SLEEP PROBLEMS AND URINARY 6-SULFATOXYMELATONIN AS POSSIBLE PREDICTORS OF SYMPTOM SEVERITY IN CHILDREN WITH AUTISM SPECTRUM DISORDER: A REVIEW ARTICLE

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Abstract

Abstract: Autism spectrum disorder (ASD) is a heterogeneous neurodevelopmental disorder characterized by difficulties in social communication and interaction, together with restricted and repetitive patterns of behavior. Sleep disturbances are highly prevalent in children with ASD and may include difficulty initiating or maintaining sleep, nocturnal awakenings, reduced sleep duration, and daytime sleepiness. These problems may negatively affect behavior, adaptive functioning, and overall symptom severity. Melatonin, a key regulator of circadian sleep–wake rhythms, has also been reported to show altered secretion in some children with ASD. Urinary 6-sulfatoxymelatonin (6-SM; aMT6s), the principal metabolite of melatonin, provides a non-invasive measure of endogenous melatonin secretion and may reflect circadian dysfunction. Evidence suggests that sleep disturbances are associated with greater social-communication impairment, restricted and repetitive behaviors, challenging behaviors, and poorer adaptive functioning. Altered melatonin secretion, particularly lower urinary aMT6s levels, has also been associated with sleep disturbances and greater impairment in verbal communication, social skills, and stereotyped behaviors. These findings suggest a possible relationship between sleep disturbance, circadian dysregulation, and ASD symptom severity. However, current evidence is mainly associative and does not establish causality. Further prospective studies are needed to clarify whether urinary 6-SM has independent predictive value and potential clinical relevance. Therefore, this literature review aimed to examine the relationship between sleep problems, urinary 6-SM levels, and symptom severity in children with ASD, and to explore the potential role of urinary 6-SM as a biological marker of symptom severity.

Keywords: Autism Spectrum Disorder, Sleep Problems, Urinary 6-Sulfatoxymelatonin, Melatonin, Symptom Severity.

1. Autism Spectrum Disorder

1.1 Overview and Clinical Characteristics

Autism spectrum disorder (**ASD)** is a neurodevelopmental disorder characterized by persistent difficulties in social communication and interaction together with restricted, repetitive patterns of behavior, interests, or activities. Symptoms begin early in development, although their recognition may be delayed, and their severity varies substantially among affected children **(Lord et al., 2018)**. ASD is clinically heterogeneous, and children may differ considerably in language, cognitive ability, adaptive functioning, sensory processing, and behavioral manifestations. This heterogeneity is important when examining factors that may modify symptom severity, including sleep and circadian regulation.

Current diagnosis is clinical and is based primarily on developmental history and behavioral assessment using established diagnostic criteria. There is no laboratory biomarker that can currently confirm ASD in routine practice; therefore, biological measures such as melatonin-related markers remain investigational rather than diagnostic (**Lord et al., 2020)**.

1.2 Epidemiology and Heterogeneity

The burden of ASD has increased substantially in surveillance studies. In the United States, the estimated prevalence among 8-year-old children increased from 6.7 per 1,000 in 2000 to 16.8 per 1,000 in 2014, representing an increase of more than 150% (**Baio, 2018)**. Parent-reported national survey data have also suggested that approximately 2–3% of children aged 3–17 years had a current or previous ASD diagnosis (**Kogan et al., 2018)**. ASD is reported more frequently in boys than girls, although differences in recognition and clinical presentation may contribute to the observed sex disparity (**Robinson et al., 2013)**.

1.3 Etiology and Biological Basis

ASD has a multifactorial etiology involving complex interactions between genetic susceptibility and environmental influences. Genetic studies demonstrate substantial heritability, while prenatal and perinatal factors may modify risk. High-confidence ASD-associated genes include those involved in synaptic development, neuronal signaling, protein synthesis, and chromatin regulation, supporting the concept of ASD as a disorder of neurodevelopment and synaptic function (**Satterstrom et al., 2020; Sauer et al., 2021)**.

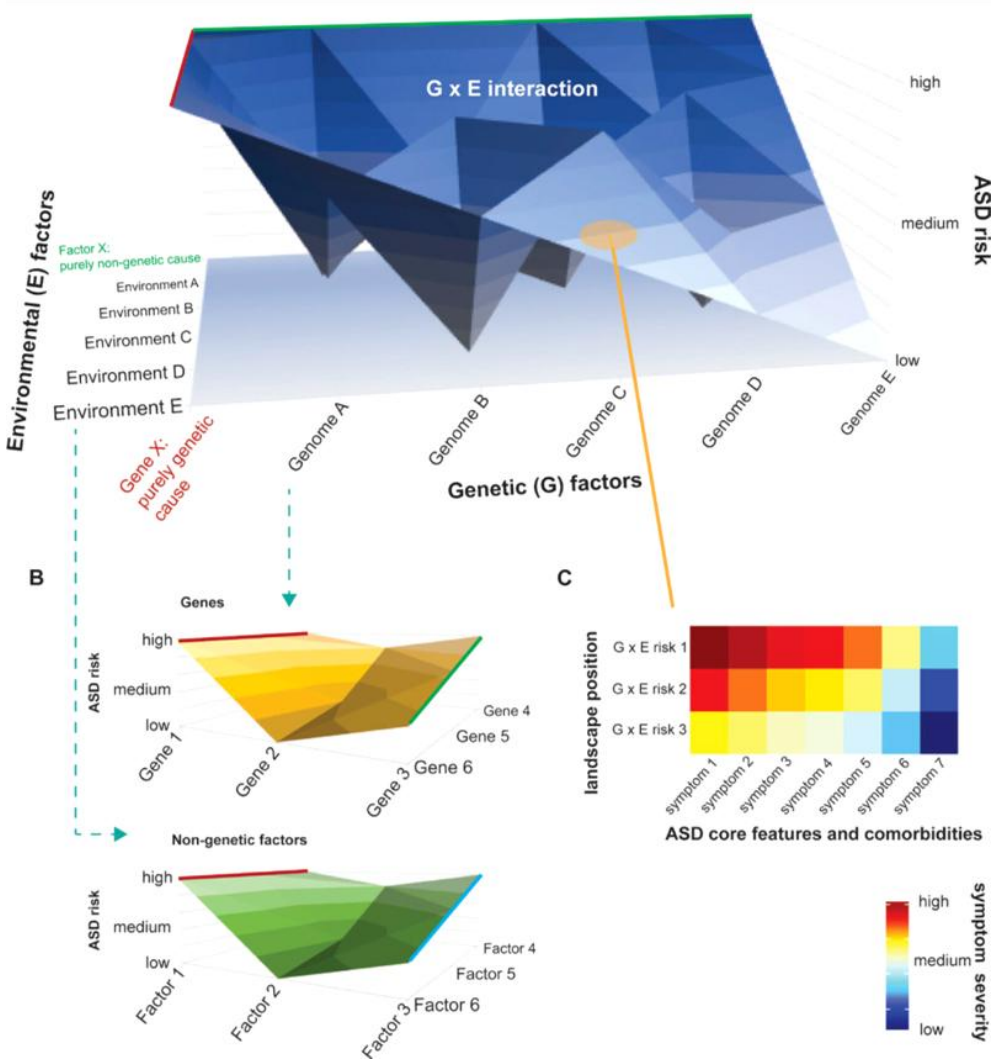

Figure 1: Model for the multifactorial etiology of ASD, illustrating interactions between genetic and environmental factors and their contribution to symptom severity and comorbidities (**Sauer et al., 2021)**.

1.4 Symptom Severity and Functional Consequences

The core manifestations of ASD include social-communication impairment and restricted or repetitive behaviors. Their expression ranges from mild to severe, and symptom burden may be accompanied by anxiety, attention problems, sensory abnormalities, gastrointestinal symptoms, and sleep disturbance. These associated problems can further impair adaptive functioning and may contribute to clinically important differences in overall severity (**Tsai et al., 2020)**. Because sleep disturbance and circadian abnormalities are potentially modifiable, their relationship with ASD severity has become an important area of research.

2. Sleep Problems in Children with Autism Spectrum Disorder

2.1 Prevalence and Clinical Importance

Sleep disturbance is one of the most frequent comorbid problems in children with ASD. Parent-reported studies estimate that approximately 40–80% of children with ASD experience sleep problems, compared with about 25–40% of typically developing children (**Baio et al., 2018)**. Other studies have reported sleep disorders in approximately 67–89% of children with ASD, including shortened sleep duration, prolonged sleep-onset latency, reduced sleep efficiency, frequent nocturnal awakenings, sleep-disordered breathing, and daytime sleepiness (**Goldman et al., 2017)**.

Sleep is essential for attention, memory consolidation, emotional regulation, and daytime functioning. Consequently, persistent sleep disturbance in ASD may have effects extending beyond nighttime sleep, potentially aggravating behavioral and adaptive difficulties. The relationship is unlikely to be purely unidirectional; autism-related behavioral and sensory characteristics may predispose to poor sleep, while poor sleep may subsequently intensify daytime symptoms (**Hollway & Aman, 2011; Verhoeff et al., 2018)**.

2.2 Common Sleep Problems

The most consistently reported problems are sleep-onset insomnia and nocturnal awakening. In a study using the Children's Sleep Habits Questionnaire, insomnia was reported in 56.3% of children with ASD, bedtime resistance in 73.9%, and daytime sleepiness in 39.6%; insomnia commonly involved nighttime awakening and reduced sleep duration (**Köse et al., 2017)**. Difficulties initiating or maintaining sleep may manifest as prolonged sleep latency, resistance to bedtime, co-sleeping, repeated night waking, early morning awakening, and daytime sleepiness (**Abel et al., 2017)**.

Nocturnal awakening may be prolonged, sometimes lasting 30 minutes to 2–3 hours, and may involve talking, laughing, crying, screaming, getting out of bed, or engaging in repetitive play. Such awakenings can reduce total sleep duration and contribute to daytime sleepiness and behavioral dysregulation (**Reynolds et al., 2019)**. Other reported disturbances include parasomnias, restless legs or periodic limb movements, bruxism, stereotypic movements, and sleep-disordered breathing (**Reynolds et al., 2019)**.

In a study of 112 children with ASD and 112 healthy controls aged 2–18 years, the total Children's Sleep Habits Questionnaire score, bedtime-resistance score, and sleep-anxiety score were significantly higher in children with ASD. Night waking, parasomnias, and sleep-disordered breathing were also more frequent, although these differences were not statistically significant (**Gunes et al., 2019)**.

2.3 Factors Contributing to Sleep Disturbance

Sleep problems in ASD are probably multifactorial. Proposed contributors include intrinsic neurobiological abnormalities, behavioral characteristics associated with core ASD symptoms, sensory hypersensitivity, anxiety, and environmental or family factors (**Hollway & Aman, 2011)**. Co-sleeping, family history of sleep problems, difficulties responding to social cues related to bedtime,

and sensitivity to environmental stimuli may further disrupt the development of a stable sleep–wake pattern (**Verhoeff et al., 2018)**.

Sensory abnormalities are particularly relevant. Repetitive sensory-motor behavior has been associated with parent-reported sleep problems, while sensory over-responsivity in young children with ASD has been identified as a longitudinal predictor of sleep-onset delay and shorter sleep duration (**Adams et al., 2014; Mazurek et al., 2019)**. These findings support the concept that behavioral and sensory features may interact with biological circadian abnormalities to produce persistent sleep disturbance.

3. Relationship Between Sleep Problems and ASD Symptom Severity

3.1 Sleep Disturbance and Core ASD Symptoms

A substantial body of evidence indicates that sleep problems are associated with greater ASD symptom severity. Shorter sleep duration has been associated with poorer social functioning and greater overall symptom burden. In a large sample of 2,714 children with ASD, greater severity of core symptoms was associated with shorter sleep duration, and more severe social impairment remained associated with shorter sleep after adjustment for age and IQ (**Veatch et al., 2017)**.

Sleep-onset delay appears particularly important. Tudor et al. reported positive relationships between sleep-onset delay, sleep duration, autism symptoms, and overall autism severity; notably, sleep-onset delay was the strongest sleep-related predictor of communication deficits, stereotyped behavior, and overall autism severity (**Tudor et al., 2012)**. Earlier work also found that parent-rated autism severity, hyperactivity, mood variability, and aggression were among the strongest predictors of sleep disturbance (**Mayes & Calhoun, 2009)**.

3.2 Restricted and Repetitive Behaviors

Restricted and repetitive behaviors (**RRBs)** include repetitive movements or language, restricted interests, ritualized routines, sensory-seeking behaviors, and sensory aversions. RRBs have been associated with bedtime resistance, insomnia, and short sleep duration (**Abel et al., 2018)**. Repetitive sensory-motor behaviors may predict sleep problems even after accounting for anxiety, whereas insistence on sameness has shown less consistent associations (**Adams et al., 2014)**.

The association may be bidirectional. Severe RRBs and sensory dysregulation can make bedtime routines difficult, while inadequate or fragmented sleep may increase daytime self-stimulatory behavior, hyperactivity, anxiety, and other maladaptive behaviors. Thus, sleep disturbance may act as an amplifier of an already vulnerable behavioral system rather than as an isolated comorbidity (**Mazurek et al., 2019)**.

3.3 Social Communication and Adaptive Functioning

Sleep disturbance is also related to social-communication impairment. Adolescents with ASD and sleep problems have shown greater impairment in social communication and interaction, while shorter sleep duration has been associated with poorer social skills (**Thenhausen et al., 2017; Veatch et al., 2017)**. In addition, daytime sleepiness and sleep–wake difficulties have been associated with poorer peer relationships in adolescents with ASD (**Phung & Goldberg, 2017)**.

Sleep duration is also associated with adaptive functioning. Children who sleep fewer hours have been reported to have poorer overall adaptive functioning, communication, daily living, socialization, and motor skills (**Taylor et al., 2012)**. In children aged 4–10 years, moderate-to-severe sleep problems were associated with lower motor and daily-living-skill scores compared with better sleepers, supporting a clinically meaningful relationship between sleep disturbance and functional impairment (**Sikora et al., 2012)**.

3.4 Challenging Behavior

Poor sleep is associated with both internalizing and externalizing behaviors. Preschool children with ASD and insomnia have shown more behavioral problems, while children with sleep disturbance may exhibit increased anxiety, anger, withdrawal, inattention, self-injurious behavior, aggression, noncompliance, and hyperactivity (**Hirata et al., 2016; Abel et al., 2018**). In one study, the total Children's Sleep Habits Questionnaire score and duration of nighttime wakefulness together explained approximately 30% of the variance in daytime behavioral problems (**Malhi et al., 2018**).

3.5 Direction of the Association

Current evidence does not establish a simple causal direction between sleep disturbance and ASD symptoms. Behavioral problems may predict subsequent sleep difficulties, while poor sleep may worsen later behavioral and neurodevelopmental outcomes. Aggressive behavior at baseline, for example, has been reported to predict poor sleep at follow-up, whereas baseline sleep problems have predicted later attention problems and somatic complaints (**Shui et al., 2018; Mazurek et al., 2019**). Overall, the available evidence favors a bidirectional, self-reinforcing relationship in which ASD-related behavioral and sensory characteristics increase vulnerability to poor sleep, and persistent sleep disturbance subsequently aggravates symptom severity and daytime functioning (**Verhoeff et al., 2018**).

4. Melatonin and Circadian Regulation of Sleep

4.1 Physiology of Melatonin

Melatonin is an indoleamine hormone produced predominantly by the pineal gland and is a major regulator of the sleep–wake cycle. Its secretion follows a strong circadian rhythm controlled by the suprachiasmatic nucleus and the light–dark cycle. In healthy individuals, circulating melatonin rises during the evening and night, commonly reaching approximately 60–200 pg/mL between 2 and 4 a.m., and falls to about 0–20 pg/mL during the day (**Sae-Teaw et al., 2013**).

Melatonin is synthesized from tryptophan through serotonin and N-acetylserotonin, with arylalkylamine N-acetyltransferase (**AANAT**) and acetylserotonin O-methyltransferase (**ASMT**) as key enzymes. Light, particularly blue-spectrum light, suppresses melatonin synthesis through effects on the circadian system (**Maronde & Stehle, 2007**).

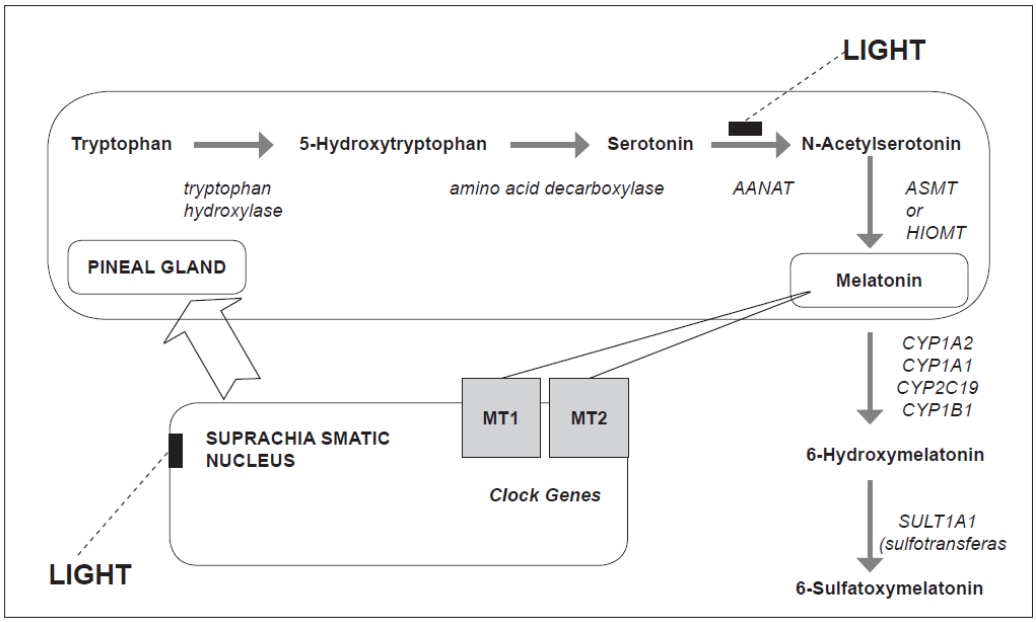

Figure 2: Melatonin synthesis and metabolism. Melatonin is synthesized in the pineal gland and is metabolized mainly through CYP1A2-dependent hydroxylation followed by sulfation, producing 6-sulfatoxymelatonin, which is excreted in urine (**Amaral & Cipolla-Neto, 2018**).

4.2 Melatonin and ASD

Increasing evidence suggests that melatonin production and circadian regulation are altered in a proportion of children with ASD. Reduced nocturnal melatonin concentrations, altered day–night secretion patterns, and abnormalities in melatonin synthesis have been reported, providing a potential biological link between circadian dysregulation and sleep problems in ASD (**Geoffray et al., 2016; Carmassi et al., 2019)**.

Melke et al. demonstrated abnormal melatonin synthesis in ASD and suggested that reduced melatonin availability may contribute to sleep and circadian abnormalities (**Melke et al., 2008)**. Differences in melatonin synthesis also appear to have a genetic component. In children with ASD and sleep-onset delay, variation in genes involved in melatonin synthesis and metabolism, particularly ASMT and CYP1A2, has been associated with sleep-related phenotypes (**Veatch et al., 2017)**.

4.3 Melatonin Abnormalities and Symptom Severity

The relationship between melatonin and ASD may extend beyond sleep. Serum melatonin concentrations have been reported to correlate inversely with autism severity, with lower levels associated with more severe symptoms and greater risk of insomnia (**Tordjman et al., 2013)**. Studies of families of children with ASD have also identified differences in melatonin synthesis, supporting a possible heritable component to melatonin dysregulation (**Benabou et al., 2017; Braam et al., 2018)**.

The serotonin–N-acetylserotonin–melatonin pathway has therefore been proposed as a candidate biological pathway in ASD. However, melatonin is not currently an established diagnostic biomarker for ASD, and the available evidence supports its role as a promising research marker rather than a clinically validated diagnostic test (**Pagan et al., 2014; Shen et al., 2020)**.

5. Urinary 6-Sulfatoxymelatonin as a Biomarker of Melatonin Secretion

5.1 Biological Basis

6-Sulfatoxymelatonin (**6-SM; also termed aMT6s)** is the principal urinary metabolite of melatonin. Circulating melatonin is metabolized mainly in the liver through CYP1A2-mediated hydroxylation to 6-hydroxymelatonin, followed by sulfation and urinary excretion as 6-SM. Because urinary aMT6s reflects melatonin production during the preceding collection interval, it can be used as a practical indirect measure of endogenous melatonin secretion (**Amaral & Cipolla-Neto, 2018; Abeysuriya et al., 2018)**.

Unlike serum melatonin, which has a short half-life and marked circadian variation, urinary aMT6s can be measured over defined intervals and may provide information about the magnitude and timing of melatonin secretion. Overnight urinary aMT6s can be assessed from the first morning urine and compared with daytime urinary fractions to characterize the day–night rhythm (**Rzepka-Migut & Paprocka, 2020)**.

5.2 Measurement and Interpretation

Urinary aMT6s concentrations are normally low during the daytime and increase at night, reflecting the physiological rise in melatonin secretion (**Ba-Ali et al., 2019)**. Interpretation should account for factors that influence melatonin production or metabolism, including age, exposure to light, season, physical activity, comorbidities, and medications or supplements that affect melatonin pathways. Exogenous melatonin is particularly important because it can interfere with interpretation of endogenous secretion (**Rzepka-Migut & Paprocka, 2020)**.

Because renal excretion is involved in clearance of 6-SM, renal function should also be considered when interpreting urinary measurements. Standardized timing and collection procedures are therefore essential when using urinary aMT6s as a potential biomarker of circadian function.

6. Relationship Between Urinary 6-Sulfatoxymelatonin, Sleep Problems, and ASD Severity

6.1 Urinary aMT6s and Sleep Disturbance

The strongest rationale for studying urinary aMT6s in ASD arises from the observed relationship between melatonin secretion and sleep architecture. In children with ASD, lower overnight urinary aMT6s has been associated with altered sleep parameters. Leu et al. reported that lower overnight 6-SM levels were related to daytime sleepiness, while abnormalities in sleep initiation and maintenance have been associated with nocturnal urinary aMT6s excretion (**Leu et al., 2011; da Silveira Cruz-Machado et al., 2021)**.

These findings suggest that urinary aMT6s may provide an objective biological correlate of the sleep disturbance that is otherwise assessed primarily through parental reports or sleep questionnaires. This is particularly relevant in children with ASD, in whom communication difficulties may make subjective assessment of sleep symptoms challenging.

6.2 Urinary aMT6s and ASD Symptom Severity

The most directly relevant evidence comes from Bartakovicova et al. (**2022)**, who examined sleep problems and urinary aMT6s in children with ASD. Lower diurnal and nocturnal urinary aMT6s concentrations were associated with more severe impairments in verbal communication, social skills, and stereotyped behavior (**Bartakovicova et al., 2022)**. These findings are highly relevant to the proposed concept that urinary aMT6s may help identify children with greater symptom burden.

The biological interpretation is plausible because reduced melatonin availability may contribute to circadian instability and fragmented sleep, while chronic sleep disruption may adversely affect attention, emotional regulation, social responsiveness, and repetitive behavior. The resulting interaction may create a reinforcing cycle in which circadian dysregulation and sleep problems contribute to greater daytime symptom expression (**Carmassi et al., 2019)**.

Importantly, the available evidence supports an association rather than proof that low urinary aMT6s causes greater ASD severity. Urinary aMT6s should therefore be considered a possible predictor or biological correlate of symptom severity rather than a definitive diagnostic or prognostic biomarker. Larger prospective studies are needed to determine whether baseline urinary aMT6s independently predicts subsequent changes in ASD symptoms after accounting for age, sex, intellectual ability, medication use, sleep disturbance, and other relevant confounders.

6.3 Integrated Relationship Between Sleep, 6-SM, and ASD Symptoms

Taken together, the literature supports a clinically relevant model linking ASD, sleep disturbance, melatonin dysregulation, and symptom severity. Children with ASD frequently experience insomnia, bedtime resistance, nocturnal awakening, reduced sleep duration, and daytime sleepiness. These disturbances are associated with greater social-communication impairment, repetitive behavior, challenging behavior, and poorer adaptive functioning (**Köse et al., 2017; Veatch et al., 2017; Taylor et al., 2012)**.

At the biological level, melatonin secretion is frequently altered in ASD, and reduced or dysregulated melatonin production may contribute to abnormal circadian timing. Urinary aMT6s provides a non-invasive measure of melatonin output and has the advantage of reflecting cumulative secretion over a collection period. The observation that lower urinary aMT6s is associated with more severe verbal, social, and stereotyped symptoms provides a specific rationale for investigating 6-SM alongside standardized measures of sleep and ASD severity (**Bartakovicova et al., 2022)**.

Accordingly, sleep problems and urinary aMT6s may represent complementary predictors: sleep measures capture the clinical expression of circadian and behavioral disturbance, whereas urinary aMT6s provides an objective biological measure of melatonin secretion. Studying both variables together may clarify whether the severity of sleep disturbance and the degree of melatonin dysregulation independently or jointly explain variation in ASD symptom severity.

7. Conclusion

Sleep problems are common in children with ASD and are associated with greater symptom severity and functional difficulties. Altered melatonin secretion and lower urinary aMT6s may contribute to this relationship. Urinary aMT6s shows promise as a non-invasive research marker of circadian dysfunction and ASD severity, but further prospective studies are required to confirm its predictive value.

References

1. **Abel, E. A., Schwichtenberg, A. J., Brodhead, M. T., & Christ, S. L. (2018).** Sleep and challenging behaviors in the context of intensive behavioral intervention for children with autism. Journal of Autism and Developmental Disorders, 48(11), 3871–3884. https://doi.org/10.1007/s10803-018-3648-0
2. **Abel, E., Kim, S. Y., Kellerman, A. M., & Brodhead, M. T. (2017).** Recommendations for identifying sleep problems and treatment resources for children with autism spectrum disorder. Behavior Analysis in Practice, 10(3), 261–269. https://doi.org/10.1007/s40617-016-0158-4
3. **Abeysuriya, R. G., Lockley, S. W., Robinson, P. A., & Postnova, S. (2018).** A unified model of melatonin, 6-sulfatoxymelatonin, and sleep dynamics. Journal of Pineal Research, 64(4), e12474. https://doi.org/10.1111/jpi.12474
4. **Adams, H. L., Matson, J. L., & Jang, J. (2014).** The relationship between sleep problems and challenging behavior among children and adolescents with autism spectrum disorder. Research in Autism Spectrum Disorders, 8(9), 1024–1030. https://doi.org/10.1016/j.rasd.2014.05.008
5. **Amaral, F. G. D., & Cipolla-Neto, J. (2018).** A brief review about melatonin, a pineal hormone. Archives of Endocrinology and Metabolism, 62(4), 472–479. https://doi.org/10.20945/2359-3997000000066
6. **Ba-Ali, S., Brøndsted, A. E., Andersen, H. U., Sander, B., Jennum, P. J., & Lund-Andersen, H. (2019).** Assessment of diurnal melatonin, cortisol, activity, and sleep–wake cycle in patients with and without diabetic retinopathy. Sleep Medicine, 54, 35–42. https://doi.org/10.1016/j.sleep.2018.10.018
7. **Baio, J. (2018).** Prevalence of autism spectrum disorder among children aged 8 years—Autism and Developmental Disabilities Monitoring Network, 11 sites, United States, 2014. MMWR Surveillance Summaries, 67(6), 1–23. https://doi.org/10.15585/mmwr.ss6706a1
8. **Bartakovicova, K., Kemenyova, P., Belica, I., Janik Szapuova, Z., Stebelova, K., Waczulikova, I., et al. (2022).** Sleep problems and 6-sulfatoxymelatonin as possible predictors of symptom severity, adaptive and maladaptive behavior in children with autism spectrum disorder. International Journal of Environmental Research and Public Health, 19(13), 7594. https://doi.org/10.3390/ijerph19137594
9. **Benabou, M., Rolland, T., Leblond, C. S., Millot, G. A., Huguet, G., Delorme, R., et al. (2017).** Heritability of the melatonin synthesis variability in autism spectrum disorders. Scientific Reports, 7(1), 17746. https://doi.org/10.1038/s41598-017-18016-3
10. **Braam, W., Ehrhart, F., Maas, A. P., Smits, M. G., & Curfs, L. (2018).** Low maternal melatonin level increases autism spectrum disorder risk in children. Research in Developmental Disabilities, 82, 79–89. https://doi.org/10.1016/j.ridd.2018.02.017
11. **Carmassi, C., Palagini, L., Caruso, D., Masci, I., Nobili, L., Vita, A., et al. (2019).** Systematic review of sleep disturbances and circadian sleep desynchronization in autism spectrum disorder: Toward an integrative model of a self-reinforcing loop. Frontiers in Psychiatry, 10, 366. https://doi.org/10.3389/fpsyt.2019.00366
12. **da Silveira Cruz-Machado, S., Guissoni Campos, L. M., Fadini, C. C., Anderson, G., Markus, R. P., & Pinato, L. (2021).** Disrupted nocturnal melatonin in autism: Association with tumor necrosis factor and sleep disturbances. Journal of Pineal Research, 70(3), e12715. https://doi.org/10.1111/jpi.12715

13. **Geoffray, M. M., Nicolas, A., Speranza, M., & Georgieff, N. (2016).** Are circadian rhythms new pathways to understand Autism Spectrum Disorder? Journal of Physiology-Paris, 110(4), 434–438. https://doi.org/10.1016/j.jphysparis.2017.06.002
14. **Goldman, S. E., Alder, M. L., Burgess, H. J., Corbett, B. A., Hundley, R., Wofford, D., et al. (2017).** Characterizing sleep in adolescents and adults with autism spectrum disorders. Journal of Autism and Developmental Disorders, 47, 1682–1695. https://doi.org/10.1007/s10803-017-3089-1
15. **Gunes, S., Ekinci, O., Feyzioglu, A., Ekinci, N., & Kalinli, M. (2019).** Sleep problems in children with autism spectrum disorder: Clinical correlates and the impact of attention deficit hyperactivity disorder. Neuropsychiatric Disease and Treatment, 15, 763–771. https://doi.org/10.2147/NDT.S195738
16. **Hirata, I., Mohri, I., Kato-Nishimura, K., Tachibana, M., Kuwada, A., Kagitani-Shimono, K., et al. (2016).** Sleep problems are more frequent and associated with problematic behaviors in preschoolers with autism spectrum disorder. Research in Developmental Disabilities, 49–50, 86–99. https://doi.org/10.1016/j.ridd.2015.11.002
17. **Hollway, J. A., & Aman, M. G. (2011).** Sleep correlates of pervasive developmental disorders: A review of the literature. Research in Developmental Disabilities, 32(5), 1399–1421. https://doi.org/10.1016/j.ridd.2011.04.001
18. **Kogan, M. D., Vladutiu, C. J., Schieve, L. A., Ghandour, R. M., Blumberg, S. J., Zablotsky, B., et al. (2018).** The prevalence of parent-reported autism spectrum disorder among US children. Pediatrics, 142(6), e20174161. https://doi.org/10.1542/peds.2017-4161
19. **Köse, S., Yılmaz, H., Ocakoğlu, F. T., & Özbaran, N. B. (2017).** Sleep problems in children with autism spectrum disorder and intellectual disability without autism spectrum disorder. Sleep Medicine, 40, 69–77. https://doi.org/10.1016/j.sleep.2017.09.021
20. **Leu, R. M., Beyderman, L., Botzolakis, E. J., Surdyka, K., Wang, L., & Malow, B. A. (2011).** Relation of melatonin to sleep architecture in children with autism. Journal of Autism and Developmental Disorders, 41, 427–433. https://doi.org/10.1007/s10803-010-1072-1
21. **Lord, C., Brugha, T. S., Charman, T., Cusack, J., Dumas, G., Frazier, T., et al. (2020).** Autism spectrum disorder. Nature Reviews Disease Primers, 6, 5. https://doi.org/10.1038/s41572-019-0138-4
22. **Lord, C., Elsabbagh, M., Baird, G., & Veenstra-Vanderweele, J. (2018).** Autism spectrum disorder. The Lancet, 392(10146), 508–520. https://doi.org/10.1016/S0140-6736(18)31129-2
23. **Malhi, P., Kaur, A., Singhi, P., & Sankhyan, N. (2019).** Sleep dysfunction and behavioral daytime problems in children with autism spectrum disorders: A comparative study. The Indian Journal of Pediatrics, 86(1), 12–17. https://doi.org/10.1007/s12098-018-2731-z
24. **Maronde, E., & Stehle, J. H. (2007).** The mammalian pineal gland: Known facts, unknown facets. Trends in Endocrinology & Metabolism, 18(4), 142–149. https://doi.org/10.1016/j.tem.2007.03.001
25. **Mayes, S. D., & Calhoun, S. L. (2009).** Variables influencing sleep problems in children and adolescents with autism. Research in Autism Spectrum Disorders, 3(4), 931–941. https://doi.org/10.1016/j.rasd.2009.04.002
26. **Mazurek, M. O., Dovgan, K., Neumeyer, A. M., & Malow, B. A. (2019).** Course and predictors of sleep and co-occurring problems in children with autism spectrum disorder. Journal of Autism and Developmental Disorders, 49(5), 2101–2115. https://doi.org/10.1007/s10803-019-03894-5
27. **Melke, J., Goubran Botros, H., Chaste, P., Betancur, C., Nygren, G., Anckarsäter, H., et al. (2008).** Abnormal melatonin synthesis in autism spectrum disorders. Molecular Psychiatry, 13(1), 90–98. https://doi.org/10.1038/sj.mp.4002016
28. **Pagan, C., Delorme, R., Callebert, J., Goubran-Botros, H., Amsellem, F., Drouot, X., et al. (2014).** The serotonin-N-acetylserotonin–melatonin pathway as a biomarker for autism spectrum disorders. Translational Psychiatry, 4(11), e479. https://doi.org/10.1038/tp.2014.120

29. **Phung, J. N., & Goldberg, W. A. (2017).** Poor sleep quality is associated with discordant peer relationships among adolescents with autism spectrum disorder. Research in Autism Spectrum Disorders, 34, 10–18. https://doi.org/10.1016/j.rasd.2016.11.008
30. **Reynolds, A. M., Soke, G. N., Sabourin, K. R., Hepburn, S., Katz, T., Wiggins, L. D., et al. (2019).** Sleep problems in 2- to 5-year-olds with autism spectrum disorder and other developmental delays. Pediatrics, 143(3), e20180492. https://doi.org/10.1542/peds.2018-0492
31. **Robinson, E. B., Lichtenstein, P., Anckarsäter, H., Happé, F., & Ronald, A. (2013).** Examining and interpreting the female protective effect against autistic behavior. Proceedings of the National Academy of Sciences, 110(13), 5258–5262. https://doi.org/10.1073/pnas.1211070110
32. **Rzepka-Migut, B., & Paprocka, J. (2020).** Melatonin—Measurement methods and the factors modifying the results: A systematic review of the literature. International Journal of Environmental Research and Public Health, 17(6), 1916. https://doi.org/10.3390/ijerph17061916
33. **Sae-Teaw, M., Johns, J., Johns, N. P., & Subongkot, S. (2013).** Serum melatonin levels and antioxidant capacities after consumption of pineapple, orange, or banana by healthy male volunteers. Journal of Pineal Research, 55(1), 58–64. https://doi.org/10.1111/jpi.12025
34. **Satterstrom, F. K., Kosmicki, J. A., Wang, J., Breen, M. S., De Rubeis, S., An, J. Y., et al. (2020).** Large-scale exome sequencing study implicates both developmental and functional changes in the neurobiology of autism. Cell, 180(3), 568–584.e23. https://doi.org/10.1016/j.cell.2019.12.036
35. **Sauer, A. K., Stanton, J., Hans, S., & Grabrucker, A. M. (2021).** Autism spectrum disorders: Etiology and pathology. In Autism Spectrum Disorders, Exon Publications, 1–15. https://doi.org/10.36255/exonpublications.autismspectrumdisorders.2021.etiology
36. **Shen, L., Liu, X., Zhang, H., Lin, J., Feng, C., & Iqbal, J. (2020).** Biomarkers in autism spectrum disorders: Current progress. Clinica Chimica Acta, 502, 41–54. https://doi.org/10.1016/j.cca.2019.12.009
37. **Shui, A. M., Katz, T., Malow, B. A., & Mazurek, M. O. (2018).** Predicting sleep problems in children with autism spectrum disorders. Research in Developmental Disabilities, 83, 270–279. https://doi.org/10.1016/j.ridd.2018.10.002
38. **Sikora, D. M., Johnson, K., Clemons, T., & Katz, T. (2012).** The relationship between sleep problems and daytime behavior in children of different ages with autism spectrum disorders. Pediatrics, 130(Suppl 2), S83–S90. https://doi.org/10.1542/peds.2012-0900F
39. **Taylor, M. A., Schreck, K. A., & Mulick, J. A. (2012).** Sleep disruption as a correlate to cognitive and adaptive behavior problems in autism spectrum disorders. Research in Developmental Disabilities, 33(5), 1408–1417. https://doi.org/10.1016/j.ridd.2012.03.013
40. **Thenhausen, N., Kuss, M., Wiater, A., & Schlarb, A. A. (2017).** Sleep problems in adolescents with Asperger syndrome or high-functioning autism. Somnologie, 21(S1), 28–36. https://doi.org/10.1007/s11818-016-0078-0
41. **Tordjman, S., Najjar, I., Bellissant, E., Anderson, G. M., Barburoth, M., Cohen, D., et al. (2013).** Advances in the research of melatonin in autism spectrum disorders: Literature review and new perspectives. International Journal of Molecular Sciences, 14(10), 20508–20542. https://doi.org/10.3390/ijms141020508
42. **Tsai, C. H., Chen, K. L., Li, H. J., Chen, K. H., Hsu, C. W., Lu, C. H., et al. (2020).** The symptoms of autism including social communication deficits and repetitive and restricted behaviors are associated with different emotional and behavioral problems. Scientific Reports, 10, 20509. https://doi.org/10.1038/s41598-020-76292-y
43. **Tudor, M. E., Hoffman, C. D., & Sweeney, D. P. (2012).** Children with autism: Sleep problems and symptom severity. Focus on Autism and Other Developmental Disabilities, 27(4), 254–262. https://doi.org/10.1177/1088357612457989

44. **Veatch, O. J., Sutcliffe, J. S., Warren, Z. E., Keenan, B. T., Potter, M. H., & Malow, B. A. (2017).** Shorter sleep duration is associated with social impairment and comorbidities in ASD. Autism Research, 10(7), 1221–1238. https://doi.org/10.1002/aur.1765
45. **Verhoeff, M. E., Blanken, L. M. E., Kocevska, D., Mileva-Seitz, V. R., Jaddoe, V. W. V., White, T., et al. (2018).** The bidirectional association between sleep problems and autism spectrum disorder: A population-based cohort study. Molecular Autism, 9, 8. https://doi.org/10.1186/s13229-018-0194-8