Sleep in Autism Spectrum Disorders: Window to Treatment and Etiology

Ruth O’Hara, Ph.D.
Associate Professor, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine

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• NONE

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Sleep Disturbances in ASD: A Substantial Concern for Parents

- Multiple Studies of Parental Reports Suggest Sleep Disturbances common in ASD
- Main Parental complaints:
  - 44% sleep initiation difficulties
  - 31% sleep maintenance difficulties
  - 30% early morning awakening

Association of Sleep Disturbances with ASD Core Symptoms

- More affective problems in children with ASD who are poor sleepers (Maslow, 2006)
- Association between sleep onset disturbance and communication impairments in low functioning ASD (Quine, 1991)
- Association between total sleep time and non-verbal communication (Richdale, 2009)

Why should we care about Sleep in Autism?

- Sleep disturbance impacts cognition, mood and behavior
- Negative impact on health and well-being of the family
- Sleep Disturbances can reflect many Sleep Disorders
- Many Sleep Disorders can be treated
- Characterizing Sleep Dysregulation in ASD may
  - Identify valuable biomarkers
  - Provide a window to etiology
  - Refine our phenotypes
What Do We Know about Sleep in ASD?

- Limited Number of Studies

- Different Assessment Methodologies Employed
  - Sleep Diaries
  - Actigraphy Measures of Activity
  - Video Recordings
  - Full Polysomnography (PSG): Gold Standard Assessment of Sleep

- Sleep Studies of ASD employ Sleep diaries and Actigraphy

Do Objective Sleep Assessments Validate Parental Observations?

Objective Sleep Disturbances in ASD

<table>
<thead>
<tr>
<th></th>
<th>AUT (n = 68)</th>
<th>DD (n = 57)</th>
<th>TYP (n = 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bedtime</td>
<td>21:00 (1:00)</td>
<td>21:07 (1:00)</td>
<td>20:46 (0:51)</td>
</tr>
<tr>
<td>Sleep start</td>
<td>21:36 (1:13)</td>
<td>21:46 (1:13)</td>
<td>21:19 (0:53)</td>
</tr>
<tr>
<td>Sleep end</td>
<td>6:58 (0:57)</td>
<td>7:24 (1:02)</td>
<td>7:11 (0:49)</td>
</tr>
<tr>
<td>Time in bed</td>
<td>9:57 (0:55)</td>
<td>10:13 (0:48)</td>
<td>10:25 (0:35)</td>
</tr>
<tr>
<td>Sleep-onset latency</td>
<td>0.39 (0:28)</td>
<td>0.42 (0:31)</td>
<td>0.35 (0:19)</td>
</tr>
<tr>
<td>WASO duration(^a)</td>
<td>0.21 (0:16)</td>
<td>0.29 (0:22)</td>
<td>0.18 (0:12)</td>
</tr>
<tr>
<td>WASO min(^a)</td>
<td>2.5 (1.2)</td>
<td>3.7 (2.6)</td>
<td>3.2 (1.8)</td>
</tr>
<tr>
<td>Sleep efficiency</td>
<td>91.3% (4.6)</td>
<td>89.7% (5.1)</td>
<td>91.8% (3.5)</td>
</tr>
<tr>
<td>24-hour sleep</td>
<td>10:36 (0:51)</td>
<td>11:06 (0:54)</td>
<td>11:14 (0:53)</td>
</tr>
<tr>
<td>Naps (n = 366)</td>
<td>AUT (n = 54)</td>
<td>DD (n = 48)</td>
<td>TYP (n = 62)</td>
</tr>
<tr>
<td>Sleep duration(^b)</td>
<td>0.47 (0:58)</td>
<td>0.58 (1:00)</td>
<td>0.54 (0:58)</td>
</tr>
<tr>
<td>No. of naps(^b)</td>
<td>0.65 (0:75)</td>
<td>0.65 (0:40)</td>
<td>0.66 (0:45)</td>
</tr>
</tbody>
</table>

Decreased sleep duration over 24h

Goodlin-Jones, J Am Ac Child & Adolescent Psychiatry 2008
Full PSG Assessment of Sleep in ASD is Rare

- Sleep Diaries, Actigraphy and Videos are valuable but limited as they Do Not Assess Sleep Architecture
- Capture sleep initiation BUT NOT sleep maintenance difficulties
- Equate lack of movement with sleep but cannot capture micro-arousals in sleep

Objective Sleep Assessment: Overnight Lab/Clinic Polysomnography


<table>
<thead>
<tr>
<th></th>
<th>Autism (66)</th>
<th>Typical (15)</th>
<th>DD (13)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>4.4 (1.9)</td>
<td>3.0 (2.4)</td>
<td>3.0 (1.4)</td>
<td>.38</td>
</tr>
<tr>
<td>Range</td>
<td>2 – 1.2 y</td>
<td>1.0 – 2.1 y</td>
<td>2.0 – 1.7 y</td>
<td>.94</td>
</tr>
<tr>
<td>Total sleep time, h</td>
<td>7.7 (2.04)</td>
<td>8.8 (1.56)</td>
<td>9.1 (1.14)</td>
<td>.004</td>
</tr>
<tr>
<td>Latency to sleep, min</td>
<td>28.5 (95.5)</td>
<td>32.5 (33.5)</td>
<td>33.0 (15.5)</td>
<td>.29</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>83.7 (15.5)</td>
<td>85.2 (11.6)</td>
<td>87.6 (8.9)</td>
<td>.28</td>
</tr>
<tr>
<td>WASO, min</td>
<td>50.1 (82.7)</td>
<td>37.0 (66.0)</td>
<td>46.1 (43.8)</td>
<td>.03</td>
</tr>
<tr>
<td>Stage 1 sleep, %</td>
<td>4.7 (4.6)</td>
<td>3.7 (2.1)</td>
<td>2.1 (2.3)</td>
<td>.14</td>
</tr>
<tr>
<td>Stage 2 sleep, %</td>
<td>56.4 (12.3)</td>
<td>58.8 (8.3)</td>
<td>57.7 (15.7)</td>
<td>.82</td>
</tr>
<tr>
<td>Stage 3 SWS sleep, %</td>
<td>21.0 (9.0)</td>
<td>19.8 (5.4)</td>
<td>18.7 (7.3)</td>
<td>.001</td>
</tr>
<tr>
<td>REM sleep, %</td>
<td>14.0 (8.4)</td>
<td>22.6 (6.3)</td>
<td>25.0 (8.8)</td>
<td>.001</td>
</tr>
<tr>
<td>REM sleep latency, min</td>
<td>106.9 (86.3)</td>
<td>104.0 (89.0)</td>
<td>109.6 (27.5)</td>
<td>.02</td>
</tr>
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</table>
Limitations of Overnight Laboratory Approaches

- Limited ecological validity
- Sample bias
- Do not Assess for Sleep Disorders
- Difficult for Patients with ASD
- One Night Effect

Sleep Disturbance Can Reflect Very Different Sleep Disorders

- Sleep Disturbance Can Reflect Very Different Sleep Disorders
  - Sleep Disordered Breathing e.g. Sleep Apnea, hypoventilation
  - Insomnia
  - Circadian Rhythm Disorder
  - Restless Legs Syndrome
  - Periodic Limb Movements
  - Rapid Eye Movement Sleep Disorder
  - Sleep Terrors

- Effective Treatments Exist for Many Sleep Disorders
- Systematic Consideration of Sleep Disorders in ASD is minimal

What Do we Know About Sleep Disorders in ASD?
Knowledge on Sleep Disordered Breathing is Minimal

- Apnea = cessation of respiration
- Hypopnea = partial decrease (>50%) of respiration
- Duration \( \geq 10 \) seconds
- Apnea/Hypopnea Index \( \geq 5/h \) of sleep
Sleep Apnea Case Studies in ASD

- Gozal et al, 2008 Pediatrics
  - Prevalence of Sleep Apnea in Typical Developing Children as high as 30%
  - Impaired School Functioning
  - Increased daytime sleepiness and napping

- Gozal et al, 2010 Pediatrics
  - Case Study of Child with ASD: Improved Following Treatment
  - Impaired cognitive function and auditory processing
  - Impaired Endothelial function
  - Increased inflammation (TNF-α)

- Malow et al., 2004, Sleep
  - One Case Study of Child with ASD with Apnea: Improved Following Treatment

Circadian Rhythms Are Dysregulated in ASD: May Reflect Reduced Melatonin Synthesis in ASD

- Nocturnal urinary 6-SMT rate ↓ in 49 ASD children (12±5) vs. 88 matched NT controls (Tordjman, 2005)
  - 63% had <1/2 nocturnal melatonin excretion rate than controls

Restless Legs Syndrome and ASD:

- Nocturnal urinary 6-SMT rate ↓ in 49 ASD children (12±5) vs. 88 matched NT controls (Tordjman, 2005)
  - 63% had <1/2 nocturnal melatonin excretion rate than controls
Iron Deficiency key in RLS
Iron Deficiency identified in ASD
RLS may be a significant sleep disorder in ASD
RLS leads to significant sleep fragmentation and dysregulation
May impact core cognitive and behavioral symptoms in ASD

Simons Foundation Grant: Characterization of Sleep Disorders in ASD

- To describe the range and type of sleep disorders experienced in individuals with ASD (n=80).
- To examine the impact of the type and severity of sleep disorders on the cognitive and behavioral symptoms in these individuals with ASD.
- To examine for specific patterns of impaired sleep architecture in ASD relative to controls, which have the potential (a) to serve as biomarkers of this disorder, and/or (b) to define specific phenotypes or subgroups.

Sleep Assessment with Ambulatory In-Home Polysomnography

- Electroencephalogram (EEG)
- Electrooculogram (EOG)
- Submental Electromyogram (EMG)
- Nasal airway pressure
- Nasal/oral airflow
- Finger Pulse Oximetry
- Snoring
- Movements of rib cage and abdomen
- ECG
- Body position
Systematic Behavioral Desensitization

- Initial visit to the home to do the consent and assent
- Bring a booklet on the process to read with the child
- On a second visit we bring non-working equipment –
  - EEG cap
  - electrode leads
  - Cannula (to assess for sleep disordered breathing)
- Child wears equipment and places it on the Sleep technician
- Leave equipment in home for wearing at night until family feels child is ready for PSG
- This process typically takes 2-4 weeks per child assessed

Study Progress to Date

- 105 subjects consented and enrolled in the investigation
  - 75 ASD subjects assessed to date with full ambulatory PSG
  - 10 Siblings assessed to date with full ambulatory PSG
  - 30 healthy, historical controls from Stanford Sleep Center

O’Hara et al:
Sleep Polysomnography Findings

<table>
<thead>
<tr>
<th></th>
<th>Autism</th>
<th>Sibs</th>
<th>Controls</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>9.65 (3.85)</td>
<td>10.60 (2.72)</td>
<td>10.81 (3.46)</td>
<td>.01</td>
</tr>
<tr>
<td>Range</td>
<td>3-16y</td>
<td>6-15y</td>
<td>3-16y</td>
<td></td>
</tr>
<tr>
<td>Total sleep time, h</td>
<td>6.20 (2.18)</td>
<td>17.1 (2.38)</td>
<td>9.25 (3.32)</td>
<td>.01</td>
</tr>
<tr>
<td>Latency to sleep, min</td>
<td>24.33 (29.2)</td>
<td>17.5 (18.4)</td>
<td>23.5 (11.5)</td>
<td>.33</td>
</tr>
<tr>
<td>Sleep efficiency, %</td>
<td>72 (25.2)</td>
<td>88.1 (18.1)</td>
<td>88.6 (10.1)</td>
<td>.06</td>
</tr>
<tr>
<td>WASO, min</td>
<td>19.7 (21.3)</td>
<td>25.9 (16.0)</td>
<td>40.1 (28.1)</td>
<td>.01</td>
</tr>
<tr>
<td>Stage 1 sleep, %</td>
<td>36 (6.4)</td>
<td>27.1 (14.4)</td>
<td>2.1 (2.9)</td>
<td>.29</td>
</tr>
<tr>
<td>Stage 2 sleep, %</td>
<td>44.4 (16.1)</td>
<td>45.2 (8.5)</td>
<td>52.3 (12.3)</td>
<td>.22</td>
</tr>
<tr>
<td>Stage 3 SWS sleep, %</td>
<td>45.48 (6.0)</td>
<td>36.1 (9.3)</td>
<td>23.4 (6.2)</td>
<td>.001</td>
</tr>
<tr>
<td>REM sleep, %</td>
<td>12.5 (6.4)</td>
<td>24.2 (15.1)</td>
<td>25.0 (9.7)</td>
<td>.001</td>
</tr>
<tr>
<td>REM sleep latency, min</td>
<td>118.1 (64.3)</td>
<td>86.0 (51.0)</td>
<td>70.0 (22.8)</td>
<td>.01</td>
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O’Hara et al: Sleep Disorders Findings

<table>
<thead>
<tr>
<th></th>
<th>Aspergers (75)</th>
<th>Sibs (10)</th>
<th>Controls (30)</th>
<th>P value</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>9.65 (3.95)</td>
<td>10.60 (2.72)</td>
<td>10.91 (2.44)</td>
<td>.40</td>
</tr>
<tr>
<td>Range</td>
<td>3-15y</td>
<td>6-15y</td>
<td>3-15y</td>
<td></td>
</tr>
<tr>
<td>Sleep Apnea %</td>
<td>40%</td>
<td>20%</td>
<td>10%</td>
<td>.01</td>
</tr>
<tr>
<td>AHI</td>
<td>&lt; 3 hr</td>
<td>3.8 (2-5.5)</td>
<td>1.2 (1-5)</td>
<td>.70</td>
</tr>
<tr>
<td>AvSaO2</td>
<td>96%</td>
<td>98%</td>
<td>97%</td>
<td></td>
</tr>
<tr>
<td>MinSaO2</td>
<td>91%</td>
<td>95%</td>
<td>95%</td>
<td>.05</td>
</tr>
<tr>
<td>Insomnia</td>
<td>55%</td>
<td>40%</td>
<td>25%</td>
<td>.001</td>
</tr>
<tr>
<td>Periodic Limb Movement</td>
<td>25%</td>
<td>15%</td>
<td>15%</td>
<td>.10</td>
</tr>
<tr>
<td>PLM</td>
<td>4.42 (0-40.8)</td>
<td>7.0 (0-8)</td>
<td></td>
<td>.01</td>
</tr>
<tr>
<td>Spontaneous Arousal</td>
<td>10.29 (0-9)</td>
<td>5.25 (0-8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Causes of Sleep Disturbances in Children with ASD

- Coexisting Medical Disorders
  - Neurological disorder (e.g. epilepsy)
  - Medical disorder (e.g. GI reflux, Sinus) or psychiatric comorbidity (e.g. anxiety, depression)

- Medications
  - Corticosteroids, bronchodilators, psychiatric medications

- Neurobiological
  - GABA, 5-HT (Serotonin), Melatonin

- Behavioral and Environmental
  - Inadequate Sleep hygiene
  - Excessive light at night, excess noise, bedroom too warm, too cold
  - Agitation from the experiences of the day, school problems, frustration

Sleep disorders Provide Treatment Opportunities for Autism Spectrum Disorders

- Insomnia
  - Behavioral therapies, including attention to daytime habits, bedtime routine, and interactions with caregivers during night
  - Supplemental melatonin

- Obstructive sleep apnea
  - Weight loss
  - Continuous positive airway pressure

- REM behavior disorder
  - clonazepam (first line), dopaminergic agents, melatonin, and home safety measures

- Periodic limb movements of sleep and/or Restless Leg Syndrome:
  - dopaminergic agents (first line)
  - Ferritin or Iron Supplementation
Sleep disorders Provide Clues to the Biomarkers and Phenotyping of ASD

- Insomnia
  - Melatonin deficiency
- Sleep apnea
  - Hypoxia during neuronal development
  - Serotonergic deficiencies
  - SCN deficiencies or dysregulation
  - Cardiac dysregulation
  - Increased agitation
- REM deficiency
  - Neurotransmitter deficiencies
  - Impaired neuronal development
  - Circadian Rhythm Disorder
  - Periodic limb movements of sleep and/or Restless Legs Syndrome
  - dopaminergic deficiencies
  - Ferritin deficiencies

Conclusions

- Data suggests Sleep Dysregulation and Sleep Disorders are very common ASD
- Neuroscience of Normal Sleep
- Circadian Rhythms
- Sleep Disorders
- Sleep Disorders Represent an important opportunity for therapeutic interventions
  - Mind and Body Relationships
  - Body and Mind Relationships
- Increased Characterization of Sleep Architecture may serve as a valuable biomarker in ASD, point to etiological basis and/or provide for phenotypic refinement

Future Directions

- Increased Characterization of Sleep Disturbances in ASD
- Increased knowledge of the prevalence of sleep disorders
- Detailed sleep architecture and EEG measures of sleep deprivation
- Investigation of the shared neurobiological factors implicated in both sleep-wake regulation and ASD
- Neurodevelopmental consequences of early-on sleep disturbance, disorders and circadian rhythm disturbances requiring longitudinal approaches