



Sleep and Autism Spectrum Disorder

Developmental Pediatrics Presentation
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+ CanMeds Objectives



- Scholar:
 - Review typical pediatric sleep physiology
 - Review the relationship between sleep and ASD
 - Review the current evidence on melatonin and children with ASD

- Educator:
 - Provide an engaging and relevant presentation
 - Provide an approach to sleep problems in children with ASD

+ Why Sleep?



- Sleep has significant effects on many aspects of daily living i.e. mood, behaviour, and academic performance
- Parents of typically developing children with sleep problems report a number of negative consequences during the day including: behaviour difficulties, affective problems, and cognitive dysfunction ¹⁴
- Optimal sleep is essential for normal growth and development, emotional health and immune function ³
- Estimated that 2/3's of children with Autism Spectrum Disorders have sleep difficulties, compared with a 9-50% of typically developing peers ⁶

+ Stages of Sleep



- Non-rapid eye movement sleep (75-80% of sleep by 5 yrs) ¹⁶
 - Stage I
 - Stage II
 - Stage III
 - Stage IV
- Rapid Eye Movement Sleep (20-25% of sleep by 5 yrs) ¹⁶
 - Characterized by burst of rapid eye movements, intense EEG activity, muscle paralysis and dreaming. EEG activity similar to an awake state
 - Time for the brain to assimilate images and learn from experiences of the day

+ Sleep



- For an event to be encoded and then consolidated into long-term memory, exposure to adequate sleep is essential after the occurrence of the event ⁶
- Slow wave sleep → critical role in memory consolidation ⁶
- REM sleep essential for processing memories with an emotional component ⁶
- Sleep plays an important role in optimizing cognition, behavioural regulation, memory and learning ⁶

+ Sleep



- Brief physiologic arousals, without waking occur as an aspect of normal sleep
- If they occur frequently, however, the restorative nature of sleep is impaired and daytime psychological function is affected
- sleep loss is known to result in increased irritability, depression, poor affect modulation, impulsivity, hyperactivity, and aggressiveness ⁵
- Health consequences: possible deleterious effects on cardiovascular, immune and various metabolic systems i.e. glucose metabolism and endocrine function as well as impaired coordination ⁵

+ Sleep



- Sleep is believed to play role in the growth and healing of tissues, learning and processing of memory and CNS repair ³
- Sleep is a period of intense brain activity involving higher cortical functions ³
- The sleep wake cycle is thought to be learned in part via social cues about sleep behaviour ⁹
- 2 main processes regulate sleep and wakefulness:
 - Circadian process → internal clock dependent on light-dark cycle
 - Homestasis process → demand for sleep builds during waking hours and is relieved by sleep

+ Sleep Needs

- 2 yr old--> 13 hours
- 3 yr old--> 12 hours
- 5 yr old--> 11 hours



+ Measuring Sleep: Subjective Measures

- Sleep diaries
- 24 hour sleep-wake schedule
- Sleep habit questionnaires



+ Measuring Sleep: Objective Measures

- Wrist Actigraphy: monitors body movements via small wrist device on non-dominant hand. Useful for measuring basic sleep wake patterns. Can be used as a outpatient.
- Polysomnography: Involves recording EEGs, EOGs and EMGs from which basic measures of NREM sleep, REM sleep and sleep continuity can be made





+ Sleep & Autism Spectrum
Disorders

+ Autism and Sleep



- 50-80% prevalence of sleep problems reported by parents of children with autism spectrum disorder ⁶
- Degree of cognitive impairment likely does not influence the prevalence of sleep problems in ASD ⁶
- Autism subtype does not influence degree of sleep problems



Common Sleep Issues in ASD



- Longer to fall asleep (increased sleep latency)
- Frequent night-time awakenings
- Reduced sleep duration
- Why is this important to recognize?

Has been associated with poor social interaction, increased stereotypy, problems in communication and overall autistic behaviour. Some studies have reported an association between sleep problems and developmental regression in ASD ¹³

+ Sleep and ASD: The Biopsychosocial Model ¹²

- Sleep problems may occur as a result of:
 - 1) Intrinsic biological or genetic abnormalities that alter brain architecture or biochemistry
 - 2) Psychological or behavioural characteristics connected with core or associated features of ASDs
 - 3) Factors in the family/home environment





Causes of Sleep Disturbance in Autism



- Poor sleep habits ¹¹
- Hypersensitivity to environmental stimuli
- Hyperarousal/difficulty with self regulation, circadian rhythm problems
- Medical issues that may cause pain/discomfort
- Repetitive thoughts or behaviours that will interfere with settling
- Inability to benefit from communication/social cues regarding sleep
- Co-existing psychiatric conditions
- Psychotropic medications
- OSA, restless leg syndrome, periodic limb movements

+ Autism and Sleep



- Internalizing behaviours i.e. anxiety and depression may influence sleep disturbances in ASD ⁶
- Anxiety is highly prevalent in ASD with estimates between 11-84% of children meeting the criteria for an anxiety disorder ⁹
- Anxiety has been shown to consistently overlap with sleep difficulties and children ⁹
- The direction of the relations between sleep disturbance and autism symptoms have not yet been established ⁹

+ Autism and Sleep



- Hyperactivity and impulsivity are highly prevalent in ASD (28-70% meeting the criteria for ADHD) ⁹
- Most studies have found hyperactive symptoms overlap with sleep disturbances in children with ASD ⁹
- Some studies have found no relation with sleep difficulties and age, whereas others have found a decline in difficulties with age, similar to typical development ⁹

+ Possible Neurobiological Etiologies

- Melatonin
- Clock Genes
- ASD and the “Hyperaroused State”



+ Melatonin



- Melatonin, a sleep promoting neurohormone that works via the MT1 and MT2 receptors on the suprachiasmatic nuclei ¹²
- synthesized by the pinealocytes in the pineal gland ¹⁷
- synthesis is controlled by ambient light under the control of the circadian clock located in the suprachiasmatic nuclei of the hypothalamus ¹⁷
- It is also a potent antioxidant, has anti-inflammatory properties, is involved in the immune response and helps regulate synaptic plasticity ¹³

+ Melatonin



- produced from the amino acid tryptophan which is then converted to serotonin and eventually transformed into melatonin ¹⁷
- The steps of transforming serotonin into melatonin are mediated by AA-NAT and ASMT ¹⁷
- In physiologic conditions, melatonin's plasmatic concentration follows a circadian rhythm (low levels in the day, and high levels at night) ¹⁷
- There are reports of abnormal platelet serotonin levels in children with autism ¹¹

+ Melatonin Synthesis





Differences in Melatonin Secretion



- Abnormally low levels of melatonin documented by multiple investigations ⁶
 - The nocturnal, urinary 6-sulphatoxymelatonin excretion rate is reported as depressed in children and adolescents with autism compared with similar age TD children ¹²
- A potential contribution of the ASMT enzyme to the observed reduced melatonin production in ASD has been considered given that several of the identified mutations of the ASMT gene reduce or abolish ASMT activity ¹⁷
- Two ASMT polymorphisms have been associated with a decrease in ASMT transcripts in blood cell lines in ASD ¹²

+ ASD and Clock-Genes



- 10 clock genes in the body
- Evidence that melatonin plays a major role in the circadian rhythms observed in the expression of several clock genes i.e. Per1 ¹⁷
- In animal models, PER1 expression is undetectable in melatonin deficient mice ¹⁷
- Per1 and NPAS2 single nucleotide polymorphisms have been found in autism ¹²

+ “Hyperaroused State”

- Another hypothesis: synaptic pathway and gene anomalies associated with ASD alter levels of monoaminergic neurotransmitters associated with the wake state ¹⁵
- This arousal dysregulation may be the underlying mechanism of high levels of anxiety, agitation and fears in children with ASD
- Children with ASD may be experiencing a “hyperaroused state” ¹⁵
- Hyperaroused state may impair cognition and produce behaviour symptoms including inattention, hyperactivity, anxiety and panic, and may result in insomnia.





+ Type of Sleep Problems in
ASD

+ Type of Sleep-Wake Disorders



- Circadian rhythm disturbances ⁶
- Behavioural Insomnia Syndromes
 - Sleep onset association type
 - Limit setting type
- REM Sleep Behaviour Disorder
- Daytime Sleepiness



Insomnia in ASD



- Difficulty initiating or maintaining sleep
- Presents as: prolonged sleep latency, bedtime resistance, decreased sleep efficiency, decreased sleep duration and continuity and increased awakening ¹¹
- Multifactorial in origin: ¹¹
 - Neurobiological
 - Medical disorders (GERD, OSA, epilepsy)
 - Psychiatric (depression, anxiety, OCD)
 - Core behavioural deficits of ASD may be contributory (i.e. difficulties with emotional regulation and transitioning)



- 84 children 7-12 years of age (46 with autistic disorder or Aspergers, 38 controls) ⁹
- 78.3% of ASD participants had CSHQ scores >41, compared to 28.9% of the control group ($p < 0.001$)
- At time 2, 65.2% of ASD participants had scores >41 compared to 31.6% of the control ($p = 0.002$)
- Significantly higher levels of difficulty in the following CSHQ subscales: bedtime resistance, sleep onset delay, sleep duration, sleep anxiety, parasomnias, daytime sleepiness



Sleep-related Movement Disorder



- Rhythmical movement disorder: characterized by repetitive motion of the head, trunk or limbs usually during the transition from wakefulness to sleep.
- Restless Leg Syndrome: sensorimotor disorder that involves an urge to move the legs that typically occurs at bedtime, is worse at rest and is relieved by movement.



Relationship between serum ferritin and PLMS



- Children with ASD may be at risk for low ferritin and anemia due to poor diet ¹⁸
- The sleep wake cycle is influenced by the dopamine-opiate system, in which iron is a necessary cofactor
- Iron deficiency may impair dopaminergic function and therefore the sleep wake cycle
- Primary objective of the study was to assess the relationship of serum ferritin levels in children with ASD with or without sleep fragmentation with or without sleep fragmentation or PLMS on PSG ¹⁸



Relationship between serum ferritin and PLMS



- Retrospective cross-sectional chart review of ASD patients seen at Boston's Childrens' Hospital Jan 2000-Dec 2013 ¹⁸
- Children < 21yrs with an ICD-9 diagnosis of ASD who had documented CBC and iron studies (including ferritin) and a PSG within 1 year of the serum ferritin level were included in the study
- An equal number of age and sex matched children without ASD referred for evaluation of various sleep complaints were also included in the study



Relationship between serum ferritin and PLMS



- Only 53 (37 boys and 16 girls) had both PSG data and ferritin data and met all inclusion criteria
- Median ferritin level was 27 ng/mL (60pmol/L) in ASD group vs. 86 ng/mL (196 pmol/L) in the control group ($P < 0.01$)
- Median ferritin level in ASD patients with PLMS did not significantly differ from those without PLMS (26.8 ng/mL)
- Children with poor sleep efficiency had a median serum ferritin of 7ng/mL as compared with 29.1 ng/ml in children with normal sleep efficiency ($P=0.01$)¹⁸

+ Limitations of this study

- children obtaining a PSG had more frequent and severe sleep complaints compared with the ASD and general population
- 37% of patients in this study had obstructive sleep apnea
- Findings only suggest a significant relationship but cannot prove causality between low serum ferritin levels and abnormal PSG findings
- Conclusion: may consider getting ferritin levels in all autistic children and getting them started on oral iron if levels come back $< 50\text{ng/mL}$ (112 pmol/L)¹⁸



+ Effect of poor sleep on ASD
behaviours



Sleep and Daytime Behaviour in ASD



- 1193 children aged 4-10 yrs of age from 14 centres across the U.S. was used to evaluate the relationship between varying levels of sleep problems and daytime behaviour ¹⁴
- Measures: CSHQ, Vineland Adaptive Behaviour Scales, Survey Interview Form 2nd edition, Child Behaviour Checklist ¹⁴
- Participants grouped based on CSHQ scores: ¹⁴
 - < 41 (good sleepers)
 - > or = to 41 (poor sleepers)
 - 41-55 mild sleep problem
 - >56 moderate to severe sleep problem



Sleep and Daytime Behaviour in ASD



- Parents completed a Vineland and Child Behaviour Checklist
- Children with ASDs and sleep problems had higher scores on the CBCL (more behaviour problems) and lower scores on the VABS-II (poorer adaptive functioning) than children with ASDs and no sleep problems ¹⁴
- Relationship between sleep and adaptive behaviour was less robust ¹⁴



+ Assessing your ASD patient
for sleep difficulties

+ History



- how alert and refreshed in the morning⁶
- daytime inattentiveness, mood swings, napping, medications
- activities that are activating 4-6 hours before bedtime
- fluctuation in bedtime environment or routine?
- anxiety and or depression?
- toys and games used around bedtime (exciting/activating influence)
- bedtime and estimated time of sleep onset
- unusual nocturnal behaviours: habitual snoring, seizures, sleep walking, etc.

+ History



- Describe the problem in detail making the distinction between¹⁶:
 - bedtime difficulties (either reluctance to go to bed or difficulty getting to sleep)
 - waking at night and not being able to go back to sleep
 - waking very early
 - other aspects of the child's sleep called poor sleep i.e. frequent nightmares

+ Examination



- Predisposition to sleep apnea:
 - maxillary hypoplasia, retrognathia, macroglossia,
 - adenoid facies, inflammed and edematous turbinates,
 - enlarged tonsils, obesity
- Can consider objective measures: i.e. actigraphy, PSG
- Children's Sleep Habits Questionnaire (4-10 yrs of age)
- Pediatric Daytime Sleepiness Scale (11-15 yrs of age)
- Family Inventory of Sleep Habits (FISH)
- Child Behaviour Checklist



Children's Sleep Habits Questionnaire (CSHQ)



- Used to screen for the most common types of sleep difficulties in 4-12 year old children ⁹
- contains 33 scoring items using a 3 point scale. Has 8 domains:
 - Bedtime resistance (6 items)
 - Sleep onset delay (1 item)
 - Sleep duration (3 items)
 - Sleep anxiety (4 items)
 - Night wakings (3 items)
 - Parasomnias (7 items)
 - Sleep disordered breathing (3 items)
 - Daytime sleepiness (8 items)
- Test-retest reliability range 0.62-0.79
- Total score can be used as a screening device with scores above 41 indicating sleep disturbance (sensitivity of 0.82; specificity of 0.72)



Child Behaviour Checklist



- Checklist completed by parents to detect emotional and behavioural problems and in children and adolescents
- There are two versions on the form, depending on the age of the patient
 - Preschool: 1.5-5 years of age (100 questions)
 - Child/Adolescent: 6-18 years of age (120 questions)
- Use a combination of syndrome scales and DSM-oriented scales



+

Interventions



Parent Based Sleep Education for ASD



- Parents of children with ASD have poorer sleep quality than parents of typically developing children ⁸
- randomized trial of individualized or group parent- based sleep education in 80 children with ASD ⁸
- Primary goals were to determine whether there group vs individualized mode of education would be superior in reducing sleep onset latency, as measured by actigraphy ⁸
- Patients drawn from the Autism Speaks Autism Treatment Network. Screened to identify parents who reported prolonged sleep latency on the CSHQ ⁸



Parent Based Sleep Education for ASD



- Group program → two 2h sessions conducted 1 week apart over 2 weeks with two follow up phone calls ⁸
- Individualized program → one 1h session with two follow up phone calls ⁸
- Asked to collect at least 21 days of continuous sleep data from the actigraphy watch and record a sleep diary ⁸
- 4 weeks post intervention completion, child wore the actigraphy device and sleep diary for an additional 1-2 weeks ⁸



Parent Based Sleep Education for ASD



- Mode of education did not differ in the effects of treatment on sleep parameters or behavioural measures ⁸
- combined mean reduction in sleep latency from 58.2 to 39.2 min with treatment (P <0.0001) ⁸
- Significant improvement from previous similar study using a pamphlet as a means of parental education (mean sleep latency → 56.7 min to 49.5 min in the pamphlet arm and 52.1 to 61.4 min in the no pamphlet arm) ⁸
- Parent sleep education was associated with improved aspects of child behaviour, pediatric quality of life, and parenting sense of competence ⁸

+ Sleep Hygiene



- Daytime Habits: adequate exercise, exposure to light, limiting caffeine and naps ⁵
- Evening Habits: decreasing stimulation, decreasing light, decreasing exposure to electronics ⁵
- Sleep Environment: cool with minimal light and sound, bedding texture ⁵
- Bedtime Routines: a series of bedtime tasks that occur at the same time and place every night ⁵



Sleep Hygiene



- There should be no more than an hour's difference in bedtime and wake up times between the week and the weekend ⁵
- Stimulation can occur in response to: new and unexpected events, anxiety, excessive noise, cold or heat, vigorous exercise, hunger, pain, etc ⁵
- The use of sleep associations that require caregiver participation is discouraged ⁵
- Regular daily routines and structure assist in reinforcing circadian rhythms by serving as time cues ⁵
- Sensory or cognitive overload can result in high levels of stress and anxiety → prolonged brain excitation → delayed sleep phase
- Sleep deprived parent often experiences helplessness, frustration, anxiety, anger and depression ⁵

+ Sleep Hygiene

- Young children with ASD may benefit from a visual schedule or "to-do list" to help remind them of each step. This will help the child to see that his/her bedtime routine will be the same events in the same order each night
- Bloorview Holland Parent Handout on Sleep

<http://www.hollandbloorview.ca/research/autism-research-centre/documents/ATNAIRPPhysicianASDSleepToolkit.Handout.pdf>



CPS on Melatonin



- Melatonin is considered by Health Canada to be a 'natural health product' ²
- No evidence to support the use of melatonin in children < 2 years ²
- Short acting forms are used primarily for problems with sleep initiation, while long acting forms are used for problems of sleep maintenance ²
- The use of melatonin in sleep-onset association type problems has been studied in randomized, double blind placebo controlled trials. School aged children received 5 mg or an identical placebo at 19:00 for 4 weeks. Melatonin improved sleep onset and sleep duration. Sleep latency improved from 60 mins to approx 30 mins ²

+ CPS on Melatonin in ASD



- Double blind crossover, random control trial involving 11 children from 5-15 yrs of age with ASD and sleep onset of at least one hour later than desired time and examined the efficacy of 5 mg of melatonin ²
- Mean sleep latency improved during melatonin treatment from 2.6h at baseline to 1.06h on treatment ²
- Night awakenings improved from a mean baseline of 0.35 to 0.08 ²
- Total sleep improved from a baseline mean of 8.05h to a treatment result of 9.84h ²
- All children completing the trial were continued on melatonin after the study ended at the request of their parents ²

+ Melatonin



■ Benefits:

- Favourable side effect profile
- Inexpensive
- Readily Available

■ Risks:

- Small # of individuals with intellectual disability have had an initial positive response to melatonin that wanes over time

+ Melatonin Meta-Analysis ¹³

- In a systemic review of 35 references on melatonin and ASD, 7 studies reported lower melatonin or melatonin metabolite concentrations in individuals with ASD
- 4 studies reported abnormal melatonin circadian rhythm in ASD compared to controls
- 2 studies reported that daytime melatonin levels were significantly higher in ASD than controls
- 2 studies commented on serotonin in ASD. One found an inverse relationship between platelet serotonin and urinary 6-SM. The other found increased plasma serotonin and depressed plasma melatonin and ASMT activity in ASD

+ Melatonin Meta-Analysis



- 18 studies reported the effects of melatonin treatment on ASD
- Dosage of melatonin ranged from 0.75mg-15mg with rare use of 25 mg
- Length of melatonin usage ranged from 14 days- 4 years
- Percentage improvement in sleep with melatonin ranged from 67-100%
- Two studies that used actigraphy reported sleep improvements of 92-93%

+ Melatonin Meta-Analysis



- Six studies reported that the night-time administration of melatonin led to improvements in daytime behaviour in some children with ASD ¹³
- Improvements included: less behavioural rigidity, ease of management, better social interaction, less irritability, etc. ¹³
- Meta-analysis of 5 randomized, double-blind, placebo controlled, cross-over studies demonstrated an overall significant improvement in sleep duration and sleep onset latency, but no overall improvement in the number of night time awakenings ¹³

+ Light Therapy



- 14 children ages 9 months-4 years with moderate to severe mental retardation and severe nocturnal sleep disturbances ⁴
- All children had previously been given medications and behavioural treatments with no effect ⁴
- Underwent intensive light therapy regimen ⁴
- 5 children responded to tx and had normal sleep wake patterns ⁴
- 2 children unable to keep up with regimen ⁴
- Treatment failed in 7 children ⁴



Conclusions



- Relationship between sleep and ASD is multifactorial and most likely bi-directional
- Sleep Hygiene and Parent Education are beneficial interventions
- Melatonin may be of use in patients with abnormal circadian rhythms or low melatonin levels
- May consider iron supplementation in patients' with low ferritin
- Be sure to rule out underlying medical pathologies i.e. OSA, GERD, pain, etc

+ Thank you



■ Questions?



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