Sleep Disturbances in ME/CFS

IOM Diagnostic Criteria for ME/CFS Committee Meeting 3
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Sleep in ME/CFS

- One of the symptoms used for diagnosing ME/CFS is “unrefreshing sleep”

- This sleep-related problem is the most common complaint among patients with ME/CFS

- Even minimal exertion produces a worsening of symptoms in ME/CFS

- Identification of objective sleep problems of ME/CFS may help understanding of pathophysiology of ME/CFS and may help developing treatment of ME/CFS
Prevalence of Primary Sleep Disorders in ME/CFS

- Primary Sleep Disorders (SD)
  Obstructive Sleep Apnea (OSA), Periodic Limb Movement Disorder (PLMD), Narcolepsy, etc.

- Approximately 45-60% of the patients with ME/CFS presented with SD (OSA and PLMD) (Le Bon et al., 2000; Fossey et al., 2004)

- Larger population-based studies found that approximately 20% of the patients with ME/CFS had SD (either OSA or narcolepsy) (Nisembaum et al., 2003; Reeves et al., 2006); approximately 10% of asymptomatic controls presented with SD (Reeves et al., 2006)

- SD appears to be moderately prevalent in ME/CFS
Primary Sleep Disorders and ME/CFS

- There is an argument in that whether SD should be considered as a diagnostic exclusion or a comorbid condition with ME/CFS.

- There is overwhelming evidence of the distinction between ME/CFS and SD (Neu et al., 2009).

- ME/CFS patients with a comorbid SD were found to have greater functional impairment (Morris et al., 1993).

- The symptoms of ME/CFS did not differ between ME/CFS patients with and without SD (Le Bon et al., 2000; Libman et al., 2009).

- CPAP therapy in ME/CFS patients with comorbid OSA did not result in any substantial changes in the symptoms (Libman et al., 2009).
Polysomnography (PSG)

- EEG, EOG, EMG, ECG, Airflow, Oximetry etc.
- Sleep Stages (R&K Criteria, AASM Modifications)

(Rechtschaffen & Kales, 1968; American Academy of Sleep Medicine, 2008)
Sleep Variables

- Total Sleep Time (TST)
  *Time spent in non-REM or REM sleep*

- Sleep Efficiency (SE)
  *Percentage of TST to time in bed*

- Sleep Latency (SL)
  *Latency to sleep onset from lights-out*

- REM sleep Latency (REML)
  *Time from sleep onset to the first epoch of REM sleep*

- Wake after Sleep Onset (WASO)
  *Time spent in W after sleep onset to lights-on*

- (%) Stages N1, N2, N3, REM
  *Time spent in each sleep stage*
  *(Percentage of time spent in each sleep stage)*

Traditional Hypnogram

![Hypnogram Diagram](Diagram.png)
No specific or consistent objective sleep characteristics have been found in ME/CFS

(Fukuda Criteria, 2nd night of PSG)

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<td>(%) N2</td>
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<td>(%N1+N2)</td>
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*Monozygotic twin pairs discordant for ME/CFS, **Medications statistically controlled; others with no medication (> 2 weeks)
Sleep Variables in ME/CFS

- No specific or consistent objective sleep characteristics have been found in ME/CFS

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<td>(% N1)</td>
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<td>n.s.</td>
<td>n.s. (N1+N2)</td>
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<td>(% N2)</td>
<td>n.s.</td>
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<td>(%N1+N2)</td>
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<td>(% N3)</td>
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<td>(% REM)</td>
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Analysis of Sleep Stage Dynamics

Traditional Hypnogram

Actual Hypnogram — Dynamic transitions between sleep stages

Traditional sleep variables are static descriptive statistics

- **Transition** and **Duration** are considered sufficient in describing the “path” to specific episodes that might lead to, e.g., poor sleep quality.
Analysis of Sleep Stage Dynamics

- Characterization/quantification of *Transition* and *Duration*

- **Transition probability** between sleep stages

  The number of the transitions
  from a specific stage to one of the other stages

  The total number of the transitions
  from the specific stage to another stage

  \[
  \left( \text{e.g., N2 to N3: } \frac{N_{N2\rightarrow N3}}{N_{N2\rightarrow W} + N_{N2\rightarrow N1} + N_{N2\rightarrow N3} + N_{N2\rightarrow R}} \right)
  \]

- **Cumulative duration distributions** of each sleep stage
  
  = Survival curve of the bout durations of each sleep stage
Sleep Stage Dynamics in CFS with or without Fibromyalgia (FM)

- Subjects:
  - 26 Healthy Controls (38 ± 8 years)
  - 14 CFS patients without FM (CFS alone, 37 ± 9 years)
  - 12 CFS patients with FM (CFS+FM, 41 ± 6 years)

- CFS and FM often have similar symptoms, including sleep-related complaints
- Despite the similarities, differences between CFS and FM exist

- We hypothesized that the analysis of sleep stage dynamics could reveal objective differences in sleep in CFS with or without FM
Sleep stage dynamics differed between CFS with or without FM

(Kishi A, et al., SLEEP, 2011)
Sleep stage dynamics differed between CFS with or without FM

REM disruptions in CFS alone

SWS disruptions in CFS+FM

Shorter N2 bout durations in CFS+FM

○ Healthy
△ CFS alone
× CFS+FM

: Greater probability in CFS alone than in controls
: Greater probability in CFS+FM than in controls
: Greater probability in CFS+FM than in controls and CFS alone

(Kishi A, et al., SLEEP, 2011)
Sleep stage dynamics differed between CFS with or without FM

- REM disruptions in CFS alone
- SWS disruptions in CFS+FM

**N2 bout durations (Burns et al., 2008)**

- Shorter N2 bout durations in CFS+FM

(Kishi A, et al., *SLEEP*, 2011)

- Greater probability in CFS alone than in controls
- Greater probability in CFS+FM than in controls and CFS alone
- Greater probability in CFS+FM than in controls
Interpretation of the Findings

(W1 N1 N2 N3): Greater probability in CFS alone than in controls
(W1 N1 N2 N3): Greater probability in CFS+FM than in controls
(W1 N1 N2 N3): Greater probability in CFS+FM than in controls and CFS alone

(Kishi A, et al., SLEEP, 2011)
Interpretation of the Findings

Specific sleep problem in CFS alone

Lower sleep pressure in CFS alone

(Sleep latency was not shortened in CFS even after the sleep deprivation [Nakamura et al., 2010])

- Greater probability in CFS alone than in controls
- Greater probability in CFS+FM than in controls
- Greater probability in CFS+FM than in controls and CFS alone

(Kishi A, et al., SLEEP, 2011)
Interpretation of the Findings

W/N1/R → N2
Increased sleep pressure in CFS+FM

R → W
Specific sleep problem in CFS alone
Lower sleep pressure in CFS alone
(Sleep latency was not shortened in CFS even after the sleep deprivation [Nakamura et al., 2010])

W/N1/R → N2
Greater probability in CFS alone than in controls

N1
Greater probability in CFS+FM than in controls

N2
Greater probability in CFS+FM than in controls and CFS alone

N3
(Kishi A, et al., SLEEP, 2011)
Interpretation of the Findings

N3→W/N1
Specific sleep problems in CFS+FM
(Disruptions of SWS result in the symptoms resembling FM [Moldofsky et al., 1975])

W/N1/R→N2
Increased sleep pressure in CFS+FM

R→W
Specific sleep problem in CFS alone
Lower sleep pressure in CFS alone
(Sleep latency was not shortened in CFS even after the sleep deprivation [Nakamura et al., 2010])
Interpretation of the Findings

R → W
Specific sleep problem in CFS alone

W → N3
Specific sleep problem in CFS+FM
(Disruptions of SWS result in the symptoms resembling FM [Moldofsky et al., 1975])

N3 → W/N1
Increased sleep pressure in CFS+FM

W/N1/R → N2
Shorter N2 durations
(Decreased sleep spindle density and power in FM [Landis et al., 2004])

N1

R

R → W
Specific sleep problem in CFS alone

W

N2

N3

Lower sleep pressure in CFS alone
(Sleep latency was not shortened in CFS even after the sleep deprivation [Nakamura et al., 2010])
Interpretation of the Findings

- The fact that the co-existence of FM alters sleep stage dynamics of CFS patients suggests that CFS and FM are different pathophysiologic underpinnings associated with different aspects of sleep regulation.

**N3 → W/N1**

*Specific sleep problems in CFS+FM*

(Disruptions of SWS result in the symptoms resembling FM [Moldofsky et al., 1975])

**W/N1/R → N2**

*Increased sleep pressure in CFS+FM*

- Shorter N2 durations
  
  (Decreased sleep spindle density and power in FM [Landis et al., 2004])

**R → W**

*Specific sleep problem in CFS alone*

*Lower sleep pressure in CFS alone*

(Sleep latency was not shortened in CFS even after the sleep deprivation [Nakamura et al., 2010])

(Kishi A, et al., SLEEP, 2011)
Exercise Effect on Sleep Stage Dynamics in ME/CFS

Subjects:
- 16 Healthy Controls (38 ± 9 years)
- 17 CFS patients (41 ± 8 years)

Experimental Procedures:
- We hypothesized that subjective symptoms in CFS might be correlated with specific sleep abnormality.

- Visual Analogue Scale (VAS) for subjective symptoms (fatigue, pain, sleepiness, feeling blue and anxiety).

Electronically braked cycle ergometer
Acceptance Condition:
- Heart Rate ≥ 80% of age predicted maximum HR
- and/or Respiratory Exchange Ratio ≥ 1.1

We hypothesized that subjective symptoms in CFS might be correlated with specific sleep abnormality.
Exercise improved sleep modestly but worsened fatigue in ME/CFS

Variables indicating better sleep
- Time in Bed (min)
- Total Sleep Time (min)
- Sleep Efficiency (%)
- N2 (min)
- N3 (min)
- REM sleep (min)

Variables indicating worse sleep
- Sleep Latency (min)
- WASO (min)
- N1 (min)
- WASO+N1 (min)

Other variables
- REM Latency (min)

Gray areas indicate better sleep after exercise

- Exercise improved sleep only modestly for controls and CFS

(Kishi A, et al., *Physiol Rep*, 2013)
Exercise improved sleep modestly but worsened fatigue in ME/CFS

Variables indicating better sleep
- Time in Bed (min)
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(Kishi A, et al., Physiol Rep, 2013)
Exercise improved sleep modestly but worsened fatigue in ME/CFS

- Exercise improved sleep only modestly for controls and CFS
- CFS reported increased fatigue in the morning after exercise compared to the baseline morning

(Kishi A, et al., *Physiol Rep*, 2013)
Exercise improved sleep modestly but worsened fatigue in ME/CFS

- Exercise improved sleep only modestly for controls and CFS
- CFS reported increased fatigue in the morning after exercise compared to the baseline morning

(Kishi A, et al., Physiol Rep, 2013)
Exercise improved sleep transitions but REM continued to be disrupted in ME/CFS

Effect of exercise on transition probability in controls and CFS

After exercise, CFS reported increased fatigue and continued to have REM sleep disruption.

(Kishi A, et al., Physiol Rep, 2013)
Correlation between Transition and Symptoms in ME/CFS

- Probability of transitions from REM to Wake was significantly positively correlated to worsening of subjective symptoms in CFS

(Kishi A, et al., *Physiol Rep*, 2013)
Correlation between Transition and Symptoms in ME/CFS

- Probability of transitions from REM to Wake was significantly positively correlated to worsening of subjective symptoms in CFS

CFS Patients

- Exercise improved sleep in CFS, but CFS continued to have REM sleep disruptions
- The degree of REM sleep disruptions was significantly correlated with the worsening of subjective symptoms (fatigue and sleepiness) over night

$\Delta$ Fatigue Over Night (Morning - Evening)

$\Delta$ Sleepiness Over Night (Morning - Evening)

$\Delta$ Pain Over Night (Morning - Evening)

$\bar{r} = .45$

$P = .009$

$\bar{r} = .37$

$P = .034$

$\bar{r} = .46$

$P = .008$

(Kishi A, et al., Physiol Rep, 2013)
Summary

• It appears that traditional sleep variables do not differ between controls and ME/CFS

• Newer approaches in analyzing sleep (sleep stage transitions) are emerging and could capture sleep disruptions in ME/CFS — but need more research

• PSG is required to diagnose PSD, which is prevalent in ME/CFS
Acknowledgment

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