalence using all 228 studies, the z-score is 11.0, and the P value for a probable difference between the groups is $P < 0.0001$. It is still high compared with some of the individual, isolated studies reporting 12% to 25% prevalence. While the HLA itself is never used to make a diagnosis of narcolepsy, our results of 43% positive for this HLA marker

in this population are over 5 times higher than the average prevalence in the 228 populations. It is substantially higher than the reported prevalence even in selected populations. While some individual studies report higher values than others, it is most meaningful to compare our results statistically with larger groups of studies rather than the individual, isolated outliers, particularly only the highest values.

Our data indicate the need for a prospective study of HLA markers in the patient population comprising CFS and FM. It also suggests that a subgroup of these patients may have an immunological basis for their disorder, as is thought to be possible in classical narcolepsy with cataplexy. Some of these patients, initially classified as FM or CFS, in fact seem to meet the full criteria for narcolepsy but are presenting to physicians with an atypical presentation. In some cases, the diagnosis was not apparent for decades.

All of the patients in this series had a diagnosis of narcolepsy made on clinical grounds during treatment, using various combinations of features. In the retrospective analysis, the data were not reviewed to establish the number or type of criteria that had been used to make the diagnosis in each case. As formal questionnaires, scoring, and formalized lists of clinical diagnostic features were not recorded, it would be difficult to retrospectively reestablish the clinical picture consistently in all these cases for study purposes.

Our retrospective study cannot establish the prevalence of classical narcolepsy accurately in these patients. This is partly because of the way the clinical features had been recorded and partly because this is a retrospective study. The extent to which patients meeting the criteria for CFS or FM may have classical narcolepsy should be evaluated in prospective studies. Our MSLT and HLA marker results suggest that this will represent a significant subgroup of these patients.

In addition to providing information on the prevalence of classical narcolepsy, a prospective study will identify and characterize more clearly the group of hypersomnic patients who does not meet that definition. Our data suggest a subgroup of patients may fall into that category. For example, patients without the HLA DQB1*0602 marker, or patients without SOREM on MSLT, may be more likely to have normal cerebrospinal fluid hypocretin, and may have another form of hypersomnia. Taken together, our data suggest the different forms of hypersomnia will be

identified in a large proportion of patients with CFS and FM.

We studied our patients while continuing medications they had taken for prolonged periods of time, often many years. Many medications are said to affect the sleep cycle. These medications had been started after the onset of, and in order to treat, existing symptoms, including fatigue and pain. In the setting of prolonged habituation to these medications, the degree of hypersomnolence seems striking. In view of the degree of objective hypersomnia, the suggestive data from the HLA markers, and the presence of a group of patients with clinical syndromes meeting the criteria for narcolepsy, we believe there is sleep dysfunction that cannot be explained by chronic, long-standing medications prescribed after the onset of symptoms.

This study points toward the presence of a frequent sleep disorder in CFS and FM, but it does not answer the question of the underlying etiology of the sleep disorder. There may be multiple pathways leading to the dysregulation of sleep. Our patients included cases who had developed symptoms following head trauma, recent viral infections, recent pregnancy and delivery, and attacks of demyelinating disease, as some examples. In other cases, the onset was insidious with no apparent precursor, or in retrospect, had begun in childhood or teenage years, or was associated with a positive HLA marker.

The role of viral agents in CFS has been studied for years. The localization of brainstem and hypothalamic control of sleep centers has been studied extensively recently,[13] and the lesions in von Economo's encephalitis could lead to sleep disorders such as those seen in our patients. Thus, a subgroup of our patients may represent this etiology, which could have a viral onset. Recently, a retrovirus has been reported in a group of patients with CFS.[14] Neuroanatomic and physiologic correlates of the fatigue in those patients are not yet known. Overall, therefore, the anatomic localization of the lesion may be the unifying common theme in these cases.

Many patients with these symptoms are classified as having a psychiatric disorder, no disorder, or have trouble establishing a diagnosis and treatment plan. They seek advice from multiple physicians without any clear answers, and physicians are in a quandary when trying to assess these patients. Sleep studies should be added to the assessment of these patients. Objective findings on sleep studies will help quantify the fatigue, provide an objective basis for its presence, reassure patients and physicians, and help guide treatment plans. While sleep studies cannot serve as a diagnostic test for CFS and FM by themselves, the presence of objective quantifiable abnormalities on these tests can assist clinicians by adding to the subjective criteria currently employed to define these syndromes. Objective tests are routinely used in this manner in many syndromes. This is conceptually similar to the consideration of a positive ANA or rheumatoid factor, which must be combined with a clinical picture, but aids in the establishment of a diagnosis.

Recently reported studies, including a double-blind placebo-controlled study[15] and results in our patients,[16] have suggested that treatment with sodium oxybate provides benefit in patients with FM. While the original rationale for this treatment had been the described nocturnal sleep disturbance, our finding of significant daytime hypersomnia further extends this rationale, provides a better understanding of the effectiveness of this medication, and may help guide future treatment studies.

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