Review Article

Circadian Dysregulation in Young Children with Autism Spectrum Disorder

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Abstract
The circadian system plays a critical role in regulating human homeostasis and circadian misalignement has been implicated in the pathogenesis of several chronic diseases including autism spectrum disorder. In recent years there have been several investigations focusing on circadian physiological and behavioral rhythms in individuals with autism spectrum disorder, namely sleep patterns and hormonal variations, and their findings have significantly contributed to our understanding of autism-related neurophysiological processes. In addition, exogenous melatonin has been thoroughly investigated as a potential treatment compound targeting autism-related sleep and behavioral disturbances. Although the majority of relevant studies have been conducted in adolescents and adults, the presence of circadian dysregulation in young children with autism is attracting a growing scientific interest. Given that the earliest behavioral markers of the disorder become evident from the first years of life, focusing on toddlers and preschoolers might provide useful insights on autism's mysteries. In this context, in the current review we attempted to critically summarize all findings regarding circadian rhythmicity in young children with autism spectrum disorder, emphasize most important and recent advances in the field and provide directions for future research.

Keywords

- Circ adian
- Autism spectrum disorder
- Young children
- Sleep
- Melatonin

ABBREVIATIONS

ASD: Autism Spectrum Disorder; SAA: Salivary Alpha- Amylase; HPA: Hypothalamo-Pituitary Axis

INTRODUCTION

The circadian system is an endogenous time-keeping mechanism which synchronizes metabolic and cellular processes with the light-dark 24-hour cycle in an attempt to achieve an optimal balance

between energy production and expenditure [1]. Harmonic circadian function is necessary for health maintenance and circadian misalignment has been implicated in the pathogenesis of several chronic diseases including cancer, cardiovascular, metabolic and neuropsychiatric disorders such as affective disorders, schizophrenia and autism spectrum disorder (ASD) [2,3].

In this context, there are numerous clinical and research reports suggesting that ASD children frequently suffer from disturbances in circadian biological rhythms, namely sleep, body temperature and hormonal variations [4,5]. Even prior to the emergence of autism-specific developmental deficits, in the first year of life, infants later diagnosed with ASD exhibit regulatory problems such as disrupted sleep and feeding patterns and excessive crying, all of which possibly reflect deficits in circadian control [6]. These disturbances impair children's physiological and psychosocial adjustment and put significant burden on their parents' lives. In this respect, their study may provide useful information that could positively affect patients' and caregivers' quality of life.

The scope of the current review is to provide a brief yet integrative summary of major findings on circadian dysfunction in young children with ASD. The current article does not constitute a systematic literature review but rather aims at emphasizing most important and recent advances in the field and delineate directions for future research.

We decided to focus on very young children, below the age of 6, in order to approach as much as possible the origins of pathophysiological processes prior to the emergence of later effects of interventions and co-morbidities. Relevant findings will be presented into two distinct but interrelated thematic categories: those regarding disturbances of behavioral rhythms such as sleep and chronotypes and those focusing on disturbances of physiological rhythms, namely body temperature and hormonal variations. We should note that studies detecting genes and genetic variants implicated in the circadian clock of ASD patients were not included in this review and readers interested in this topic are encouraged to refer to two well- elaborated earlier reviews [7,8].

Studies on sleep and chronotypes

There is accumulating evidence that school-age children, adolescents and adults with ASD exhibit disruptions in the sleep-wake cycle such as increased sleep onset latency, shorter total sleep duration and more frequent awakenings and altered sleep architecture including a decrease in REM sleep [9,10]. However, sleep patterns have not been adequately studied in ASD preschoolers, toddlers and high-risk infants. In a study by Barnevik-Olssen et al [6], ASD preschoolers were more likely to display feeding and sleeping problems and excessive crying during infancy compared to children of typical development. In addition, regulatory problems during the first two years are considered early behavioral markers of ASD [11]. In two recent investigations using parent-report questionnaires [12,13] very young ASD children (mean age 4.7 and 3.3 years respectively) presented with more frequent sleep problems compared to typically developing peers. In contrast, in an earlier study, actigraphic recordings revealed that ASD children were less likely to suffer from behavioral insomnias compared to children with other developmental disorders and typically developing children, although parents of ASD children were twice as like to complain of sleep problems for their children [14]. This discrepancy is probably attributed to methodological differences and is indicative of the fact that parents' reports may be biased and should be corroborated by more objective measures of sleep physiology.

Chronotype is a basic biological trait which reflects individual preferences for bed and wake time and for peak cognitive and physical performance and is strongly correlated with melatonin and cortisol circadian variations [15]. To our knowledge, no study so far has evaluated chronotype in ASD preschoolers, given that the only relevant investigation included a sample of school-age children [16]. That literature gap should be addressed in future research, since chronotype constitutes a reliable behavioral marker of circadian function, whose evaluation is more cost-effective compared to other measures of circadian pathophysiology.

Studies on hormonal secretion and body temperature circadian variations

Cortisol and salivary alpha-amylase (sAA) constitute fundamental components of the hypothalamo-pituitary-adrenal axis and the autonomous nervous system respectively and represent characteristic paradigms of hormones whose secretion follows a circadian rhythm. In a recent review of the topic, Taylor et al [17] summarize all studies measuring cortisol's diurnal variations and responsiveness in ASD children, adolescents and adults. Among relevant investigations, only one study assessed cortisol's secretion in ASD preschoolers [18], while two other studies included very young children in their samples, however the authors do not present separately the findings derived from that age group [19,20]. In addition, in an earlier investigation of attachment in ASD toddlers, the authors found that ASD children had a lower cortisol response to parental separation compared to typically developing peers [21].

According to Kidd et al [18], no significant differences were detected in cortisol's and sAA's circadian variation between ASD and typically developing preschoolers. However, ASD children exhibited greater day-to-day variability in cortisol and sAA secretion compared to the control group [18], which is suggestive

of a potential dysregulation of the HPA axis and the autonomous nervous system. Moreover, the low functioning group had higher cortisol and sAA levels. These findings are partially in conflict with studies in older children which revealed greater disturbances in cortisol diurnal rhythm and response, probably suggesting that the origins of autism-related circadian misalignment lie on an instability of the circadian regulation system which in time and through the effect of several stressors may eventually lead to disturbed hormonal circadian rhythms. In addition, the fact that the level of children's functioning was negatively correlated with cortisol and sAA concentrations raises the question of whether circadian rhythms are associated with autism-related cognitive deficits and their underlying neurophysiological background.

Another hormone which plays a key role in circadian pathophysiology is melatonin, given that it serves as the major endogenous chemical regulator of circadian rhythmicity. There are several studies focusing on melatonin secretion in autism and other neurodevelopmental disorders, however the vast majority of these investigations included children of various age groups and thus their findings are not necessarily applicable to toddlers and preschoolers [22,23]. A recent Italian study in a small sample of ASD children, aged 2-7 years old, revealed great reduction in melatonin synthesis [24]. Likewise, among all studies assessing the effect of exogenous melatonin on autism-related sleep disturbances, only in one well-designed randomized double- blind trial of prolonged release melatonin, the authors explicitly reported that for the sub-group of very young children, aged 2-5, melatonin significantly increased total sleep duration and decreased sleep onset latency [25]. The role of melatonin in autism pathogenesis seems to be evident from the earliest phase of human development, given that maternal melatonin has been shown to affect fetal neurodevelopment and

low melatonin levels during pregnancy have been associated with increased ASD risk [26,27].

Body temperature in humans exhibits diurnal variation which is regulated by the circadian clock and constitutes probably the more characteristic and resistant to change physiological marker of circadian rhythmicity [28]. Nonetheless, our search failed to detect any study assessing body temperature variations in ASD patients, apart from a small-scale investigation in the late 70s which revealed a disturbed pattern of body temperature regulation in 4 ASD school-age children compared to healthy controls [29].

CONCLUSIONS

In conclusion, there are extremely limited data on circadian dysregulation in toddlers and preschoolers with ASD, derived from a small number of participants. Existing findings suggest that very young ASD children suffer from significant disturbances in sleep circadian rhythmicity, however these accounts are entirely based on parental reports and have not yet been corroborated by more objective measures of the sleep-wake cycle. In a similar vein, ASD preschoolers appear vulnerable to circadian dysregulation at the level of hormone secretion, however it seems that circadian misalignment becomes more evident in older children. In recent years, ASD research is growingly focusing on early pathophysiological and behavioral markers of the disorder from fetal life to toddlerhood. In this context, there is strong evidence that melatonin abnormalities during pregnancy and early regulatory problems during infancy may lead to increased ASD risk, suggesting that circadian abnormalities may be causally associated with ASD-specific disturbances in neurogenesis and synaptogenesis. Further, large-scale studies are therefore needed that would focus on assessing chronotypes, sleep physiology, body temperature and hormonal secretion in young ASD children in an attempt to elucidate the role of the circadian clock in ASD pathogenesis and provide thus novel directions for potential therapeutic targets

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