Review

ASD and Sleep Disorders

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Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by social communication deficits and repetitive behaviors/limited interests. There have been accumulated reports of significant sleep problems in ASD. The most common sleep problems include difficulties in sleep initiation and maintenance, irregular sleep- awakening rhythm, and disordered sleep pattern. Some investigators have suggested that sleep problems in children with ASD may be due to abnormal circadian rhythm. Neuroendocrine markers provided another perspective to study biological clock, these biomarkers are nearly not affected by social domains, such as cortisol and melatonin levels in ASD. Many sleep related genes are associated with ASD, especially single nucleotide polymorphisms in core circadian clock genes have been convinced the linkage. The abnormal expression of key genes causes alteration of protein synthesis in some critical pathways associated with ASD. Effective sleep therapy is critical to the improvement of the core symptoms of ASD.
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INTRODUCTION

Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder characterized by social communication deficits and repetitive behaviors/limited interests.[1] Parental-based surveys showed that the prevalence of sleep disorders is about 44%-83%.[2-5] While in typically developed infants and preschool children is about 9% to 50%[6,7] The sleep disorders in ASD are mostly manifested as difficulty in falling asleep and awakening during sleep, which in turn affects the behavior of ASD individuals. Sleep disorders greatly reduce the quality of life of ASD individuals and their families. The sleep study in children with ASD is becoming a hot topic in ASD and sleep research fields. This review article summarizes the most recent clinical and basic research advances of ASD and sleep disorders.

Characteristics of Sleep Disorders in Patients with ASD and Their Relationship with Behavioral Issues

There have been accumulated reports of most common sleep problems in ASD over the past three decades. In recent years, the number and quality of related reports are significantly increased. The incidence of sleep disorders in ASD is considerably higher than normally developed children, and also higher than those with other developmental disorders.

The most common sleep problems in children with ASD are sleep initiation difficulties, sleep maintenance problems, irregular sleep-awakening rhythm, and disordered sleep pattern[6,8] A sleep questionnaire from Japan[9] assessed 965 cases of normal preschool children and 193 ASD preschoolers, 107 from ASD group were evaluated for the behavioral problems. The results showed that ASD children had significant sleep problems compared with normal preschool children. The further analysis showed that the sleep disorders in ASD are mainly falling into the following categories: insomnia including problems of falling sleep and frequent night awakening; waking up crying; irregular sleep rhythm; parasomnia; sleep disordered breathing or obstructive sleep apnea, daytime sleepiness.

ASD children have a lot of behavioral problems, including physical aggression, hostility, inattention, hyper-responsiveness, irritability, and hyperactivity. ASD children with sleep problems show more behavioral problems than children who do not have sleep problems. The severity of sleep problems, especially the severity of insomnia, is highly correlated with the behavioral problems they have. Several studies in ASD children describe the relationship between sleep deprivation and behavioral affective disorders, which can present as hyperactivity, mood instability, worsen aggression, emotional abnormalities,[10] behavioral problems

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and poor adaptive skill development,[11] in addition, preliminary studies showed lack of sleep correlates with nonverbal intelligence defects,[12] reduced communication skills[13] and academic performance.

As stated above, sleep problems are well recognized in ASD children, especially obstructive sleep disorders are common in preschool children with ASD. Current studies suggested that the sleep problems, particularly insomnia, are associated with behavioral problems in ASD preschool children, which highly suggested that routine assessment and treatment of sleep problems should be greatly beneficial to autistic children and their families.

CHANGES OF BIOLOGICAL CLOCK IN ASD

The biological clock is also referred as circadian rhythm, the human sleep-wake cycle, the body's inner clock, a biological process that displays an oscillation of about 24 hours. Most recently, Jeffrey C. Hall, Michael Rosbash, Michael W. Young share won 2017 Nobel prize for their discoveries of molecular mechanisms controlling the circadian rhythm.[14]

Some investigators have suggested that sleep problems in children with ASD may be due to abnormal circadian rhythm.[15] Previously the clear association between sleep disorders and circadian rhythm disturbances in ASD children had been rarely reported.[16,17] More studies have been published in recent years.

Sleep duration was more a focus of the studies, which indicated its association with ASD. Veatch and colleague found sleep duration negatively correlated with the severity of ASD core symptoms, and positively correlated with IQ scores [18] Limoges and colleague[19] illustrated that the shorter sleep duration is associated with social impairment and comorbidities in ASD. This study indicated a significant negative correlation between slow-wave sleep (SWS) and learning capacity of a sensory-motor procedural memory task. Another ASD study involved 5-16-year-old male patients [20] found that the total sleep time of ASD individuals was significantly less than the control group. A study[21] with ASD individuals aged 12 to 24, reported more reduced effective sleep time and increased night awakening in autistic patients than the normal controls.

Other ASD sleep disturbances include difficulty to fall in sleep; frequent night awakening, lower sleep efficiency (sleep fragmentation). Wiggs and colleagues[22] confirmed that autistic children have more prolonged incubation periods, delayed or advanced sleep phases, and increased night awakening, which were consistent with the previous findings from sleep diaries and questionnaires. These patterns of sleep abnormalities are very similar to those circadian rhythmic sleep disorders described above. The study showed that eight children were identified as biological clock sleep awakening problems, which could be good representations of the biological clock sleep disorders. The other studies in children with ASD, also indicated the longer sleep latency,[23,24] frequent night awakenings,[25] lower sleep efficiency (e.g., sleep time and bedtime ratio),[26] reduced non-REM and SWA sleep, lower sleep spindle density, REM sleep abnormality, periodic limb movement during sleep, decreased the first two thirds of the sleep time.[27-30] Another study involved 21 ASD patients aged 4-10 years old, used the more strict inclusion criteria[31] excluded those with mental retardation, seizures, and drug use, still showed reduced sleep efficiency, delayed sleep latency, and reported as "poor sleepers" by parents. The early stage of the SWA reduction is a sign of the weakening of steady-state sleep function.

The study methods of circadian rhythm developed with the advancement of physical technique.

The wrist actigraphy and polysomnography have more advantage than parental subjective reporting and sleep diaries. Several studies used objective tests have confirmed the findings from sleep diaries and questionnaires. Particularly, polysomnography has been used as a more reliable method of studying sleep structures under relatively controlled conditions.

The previous work mainly focused on the sleep disturbance of ASD individuals, most commonly reported above problems indicated an involvement of the biological clock system, although it seems that the irregular sleep mode initiated by the biological clock is only part of the problems. This subtype also represents a relatively large portion of the previous reports. The future work may focus on circadian rhythm gene and protein expression, as mentioned above.

HORMONE CHANGES ASSOCIATED WITH BIOLOGICAL CLOCK ALTERATIONS IN ASD

There have been reported studies of melatonin as well as cortisol levels in autistic children using blood, urine and saliva specimens. These studies provided a better understanding of alterations of biological clocks in children with ASD.

MELATONIN

Melatonin is produced in the dark by the pineal gland and is a key regulator of circadian and seasonal rhythms.[32] A lower melatonin level has been reported in individuals with ASD.

Chamberlain and Herman[33] first noted that melatonin secretion was abnormal in children with ASD in 1990, suggesting that there was a high secretion status of this hormone in a subgroup of these children, while the subsequent studies [34-36] showed problems of producing Melatonin in ASD.

Two studies [34,36] have found that the magnitude of melatonin rhythm is generally reduced, and the level is decreased in the nighttime. Kulman[34] reported 14 cases of autistic patients not only had a lower average level of melatonin at night, but also showed abnormal melatonin rhythm comparing with control group. In particular, most autistic patients showed a decrease in the gap between daytime and nighttime melatonin levels, one of the smaller subgroups showed a reversal of the

circadian rhythm, which can also be observed in Smith-Magenis syndrome (SMS).[37] Tordjmanand his colleagues [38,39] conducted a larger controlled study and got similar results. Autistic children showed abnormal nighttime 6-sulpho melatonin levels. 63% of autistic children has less than half of 6-sulphated melatonin levels compared with the mean of the control group, the night time 6-sulphated melatonin levels were found to be negatively correlated with severity of autistic impairments in verbal communication and play.[38,50]

Nir and colleagues[36] have found that older autistic (26-30 years) patients do have a tendency of increased melatonin at night. Other study[35] found that most autistic patients had lower plasma melatonin levels in the early morning. This significant inheritance may be due to mutations in the potential genetic component ASMT, which encodes an enzyme that affects melatonin synthesis.[35]

CORTISOL

Cortisol is a corticosteroid hormone found in humans, there are variations different times of the day.[40,41] The peak level of cortisol is in the morning after awakening, stays a while then rapidly declines, the rate of the reduction will slow down in the afternoon, reach the lowest level in the evening.[40,42,43] The studies of cortisol levels and rhythms in children with ASD showed mixed results, because there may be the potential confounding effects of hormones under stress. The blood draw for cortisol studies itself could be a stress and also may contain more influential factors.[44] In order to minimize the potential impact caused by the stress, most of the laboratory studies of cortisol are using saliva [42,43] or urine specimens rather than blood samples, thus the collection can be carried out at home, this case the patient doesn't to enter the external environment, and the stress should be minimal.

Corbett and his colleagues[45] reported that the ASD group's peak-to-trough cortisol level was different from the control group. Results showed abnormal daytime fluctuations in autistic individuals. Hill's study[46] indicated relatively advanced cortisol peak level, reduced overall daytime level and multiple peaks in ASD group. However, Richdale and Prior[47] implied that increased cortisol in ASD could be related to stress. Interestingly, Nir's study[36] showed no differences in serum cortisol levels among various ASD groups compared with control. Goldman's results[48] also showed no difference of salivary cortisol between ASD and control in adolescents/young adults, although they compared the morning cortisol, evening cortisol, and the morning-evening difference between two groups.

As mentioned above, there are special challenges to check the hormone level by collecting a variety of samples within 24 hours, particularly for ASD individuals with low tolerability. Besides, there are individual differences, broad-spectrum functional deficiencies, which constitute the heterogeneity of ASD and sleep behavior. In addition, differences in methodologies and analytical methods can also partly explain the inconsistency of the results, especially when the differences in assay methods and the collection techniques (such as saliva, blood, etc.) can lead to sensitivity to changes in the measured hormones. This is a major problem to study the overall profile of melatonin and cortisol particularly cortisol. It may be helpful to evaluate cortisol levels over a few days to obtain the overall picture of its biorhythm. It's worth mention that, Melatonin can be strongly inhibited by light32, further research must include strict control of lighting and photometric determination.

CHANGES IN SLEEP-RELATED GENES AND PROTEIN SYNTHESIS IN ASD

Many sleep-related genes are associated with ASD, especially single nucleotide polymorphisms in core circadian clock.[49] There are twenty-three genes involved in ten biological Circadian rhythms, which are associated ASD.[50]

Many genes (ATP13A4, CDH9, CDH13, CNTNAP2, CTNNA3, DIAPH3, GRIN2A, MDGA2, NLGN3, NLGN4, NRXN1, SHANK3 et, al) have been associated with ASD.[51] Genetic studies revealed many genes encoding synaptic proteins are associated with susceptibility to ASD, which includes genes NLGN3, NLGN4, and NRXN1 encoding the synaptic cell adhesion molecules and SHANK3 encoding a postsynaptic scaffolding protein. This protein complex is crucial for the maintenance of functional synapses as well as the adequate balance between neuronal excitation and inhibition.[52] Sarowar T, et al [53] found that Circadian rhythms may be able to modulate Shank3 signaling and then synaptic function. The expression of Shank3alpha increases rapidly by induced activity in thalamus and cortex. In the hippocampus, changes in synaptic Shank3 expression levels are influenced by circadian rhythm/melatonin concentration, while running activity increases Shank[3] expression in the cortex and decreases its expression in the striatum.[53]

Veatch et al found out that sleep onset delay relates to melatonin pathway genes.[54] They observed that decreased ASMT expression and related to decreased CYP1A2 enzyme activity. There is a relationship between genotypes in ASMT and CYP1A2. A recent study suggested that functional defects from NR1D1 may be related to ASD pathogenesis.[55] Nr1d1 was found to play a pivotal role in corticogenesis via regulation of excitatory neuron migration and synaptic network formation. Mutations in ASMT gene, encoding the last enzyme of the melatonin pathway have been reported as a risk factor for ASD.[56]

Diaz-Beltran L, et al identified a set of 19 genes not previously linked to ASD that were significantly differentially regulated in individuals with ASD. These genes were of potential etiologic relevance to ASD, given their critical roles in neurological processes crucial for optimal brain development and function, learning and memory, cognition and social behavior.[57] A recent study showed that there is a significant association between rs7794745 CNTNAP2 gene polymorphism and ASD in the studied population.[58]

ASD behavior subtypes may represent different biological phenotypes. The resulting gene expression profiles distinguish between ASD subtypes, which correlates the "biotype" and the behavior or symptom.

The treatment of sleep disorders should focus on the abnormal expression of key genes. For example, aryl-alkylamine N-acetyl transferase (AANAT) is a rate-limiting enzyme in the process of melatonin synthesis. It is down-regulated in this subtype of ASD. The enzymatic mechanism for melatonin deficit in ASD, involving a reduction of the enzyme activities contributing to melatonin synthesis (AANAT and ASMT), was observed in the pineal gland as well as in gut and platelets of patients.[59] This finding suggested that melatonin supplementation can improve the circadian rhythm and relevant neurological function.

In fact, the synaptic function and its relation to the biological clock were previously proposed. Another possible factor within the network with therapeutic potential is dihydropyrimidine dehydrogenase (DPYD). Lacking enzymes produced by DPYD will cause individuals to suffer from epilepsy and mental retardation, as is the case with ASD60. Due to the high risk of epilepsy and related neurological problems, individuals with ASD who lack DPYD showed to have the greatest sensitivity to antagonize convulsive drugs. In this way, AANAT and DPYD, as disease markers, can serve as potential diagnostic markers for ASD severe subtypes as well as potential therapeutic targets, especially when these enzymes are reduced in affected individuals.

Ca(2)(+)-dependent activator protein for secretion 2 (CAPS2) protein are critical for normal brain development and behavior, and that allelic changes due to copy number variation (CNV) may contribute to autistic symptoms in combination with deficits in other autism-associated genes.[61]

Fragile X syndrome (FXS) is the most common monogenic form of autism spectrum disorder (ASD). FXS results from the loss of fragile X mental retardation (FMR1) gene products, fragile X mental retardation protein (FMRP), which triggers a variety of physiological and behavioral abnormalities.[62] This disorder is also correlated with clock components underlying behavioral circadian rhythms and, thus, a mutation of the FMR1 gene can result in disturbed sleep patterns and altered circadian rhythms.

Retinoic acid-related orphan receptor alpha gene (RORa) and the microRNA MIR137 have both recently been identified as novel candidate genes for neuropsychiatric disorders. According to the RORA-deficient staggerer mouse model study, these functions include cerebellar development, differentiation and survival of Purkinje cells,[63] regulation of neuroprotection and circadian rhythm.[64] Devanna and Vernes found the role of MIR137 as an ASD candidate gene and demonstrated a direct biological role of these previously unrelated ASD candidate genes.[65]

The sleep mechanism is well-characterized in zebrafish and key regulators of the sleep/wake cycle are conserved, including melatonin and hypocretin/orexin (Hcrt), whereas novel sleep-regulating proteins, such as Kcnh4a, Neuromedin U, and QRFP, are continually being identified.[66]

More studies [67-69] have found circadian rhythm associated with genes which encode predominantly nuclear protein in adult Drosophila.[70-73] There is little genetic study focus on circadian rhythm and ASD. We believe that it is an attractive field to explore. Genetic study, protein expression and treatment targeting specific genes or proteins associated with ASD circadian rhythms may become a promising research area in the future.

CONCLUSION AND TREATMENT PERSPECTIVE

We discussed the various sleep disorders in ASD and their high correlation, emphasized the biologic clock changes, related biomarkers, genes, and protein synthesis, offered further understanding of molecular mechanism of circadian rhythm. More importantly the effective sleep therapy is critical to the improvement of the core symptom of ASD and the life quality of those affected individuals and their families.[74]

Conducting sleep education and developing appropriate and individualized behavioral therapy strategies are first-line treatments for ASD children with sleep disorders.[75] The drug interventions are considered only when the behavioral treatment is unsuccessful or there is no short-term drug-assisted implementation of behavioral therapy.[76] Some medications approved to treat aggressive or self-injurious behavior, severe mood swings, irritability, such as Risperidone, the serotonin-2 receptor and antagonizes dopamine D2 receptors, which increased daytime sleepiness and insomnia at night as common side effects.[77-79] Selective serotonin reuptake inhibitors (SSRIs) is commonly used to treat repetitive behavior in ASD.[80] Melatonin supplement is increasingly used in the treatment of ASD children, currently proven to be effective in improving sleep.[81-84] It can restore the circadian rhythm of ASD.[85,86] Exogenous melatonin supplementation can also be effective in treating sleep bursal disorders such as sleep phase abnormality, in which case melatonin should be administered at a specific point of time based on the onset or advancement of sleep initiation time.[74] It has been reported that melatonin treatment of insomnia can improve the problem behavior and academic performance of children with Asperger's syndrome.[87] When behavioral therapy and melatonin treatment are ineffective, other medications can be considered including clonidine, mirtazapine, gabapentin.[88,89] Although Risperidone can shorten sleep latency, the side effects are serious, it's not recommended for insomnia alone.[90] Hyperbaric oxygen (HBOT) therapy should not be used for the treatment of ASD.[91]

Sleep apnea (SDB) is common in ASD children, SDB treatment mainly includes ventilator CPAP and surgical intervention, the first-line surgical treatment of children with

OSA is most commonly used tonsillectomy,[92] which has been reported in a 5-year-old ASD Child[10] with obstructive sleep apnea underwent tonsillectomy improved their daytime behavior, while in another 4-year-old child with ASD,[93] successful sleep intervention improved the patient's self-injury behavior and night awakening. Some children require continuous positive airway pressure (CPAP) or additional surgical treatment after tonsillectomy, especially those obese children and those with concealed craniofacial deformities.[94] Other treatments include rapid maxillary dilatation, weight loss postural treatment.[95]

Sleep disorder is highly related to ASD. Obstructive sleep disorders are very common in preschool autistic children. Current studies suggest that sleep problems, especially insomnia, are associated with behavioral problems of ASD preschool children. These results highly suggest that routine assessment and treatment of sleep problems will greatly contribute to autistic children and their families. Early identification and intervention of childhood sleep problems for children with ASD are essential to prevent later negative outcome and complications. In the future, novel drug targets for ASD may have a great advancement based on proteomic studies.[96] Genetic treatment targeting specific genes or proteins associated with ASD circadian rhythms may become a promising research area.

CONFLICT OF INTEREST

None.

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