Physiology of sleep disturbances in ASD and naturopathic treatment strategies

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Introduction

In recent years the emerging study of sleep science has established that sleep is one of the cornerstones of health in adults and children. Poor sleep quality and quantity can have deleterious effects on child development in the following areas: physical growth, immune function, cognitive development, behavior, emotional regulation, attention, memory, learning, speech and language development, and sensory integration. Poor sleep predisposes adults to myriad negative health outcomes as well, such as depression, hypertension, type 2 diabetes, asthma, allergy, and cardiovascular disease.[1] Sleep problems are reported in up to 80% of children and up to 50% of adults with Autism Spectrum Disorders (ASD) making this an issue that affects the ASD population and their caregivers across the lifespan.[2] The author of the main manuscript conducted a small study, which revealed that improvement in sleep quality and quantity has positive outcomes for both patient and caregiver. The purpose of this paper is to review common causes of sleep disturbance in ASD and highlight naturopathic treatment options for improved sleep outcomes.

Physiology of Sleep disturbances in ASD

Sleep disturbances fall into two categories: Insomnia and Circadian Sleep-Wake disorder. Insomnia is defined as the difficulty falling or staying asleep. Circadian Sleep-Wake disorder is defined by difficulty aligning the timing of the sleep wake cycle.[3] Sleep disorders are regulated by exogenous processes like sleep environment, sleep hygiene, and routine, or endogenous processes like hormone and neurotransmitters production and regulation, and the gut microbiome.[3] Successful interventions depend on determining which process, or combination of processes are implicated in each person's sleep disorder. This person-centered approach requires thorough biomedical assessment and patient specific intervention.

Sleep Hygiene and Environmental Factors

Establishing successful sleep habits can be challenging for the ASD population but is essential in obtaining adequate sleep for children and caregivers. Sleep hygiene has an important role in sleep quality and quantity, especially when established early in childhood.[4] Establishing a regular bedtime routine, even on weekends, prohibiting television in the bedroom, and eliminating caffeinated drinks are important tenets of sleep hygiene.[4] It is also important for parents of children with ASD to closely monitor and curb access to electronic media devices such as tablets, smart phones, and computers. Access to these devices, especially in the bedroom, results in shorter sleep duration and daytime sleepiness when compared with those who did not have bedroom access.[5] Studies show that children with ASD spend more time playing video games rising to the level of "problematic" video game use than their non-ASD peers.[5]

Neurotransmitters

Transition from the sleep-wake cycle is regulated by a complex interplay between neurotransmitters and hormones. Sleep promotion is governed by gaba-aminobutyric acid (GABA) and melatonin. Arousal and wakefulness are governed by serotonin, acetylcholine and glutamate.

GABA is an inhibitory neurotransmitter important for transition into sleep. A recent study found a reduction in GABA-A receptors in people with ASD caused disruption in sleep-wake behaviors.[6] Perhaps as important as adequate levels of GABA and function of the GABA receptors, is the balance between GABA's inhibitory effect and glutamate's excitatory effect. These two neurotransmitters act in tandem to function as a "switch" to transition between sleep and wakefulness, so balance here is key for optimum sleep.[7]

Melatonin is the other sleep promoting neurotransmitter. Melatonin is produced in the pineal gland in response to light/dark exposure. Disruptions in metabolism and/or production of melatonin are common in the ASD population and are implicated in sleep disturbances.[8] Other studies show that some individuals with ASD produce lower levels of melatonin than typical night-time levels causing delayed transition into sleep.[9] Exposure to blue light from electronics, especially in the hours before bedtime, suppresses melatonin and can further contribute to sleep disturbances.[10]

Acetylcholine is necessary for rapid eye movement (REM) sleep which is highly active in the developing brain. Acetylcholine is markedly reduced in ASD.[11] In a small study, it was concluded that children benefitted from improving acetylcholine levels by inhibiting acetylcholinesterase, which resulted in improved outcomes in REM sleep, behavior, and attention.[12]

Cortisol Dysregulation in ASD

Many children with ASD have a dysfunctional hypothalamic-pituitary-adrenal (HPA) axis contributing to abnormal cortisol patterns. The HPA axis releases cortisol from the adrenal cortices in response to stress. Typically,

cortisol is released in a binaural fashion. It is highest in the morning, decreasing throughout the day and at its lowest level in the evening. Studies have shown that children with ASD have higher evening cortisol[13] and lower morning cortisol levels[14] contributing to blunted diurnal slope in comparison to neurotypical children.[13] The research has shown that there is no difference in cortisol output between neurotypical children and children with ASD. This suggests that HPA axis dysfunction may be due to an accumulation of stress throughout the day, which leads to the increased evening cortisol levels seen in children with ASD.[14] In addition, increased cortisol response in children with ASD has been associated with increased stress response, sensory sensitivity, and anxiety.[15] Abnormal cortisol levels due to dysfunctional HPA axis contributes to various symptoms associated with the ASD diagnosis, such as sleep disturbances, anxiety, sensory overload, hyperactivity, OCD, perseverations, aggression, weight issues, etc.

Gut Microbiota and Sleep in ASD

Many children with ASD have imbalances in their gut microbiome. Candida overgrowth, parasitic infections, and bacterial imbalances in the gut microbiome can be found in children with ASD. Differences in sensory patterns resulting in restricted eating, altered ability to fend off gut infections, and increased intestinal permeability are all common in the ASD population.[16] Emerging research demonstrates the necessity of a healthy gut for the production of serotonin and its effect on the gut-brain axis. For example, sleep disturbances that occur around the lunar cycle may be due to parasitic activity based on our body's natural fluctuation in serotonin and melatonin levels. Around the full moon, more serotonin is produced and parasites respond to elevated serotonin production with increased activity.[17] In addition, candida albicans may increase production of serotonin in the intestines at the expense of decreasing serotonin production in the brain.[18] Therefore, alterations in gut microbiome may negatively affect serotonin production and metabolism and therefore impact sleep regulation in those with ASD.

Seizures and Sleep in ASD

It is estimated that 2/3 of children with ASD will have abnormal EEG findings. 1/3 will be diagnosed with epilepsy and demonstrate typical signs of seizure activity. The other 1/3 may have subclinical EEG changes with no outward signs of seizure activity.[19] Abnormal electrical discharge and seizures can negatively affect sleep and should be assessed in children with an ASD diagnosis. Given that a third of children with autism do not have a diagnosis of epilepsy, but are experiencing subclinical EEG changes, this underlying cause of sleep disturbance often goes undiagnosed. Causes of abnormal EEG findings in the ASD population can include metabolic disturbances, mitochondrial disorders, cerebral folate deficiency, inflammation, and genetic disorders.[20] Sleep disorders and epilepsy (abnormal neural discharges) have a reciprocal relationship. Disordered sleep, common in ASD, predisposes this population to abnormal neural discharges, and conversely abnormal neural discharges can cause or exacerbate sleep disorders.[21] Therefore, if a child with ASD is experiencing sleep disturbances it is important to rule out seizure activity.

Naturopathic Interventions for Sleep in ASD

While most pediatricians recognize the prevalence of sleep disorders in the ASD population, after sleep hygiene is addressed, pharmacologic intervention is the next step of intervention.[22] Naturopathic interventions provide safe and effective alternatives to pharmacologic solutions for those whom medications were not successful and/or those looking for natural alternatives to prescription interventions. After extensive biomedical testing to determine functional levels of gut dysbiosis, neurotransmitters, hormones, and nutritional status, appropriate supplementation can restore homeostasis.

Practitioners can balance neurotransmitter levels directly by appropriate supplementation. Levels can also be altered by supplementation of cofactors and food sources that support the body's ability to produce neurotransmitters naturally. GABA requires B6 for its synthesis so ensuring adequate levels of B6 is an important consideration for treatment.[23] Vitamin D, magnesium, and zinc should also be considered to support optimal GABA levels.[24] Lactobacillus plantarum and Lactobacillus brevis are helpful in reestablishing healthy gut flora and have also been found to increase the conversion of GABA from glutamate.[25] In this way Lactobacillus can act to indirectly support sleep via two mechanisms. Food sources of GABA include fermented soy and milk products, although children with food sensitives or allergies to milk or soy should continue to eliminate them from their diets.[26] Exercise has also been shown to increase GABA levels and should be included as a treatment strategy to support sleep.[27]

Melatonin is synthesized from serotonin and both play an important role in the sleep-wake cycle. This biochemical pathway, starting with tryptophan, requires multiple B vitamins including folate and Vitamin B12, as well as, zinc, and magnesium. A well-balanced diet supports melatonin production especially when diet is focused on vegetables, fruits, and grains.[28] Perhaps the most important way to support melatonin production is decreasing exposure to light sources before bed.[28] Removing electronic devices like tablets, computers, smart phones from the bedroom and limiting their use in the hours before bedtime should be an important part of the treatment of sleep disturbance in ASD. Decreasing electronic use can be very beneficial for regulating cortisol. In addition to decreasing screen time, supporting one's adrenal glands with the use of adequate hydration, salt, and herbal adaptogens may be necessary to regulate cortisol patterns in children with ASD. Ashwagandha root (Withania somnifera)

is an herbal that can improve sleep quality and sleep onset in those suffering from insomnia.[29]

Adequate levels of acetylcholine are required for restorative REM sleep. Vitamin B5 (Pantothenic acid) is required to produce acetylcholine in the body, so this should be considered in treatment of sleep in ASD. Adequate levels of vitamin B12 are also helpful in optimizing this neurotransmitter, as well as dietary sources of choline such as fish, eggs, beef, soybeans, and chicken breast.[30]

Addressing gut dysbiosis is an important part of treating sleep in ASD as many children with ASD suffer from some form of dysbiosis. Testing to determine levels of pathogenic microbiota and accurately assessing imbalances should be done at the initiation of treatment. This information can then be used to establish an individualized treatment plan to establish healthy flora. For yeast overgrowth, antimicrobials such as grapefruitseed extract, pau d'arco, and gynmena slyvestre could be considered. Grapefruitseed extract inhibits the growth of candida biofilms.[31] Pau D'arco inhibits the biochemical process that fungi need to produce oxygen and energy to survive.[32] Gymenma Slyverstre blocks the virulence properties of fungus by inhibiting the hyphal growth of Candida albicans.[33] In addition, Saccromyces Boulardii, which has prebiotic and probiotic properties, decreases candida ability to form filaments, adherence to the intestine, and biofilm formation.[34] For anti-parasitic support, treatments may include antimicrobials herbals such as artemisia and black walnut. Artemisia contains artemisinin, which has potent anti-malarial and anti-parasitic properties.[35] A major constituent in Black Walnut, known as Juglone, inhibits enzymes necessary for parasites metabolic function.[36] Therefore, antimicrobial herbals against the specific germ can be effective at reestablishing a healthy microbiome and improve symptoms.

For those children with ASD who have abnormal EEG activity as a causal factor, identifying the underlying cause is paramount. Once causal factors are identified, person-centered treatment can be utilized to remediate specific processes. In general, people with abnormal EEG activity benefit from adopting a ketogenic diet given its ability to calm neuroinflammation.[37] Nutritional interventions may be beneficial in treating epileptic encephalopathies including Taurine, Vitamin B6, Magnesium, Omega 3 fatty acids, L-Carnosine, and Folinic acid.[38] Identifying and treating cerebral folate deficiency with Folinic acid can help remediate metabolic causes of sleep disturbances in ASD.[39]

Further attention should be given to nutritional deficiencies of iron and magnesium levels in children with ASD experiencing sleep disturbances. Given the restrictive diets of many children with ASD, nutrient deficiencies are common. Research shows that while many children with ASD have lower hematocrit, hemoglobin, and iron levels the levels may not result in anemia.[40] Ferritin levels less than 50 ng/ml have been associated with Restless Leg Syndrome and Periodic Limb Movement Disorder in children.[41] Given that iron deficiency and ferritin levels less than 50 ng/ml are associated with sleep disturbances, it is prudent to assess and remediate iron deficiency in those with ASD and sleep disturbances.[42] It is important to implement iron under the guidance of one's physician due to the potential of iron complicating underlying gut dysbiosis inadvertently by "feeding" pathogenic bacteria that thrive on iron (and reduce available iron for absorption via the gut).[43] Decreased magnesium status has been associated with ASD and sleep disturbances. Supplementing magnesium has been found to improve sleep quality regardless of cause.[44] Magnesium is a cofactor for the production of GABA, and this may explain the improved sleep quality and quantity noted with supplementation of magnesium. Magnesium also antagonizes the NMDA (glutamate) receptor so optimizing magnesium levels will help balance GABA/glutamate levels needed to regulate the sleep-wake cycle.

Conclusion

Sleep disorders are prevalent in 80% of children and 50% of adults with ASD. Sleep disorders, although very common in ASD, have myriad causes. Using a person-centered approach to identify and treat specific causes can provide significant improvement in sleep outcomes. Naturopathic interventions provide powerful ways to remediate imbalances and can have profound effect in reducing or eliminating sleep disorders, improving the quality of life for the individuals with ASD and their caretakers. Interventions explored in this paper include balancing important neurotransmitters and hormones, treating gut dysbiosis, assessing nutritional deficiencies, dietary interventions, and establishing good sleep hygiene. Neurological workup should be included to rule out seizure and subclinical seizure activity as a causal factor for sleep disorders. In addition to topics discussed above, mitochondrial function, food sensitivities, allergies, enlarged tonsils/adenoids, constipation, medication reactions, cerebral folate deficiency, blood sugar regulation, and identification of genetic SNPs should all be considered as part of a thorough treatment plan.

References:

1. Bollu PC, Kaur H. Sleep medicine: Insomnia and sleep. *Mo Med*. 2019;116(1):68-75.

2. Ballester P, Richdale AL, Baker EK, Peiró AM. Sleep in autism: A biomolecular approach to aetiology and treatment. *Sleep Med Rev*. 2020;54:101357.

3. Matenchuk BA, Mandhane PJ, Kozyrskyj AL. Sleep, circadian rhythm, and gut microbiota. *Sleep Med Rev*. 2020;53:101340.

4. Bathory E, Tomopoulos S. Sleep regulation, physiology and development, sleep duration and patterns, and sleep hygiene in Infants, toddlers, and preschool-age children. *Curr Probl Pediatr Adolesc Health Care*. 2017;47(2):29-42.

5. Mazurek MO, Engelhardt CR, Hilgard J, Sohl K. Bedtime Electronic Media Use and Sleep in Children with Autism Spectrum Disorder. *J Dev Behav Pediatr.* 2016;37(7):525-531.

6. Mesbah-Oskui L, Penna A, Orser BA, Horner RL. Reduced expression of a5GABAA receptors elicits autism-like alterations in EEG patterns and sleep-wake behavior. *Neurotoxicol Teratol*. 2017;61:115-122.

7. Schneider L. Neurobiology and Neuroprotective Benefits of Sleep. *Continuum* (Minneap Minn). 2020;26(4):848-870.

8. Rossignol DA, Frye RE. Melatonin in autism spectrum disorders: a systematic review and meta-analysis. *Dev Med Child Neurol*. 2011;53(9):783-792.

9. Goldman, S.E., Adkins, K.W., Calcutt, M.W. et al. Melatonin in Children with Autism Spectrum Disorders: Endogenous and Pharmacokinetic Profiles in Relation to Sleep. *J Autism Dev Disord* 44, 2525—2535 (2014).

10. West KE, Jablonski MR, Warfield B, et al. Blue light from light-emitting diodes elicits a dose-dependent suppression of melatonin in humans. *J Appl Physiol* (1985). 2011;110(3):619-626.

11. Omura Y, Lu D, Jones MK, et al. Early Detection of Autism (ASD) by a Non-invasive Quick Measurement of Markedly Reduced Acetylcholine & DHEA and Increased ß-Amyloid (1-42), Asbestos (Chrysotile), Titanium Dioxide, Al, Hg & often Coexisting Virus Infections (CMV, HPV 16 and 18), Bacterial Infections etc. in the Brain and Corresponding Safe Individualized Effective Treatment. *Acupunct Electrother Res*. 2015;40(3):157-187.

12. Ballester P, Richdale AL, Baker EK, Peiró AM. Sleep in autism: A biomolecular approach to aetiology and treatment. *Sleep Med Rev*. 2020;54:101357.

13. Muscatello R & Corbett BA (2018). Comparing the Effects of Age, Pubertal Development, and Symptoms Profile on Cortisol Rhythm in Children and Adolescents with Autism Spectrum Disorder. *Autism Research*, 11, 110 -120.

14. Corbett BA, Schupp CW, Levine S & Mendoza S (2009). Comparing cortisol, stress, and sensory sensitivity in children with autism. *Autism Research*, 2, 39-49.

15. Corbett BA, Mendoza S, Abdullah M, Wegelin JA & Levine S (2006). Cortisol circadian rhythms and response to stress in children with autism. *Psychoneuroendocrinology*,31, 59-68.

16. Ristori MV, Quagliariello A, Reddel S, et al. Autism, Gastrointestinal Symptoms and Modulation of Gut Microbiota by Nutritional Interventions. *Nutrients*. 2019;11(11):2812.

17. Bagnaresi P et al. (2012) The role of melatonin in parasite biology. *Molecular and Biochemical Parasitology*, 181, 1-6.

18. Srikantha P, Mohajeri MH. The possible role of the microbiota-gut-brain-axis in autism spectrum disorder. *Int. J. Mol. Sci*. 2019;20:2115

19. Spence S, Schneider M. The Role of Epilepsy and Epileptiform EEGs in Autism Spectrum Disorders. *Pediatr Res*. 2009;65: 599-606.

20. Frye RE. Metabolic and mitochondrial disorders associated with epilepsy in children with autism spectrum disorder. *Epilepsy Behav.* 2015;47:147-157.

21. Malow BA. Sleep disorders, epilepsy, and autism. *Ment Retard Dev Disabil Res Rev*. 2004;10(2):122-125.

22. van der Heijden KB, Stoffelsen RJ, Popma A, Swaab H. Sleep, chronotype, and sleep hygiene in children with attention-deficit/hyperactivity disorder, autism spectrum disorder, and controls. *Eur Child Adolesc Psychiatry*. 2018;27(1):99-111.

23. Jewett BE, Sharma S. Physiology, GABA. FL: StatPearls Publishing;2021.

24. Mills DJ. The Aging GABAergic System and Its Nutritional Support. *J Nutr Metab*. 2021;2021:6655064.

25. Yunes RA, Poluektova EU, Vasileva EV et al. A Multi-strain Potential Probiotic Formulation of GABA-Producing Lactobacillus plantarum 90sk and Bifidobacterium adolescentis 150 with Antidepressant Effects. *Probiotics & Antimicro. Prot*. 2020;12:973-979.

26. Oketch-Rabah HA, Madden EF, Roe AL, Betz JM. United States Pharmacopeia (USP) Safety Review of Gamma-Aminobutyric Acid (GABA). *Nutrients*. 2021;13(8):2742.

27. Kramer JM, Beatty JA, Plowey ED, Waldrop TG. Exercise and hypertension: a model for central neural plasticity. *Clin Exp Pharmacol Physiol*. 2002;29(1-2):122-126.

28. Peuhkuri K, Sihvola N, Korpela R. Dietary factors and fluctuating levels of melatonin. *Food Nutr Res*. 2012;56:10.

29. Langade D, Kanchi S, Salve J, Debnath K, Ambegaokar D. Efficacy and Safety of Ashwagandha (Withania somnifera) Root Extract in Insomnia and Anxiety: A Double-blind, Randomized, Placebo-controlled Study. *Cureus*. 2019;11(9):e5797.

30. Hollenbeck CB. An introduction to the nutrition and metabolism of choline. *Cent Nerv Syst Agents Med Chem*. 2012;12(2):100-113.

31. Tsutsumi-Arai C, Takakusaki K, Arai Y, Terada-Ito C, Takebe Y, Imamura T, Ide S, Tatehara S, Tokuyama-Toda R, Wakabayashi N, Satomura K. Grapefruit seed extract effectively inhibits the Candida albicans biofilms development on polymethyl methacrylate denture-base resin. *PLoS One*. 2019;14(5).

32. Portillo A, Vila R, Freixa B, Adzet T, Canigueral S. Antifungal activity of Paraguayan plants used in traditional medicine. *J Ethnopharmacol*. 2001;76:93-98.

33. Vediyappan G, Dumontet V, Pelissier F, d'Enfert C. Gymnemic acids inhibit hyphal growth and virulence in Candida albicans. *PLoS One*. 2013 Sep 11;8(9).

34. Tomicic ZM. Beneficial properties of probiotic yeast Saccharomyces boulardii. *Food Feed Res*. 2016;43(2):103-110.

35. Krishna S, Bustamante L, Haynes RK, Staines HM. Artemisinins: their growing importance in medicine. *Trends Pharmacol Sci*. 2008 Oct;29(10):520-7.

36. Jha BK, Jung HJ, Seo I, Suh SI, Suh MH, Baek WK. Juglone induces cell death of Acanthamoeba through increased production of reactive oxygen species. *Exp Parasitol*. 2015;159:100-6.

37. Koh S, Dupuis N, Auvin S. Ketogenic diet and Neuroinflammation. *Epilepsy Res*. 2020;167:106454.

38. Agadi S, Quach M, Haneef Z. Vitamin-Responsive Epileptic Encephalopathies in Children. *Epilepsy Research and Treatment*. 2013; 1-8.

39. Rossignol DA, Frye RE. Cerebral Folate Deficiency, Folate Receptor Alpha Autoantibodies and Leucovorin (Folinic Acid) Treatment in Autism Spectrum Disorders: A Systematic Review and Meta-Analysis [published correction appears in J Pers Med. 2022 Apr 29;12(5):]. *J Pers Med*. 2021;11(11):1141.

40. Gunes S, Ekinci O, Celik T. Iron deficiency parameters in autism spectrum disorder: clinical correlates and associated factors. *Ital J Pediatr.* 2017;43(1):86.

41. Donskoy I, Loghmanee D. Iron and Insomnia in Autism Spectrum Disorder. *Pediatr Neurol Briefs*. 2020 Dec 9;34:17.

42. Leung W, Singh I, McWilliams S, Stockler S, Ipsiroglu OS. Iron deficiency and sleep - A scoping review. *Sleep Med Rev*. 2020;51:101274.

43. Seyoum Y, Baye K, Humblot C. Iron homeostasis in host and gut bacteria - a complex interrelationship. *Gut Microbes*. 2021 Jan-Dec;13(1):1-19.

44. Skalny AV, Mazaletskaya AL, Ajsuvakova OP, et al. Magnesium Status in Children with Attention-Deficit/Hyperactivity Disorder and/or Autism Spectrum Disorder. *Soa Chongsonyon Chongsin Uihak*. 2020;31(1):41-45.