REVIEW ARTICLE

Sleep disturbances in children with autism spectrum disorder

Kristína Bartakovičová, Petra Keményová, Lenka Siklenková, Daniela Ostatníková, Katarína Babinská

Institute of Physiology, Academic Research Centre for Autism, Comenius University Faculty of Medicine in Bratislava, Slovakia.

Correspondence to: Kristína Bartakovičová, Institute of Physiology, Comenius University, Sasinkova 2, 813 72 Bratislava, Slovakia; email: kristina@bartakovic.sk

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disability that can result in a high social, emotional and behavioural dysfunction. Sleep disturbances occur often in children with ASD. The purpose of this article is to provide an overview of the recent findings about this common comorbidity in children with ASD. We focused on types of sleep disorders, assessment methods, possible biological, psychological and behavioural risk factors of sleep problems as well as the effects of sleep disorders on the core symptoms of ASD. Finally, the most successful intervention strategies are indicated that have potential to improve the quality of life of children with ASD and their families.

Introduction

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders with multiple manifestations, characterized by problems in social communication and social interaction, and restricted, repetitive patterns of behaviour, interests and activities, and sensory abnormalities (American Psychiatric Association 2013). Children with ASD suffer from a variety of comorbid conditions; therefore it is hypothetised that ASD are not only a dysfunction of the central nervous system but a systemic disorder (Babinská *et al* 2017). Sleep disturbances are one of the most common problems (Reynolds & Malow 2011) with prevalence ranging from 40 to 88% (McCue *et al* 2017). Sleep problems occur also in typically developing children, however, their prevalence is considerably lower, ranging within 20–30% (Maski & Owens 2016). Children with ASD are more likely (47%) to have sleep difficulties compared to their healthy siblings (16%) (Park *et al* 2012). Even parents of the children later diagnosed with ASD report a more frequent occurrence of sleep problems and reduced total time of sleep during the first two years of their child's age (Dewrang & Sandberg 2010). The most sensitive period for the occurrence of sleep problems is between 2–6 years of age, and then their frequency gradually decreases (Kothare & Kotagal 2011). Besides the negative impact on the childrens' quality of life including their daily activities, sleep problems in children with ASD adversely influence also quality of sleep of their parents and correlate with the mother's increased level of stress (Devnani & Hegde 2015). For these reasons early diagnosis of sleep disorders, and follow-up treatment are essential.

Characteristics of sleep disorders in children with ASD

According to the International Classification of Sleep Disorders (ICSD-3), there are 6 main categories: insomnia, parasomnia, circadian rhythm sleep-wake disorders, sleep-related breathing disorders, central disorders of hypersomnolence and sleep-related movement disorders (American Academy of Sleep Medicine 2014).

Even in children with typical development (TD), early childhood includes common problems with insomnia, especially frequent waking up at night (Hysing *et al* 2014; Wang *et al* 2013). Insomnia is the most common sleep disorder also in children with ASD. It appears as a delayed onset of sleep of more than 30 minutes on average after going to bed and/or frequent and sometimes even long-lasting problems with waking up at night. All of that affects the child's daily life and behaviour as described later in this article (Owens & Mindell 2011). Other sleep disorders most likely occur at a similar frequency to that of the TD children (Malow *et al* 2006). Although in some studies parasomnias (presenting by night terrors, sleepwalking, teeth grinding, vocalization, etc.) have been reported to occur more frequently in children with ASD, these were based on a parent report, and not objective measures (Goldman *et al* 2011; Honomichl *et al* 2002). Symptoms of insomnia – reduced total sleep time, prolonged sleep latency and an increased frequency of waking up at night have been reported by parents of children with ASD using questionnaires (Giannotti *et al* 2011; Richdale & Schreck 2009). In addition, Humphreys *et al* (2014) have reported a reduced duration of total sleep time in children with ASD from 30 months persisting up to adolescence. Across reports based on objective measurements such as polysomnography and actigraphy, the most commonly occurring presentations of sleep disorders in children with ASD included: reduced total sleep time, prolonged sleep latency, prolonged wake-up time after sleep onset (WASO), fewer REM (Rapid Eye Movement) sleep stages, overall lighter sleep, and decreased sleep efficiency (Deliens *et al* 2015). Several studies have found out that types of sleep disorders vary in different age groups. Based on information as reported by parents in sleep questionnaires, toddlers less than 2 years old most commonly wake up with crying and get less sleep time per day (Guinchat *et al* 2012; Dewrang & Sandberg 2010). A cross-sectional life study shows that children with ASD suffer from bedtime resistance, anxiety, parasomnia, and sleep walking, while adolescents with ASD suffer in particular from prolonged time of falling asleep, daytime somnolence, and reduced total sleep time (Goldman *et al* 2012). The differences within development are also supported by data obtained by objective measurements, e.g. actigraphy (Allik *et al* 2008; Baker *et al* 2013).

Causes of sleep disturbances and the role of melatonin

The aetiology of sleep disturbances in children with ASD is a multifactorial combination of biological, psychological and environmental impacts (Deliens *et al* 2015). The coincidence of other comorbidities in children with ASD also plays an important role in this process, however, this is discussed in the following section. Biological factors include, in particular, the deviations in the circadian cycle. Evidence indicates that they are associated with changes in melatonin secretion.

The circadian cycle is based on endogenous clock that is located in the suprachiasmatic nucleus of the anterior hypothalamus, but it is influenced by light-dependent factors through the retinohypothalamic tract, and light-independent factors such as e.g. social interaction, stress, exercise, and eating habits (Brzezinski 1997).

Melatonin is a hormone produced in the pineal gland and its main function is to regulate circadian rhythm, body temperature and hormone release (Pandi-Perumal *et al* 2007). It's precursor is serotonin and in the pathway of melatonin synthesis enzymes aralkylamine N-acetyltransferase (AANAT) and acetylserotonin O-methyltransferase (ASMT) play key role (Ackermann & Stehle 2006). Melatonin is metabolised to 6-sulfatoxymelatonin and excreted in urine (Braam *et al* 2018). During the night, melatonin concentrations increase several times with a peak in the middle of the night (Arendt 1988). Melatonin secretion is affected by sex, age and pubertal stage and also seasonal changes (Cavallo & Ritschel 1996; Touitou 2001; Wehr 1997). 6-sulfatoxymelatonin in urine is commonly used as a marker of melatonin status (Nowak *et al* 1987). In study of Leu *et al* (2011) overnight concentractions of 6-sulphatoxymelatonin were overall low in children with ASD and were negatively correlated with daytime sleepiness. Also, Tordjman *et al* in their study of larger samples of children of different ages with ASD found significantly lower nocturnal and daily 6-sulphatoxymelatonin concentrations in the urine of children with ASD compared to control groups. In addition, levels negatively correlated with verbal communication level, social game capabilities and repetitive behaviour, however, they did not correlate with sleep problems (Tordjman *et al* 2005, 2012).

An interesting observation in a study by Melke *et al* (2008) was that in addition to showing a lower nocturnal and early morning plasma melatonin levels in the adolescent group with ASD compared to the healthy group, low levels of melatonin were also shown in parents of children with ASD, suggesting a possible genetic effect. Based on these findings, the deficiency of the ASMT enzyme and increased levels of N-acetylserotonin in patients with ASD were revealed in the same group (Pagan *et al* 2014). These findings support hypothesis that low melatonin level in ASD can be associated with high serotonin levels (Melke *et al* 2008; Mulder *et al* 2010).

It has been shown that melatonin is also important during prenatal development due to its effects on neurodevelopment, establishment of diural rhythms, in addition, it has direct effects on placenta (Tordjman *et al* 2012). Approximately six to eight weeks after birth, a circadian rhythm of melatonin biosynthesis develops

(Chen *et al* 2012). Until that time, the baby is dependent on melatonin from the mother, thus breastfeeding is regarded as protective factor of it's deficiency (Braam *et al* 2018).

Several studies have focused on the genetic basis of melatonin synthesis, particularly ASMT. Although the results of two studies (Melke *et al* 2008; Pagan *et al* 2014) did not support the ASMT gene abnormalities in children with ASD, Veatch *et al* (2017) found significantly more dysfunctional polymorphisms of ASMT and also CYP1A2 genes in patients with ASD (Braam *et al* 2013). It is noteworthy that in disrupt pregnancies compared to normal pregnancies, the concentration of melatonin and the activity of the AANAT and ASMT genes are lower (Lanoix *et al* 2012; Tamura *et al* 2008). In a pilot study of Braam and his colleagues, lower levels of 6-sulfatoxymelatonin were found in the urine of mothers who had a child with ASD (Braam *et al* 2018). These findings support the theory about a role of melatonin in the etiology of ASD.

Several authors have pointed to the possible genetic origin within the etiopathogenesis of sleep disturbances of patients with ASD. The so-called clock genes of the circadian cycle, e.g. PERIOD, TIMELESS, NPAS2, CRY 1,2, their mutations and variants, that could be associated with ASD, were found. It is hypothetised that genes that are common to sleep and neurological diseases, may be linked together. E.g. it has been observed that the SHANK3 gene, that encodes the postsynaptic skeletal protein, is associated with the combined phenotype of ASD symptoms with sleep disturbances and mental disability (Souders *et al* 2017).

The effect of comorbidities on the sleep-wake-cycle

Children with ASD suffer from many comorbidities (Babinská *et al* 2017). It is well established that psychiatric comorbid conditions frequently co-occur in these children and are involved in dysregulation of sleep. Conditions like anxiety and attention-deficit hyperactivity disorder (ADHD) in the ASD population may increase arousals, sleep onset delay, and result in insomnia (Ben-Sasson *et al* 2007).

Anxiety with a prevalence of about 39.6% is a relatively frequently occurring comorbidity in children with ASD (van Steensel & Heeman 2017). Anxiety is associated with sleep problems even in TD children. This is also supported by the fact that 70% to 90% of patients suffering from anxiety have problems with sleeping (insomnia) at the same time (Alfano *et al* 2006). Paavonen *et al* (2008) confirmed this relationship also in children with ASD. A recent large-scale study of 1347 children with ASD reports a link of anxiety with all types of sleep problems such as sleep onset delay, bedtime resistance, sleep duration, and night waking (Mazurek & Petroski 2015). However, the type of anxiety differs between children with ASD and healthy individuals: Richdale and Baglin report that poor sleep in children with ASD is associated with somatic-panic disorder, while in neurotypical children it is their fear of school, separation, and general anxiety (Richdale & Baglin 2015).

Another frequently occurring comorbidity in children with ASD is sensory dysfunction, characterized as a reduced or escalated, excessive response to sensory stimuli or unusual interest in factors of the environment (American Psychiatric Association 2013). Children with ASD have been found to be more sensitively responsive to their surrounding environment, e.g. when it comes to sleep habits, they are often disturbed by the room, noise in the room, and complain about their uncomfortable bed (Shochat *et al* 2009). Another study has shown a correlation between sensory behaviour, stress markers and sleep disorders in children with ASD (Reynolds & Malow 2011). The cause of this disorder is still unknown, but it is thought to be a consequence of dysregulation of the autonomic nervous system (ANS). Also in the literature, association between ASD symptoms and structural and functional abnormalities of ANS has been suggested (Filčíková & Mravec 2016). Several smaller studies have evaluated the effect of the sympathetic branch of ANS on sensory excitement through electrodermal activity in children with ASD compared to controls, but the results are inconclusive (Souders *et al* 2017). However, Ming *et al* (2005) used neuroscope in their research on autonomic dysfunction, and found increased sympathetic activities in all children with ASD compared to the control group (Ming *et al* 2005).

Neurological comorbidities in children with ASD include mainly epilepsy (6–60%). Sleep deprivation is a predisposing factor in the onset of an epileptic seizure and, in turn, the seizures have a negative impact on sleep cycle (Cohen *et al* 2014). Seizures can cause frequent awakenings, sleep deprivation, and disruption in the sleep cycle (Relia & Ekambaram 2018).

Gastrointestinal disorders (GI) are another prevalent comorbidity in ASD with possible impact on sleep. It is a diverse group of problems that include eating problems, constipation, diarrhea, abdominal pain, and discomfort, gastroesophageal reflux, heartburn, increased flatulence, belching, stool incontinence (Holingue *et al* 2018). The aetiology of these problems is not fully clear. Possible mechanisms include inflammation, composition of intestinal microbiota, mitochondrial dysfunction or irritable bowel syndrome (Gagnon & Godbout 2018). Studies have shown a higher coincidence of gastrointestinal and sleep disturbances in children with ASD compared to healthy controls (Yang *et al* 2018). These difficulties are also reported as a risk factor for sleep problems (McCue *et al* 2017; Hollway *et al* 2013). Night waking and going to the toilet is a problem for more than 50% of the children just due to diarrhea and / or constipation (Cohen *et al* 2014).

Associations with behaviour and cognition

Sleep disorders and behaviour of children with ASD influence each other (Tye *et al* 2019). Some studies have shown that sleep problems e.g. reduced total sleep time, sleep onset delay, frequent waking up during the night can lead to impairments in communication skills, deterioration of adaptive behaviour, daily skills and reduced motor development in children with ASD (Elia *et al* 2000; Taylor *et al* 2012). In another study, sleep onset delay was associated with stereotyped behaviours and impairment of social interaction, but not communication deficits, while parasomnias have been linked to symptom severity, communication problems and an increase in stereotyped behaviours (Tudor *et al* 2012). Also, Veatch *et al* (2017) found that children with ASD who had a generally reduced sleep time, had increased severity of ASD core symptoms, higher frequency of maladaptive behaviour and lower IQs.

The effect of sleep problems on the behaviour of children with ASD varies by age. In toddlers, increase of sleep disturbances was associated with lower developmental quotient (Kozlowski *et al* 2012). In adolescents and adults with ASD suffering from mild sleep disorder, an increased risk of problem behaviours was observed, while moderate to severe sleep disorder was more likely to be associated with aggressive behaviours (Matson & Rivet 2008).

It is now well known that cognition is influenced by sleep (Astill *et al* 2012). Picchioni *et al* (2014) suggest that sleep disorders result in abnormalities in cortical connections. Krakowiak found that a lower cognitive and adaptive function was associated with more problems with sleep onset and night awakening, as well as shorter duration of sleep. However, in the ASD group alone, cognitive level and adaptive function did not predict the severity of either type of sleep problem or sleep duration (Krakowiak *et al* 2008). In several studies, parents of children with intellectual disabilities of moderate to severe degrees of various etiology reported sleep problems, especially delayed sleep and sleep interruption (Richdale *et al* 2000; Didden *et al* 2002).

Sleep also plays an important role in the development of language skills (Deliens *et al* 2015). Reduced activity of sleep spindles was associated with decreased the child's ability to access previously learnt vocabulary and also the child's ability to form understandable language in children with ASD compared to TD children (Henderson *et al* 2014). Also Limoges *et al* (2013) showed that individuals with ASD who present more sleep spindles during the night exhibit better learning performance on the sensory motor procedural memory task.

Sleep measurement: subjective and objective methods

Sleep disorders occur in children with ASD from early childhood. Mainly due to the high prevalence and impact of sleep problems that can affect the whole family, early diagnosis and subsequent intervention is essential. To identify sleep problems in children with ASD, subjective and objective methods can be used. Subjective measures include parent-report questionnaires or completion of a sleep diary record. In contrast, objective measures directly measure aspects of sleep by using various technologies. Some of the most common objective approaches used to assess sleep in children with ASD include polysomnography, actigraphy, and video-recording (Moore *et al* 2017). Although polysomnography is regarded as a gold standard in sleep disorder diagnosis, questionnaires also have their importance. Particularly in children with ASD, the questionnaires are a commonly used method that provides valuable information (Gregory & Sadeh 2016).

Polysomnography (PSG) is the most comprehensive objective method of sleep architecture measurement and it is performed in the sleep laboratory. It is considered the golden standard for sleep disorder diagnostics (Haynes 2005). It is used to measure sleep stages (using electroencephalography, electrooculography and electromyography), in addition, it provides information about respiratory system (recording air and nose flow, chest movements and blood oxygenation level), cardiovascular system (using electrocardiography) and limb movements. At the same time, a microphone can be used to detect patient's vocalization and the video recording to see the movements and overall behaviour during sleep (Wise & Glaze 2018). The negative aspects of this method include the fact that it is performed in an environment unknown and sometimes stressful for the child with ASD, therefore the data recorded especially during the first night may not be sufficiently relevant (Buckley *et al* 2013; Malow *et al* 2006). Fortunately, new modern polysomnographic devices are available that are portable and capable of recording EEG activities and child's behaviour over several days in a row, which may be helpful in clinical diagnostics (Doran *et al* 2006).

Actigraphy: The purpose of an actigraph is to detect a person's bodily movement during sleep and to analyse different phases of the sleep-wake cycle. An actigraph resembles a watch, and therefore it is easily portable (Morgenthaler *et al* 2007). In comparison to polysomnography it is easy to use and relatively inexpensive. In addition, this device captures information in the home environment (Ancoli-Israel *et al* 2015). On the other hand the device has some disadvantages, e.g. if the child has long motionless periods during the awake period it can be incorrectly evaluated by actigraph (Sadeh & Acebo 2002). The data is collected and stored in specific time intervals, referred to as epochs. Their duration ranges from 1 second to 5 minutes, but most validated and commonly used are 30 seconds to 1 minute (Ancoli-Israel *et al* 2015). Data from the actigraph's memory need to be downloaded to the computer (Allik *et al* 2008). Through a software package information about total sleep time can be obtained, as

well as about sleep onset time, sleep latency, morning waking time, activity, frequency of night awakenings, longest sleep period, sleep efficiency and acceleration index (Wiggs & Stores 2004). Concering the duration of the measurement and placing of the device, in order to obtain sufficiently reliable data, it is recommended to do the measurements for 7 days, with minimum of 5 days. Most studies place the actigraph on the child's non-dominant wrist, but alternative placements have been used to improve tolerance (e.g., non-dominant shoulder, ankles, and trunk) (Moore *et al* 2017).

Children's Sleep Habits Questionnaire (CSHQ): This is a 33-item parent report measure created to detect sleep difficulties and originally designed to screen sleep problems in typically developing children aged 4 to 10 (Johnson *et al* 2016). Currently, it is the most widely used sleep assessment for children with ASD. It includes eight subscales: (1) Bedtime Resistance; (2) Sleep Onset Delay; (3) Sleep Duration; (4) Sleep Anxiety; (5) Night Wakings; (6) Parasomnias; (7) Sleep Disordered Breathing; and (8) Daytime Sleepiness. Parents use a 3-point scale for answers: 3 = usually (5–7 nights per week); 2 = sometimes (2–4 nights per week); and 1 = never / rarely (0–1 nights per week). The total score is based on 45 items. The higher score increases the severity of the sleep disorder (Owens *et al* 2000; Moore *et al* 2017). The modified CSHQ version was created specifically for children with ASD. It consists of 27-items and 5 subscales: (1) Sleep Routine Problems; (2) Insufficient Sleep (3); Sleep-Onset Association Problems (4) Parasomnia/Sleep Disordered Breathing; and (5) Sleep Anxiety. A study of Johnson *et al* demonstrated adequate psychometric properties of this tool (Katz *et al* 2018).

Sleep diary: parents record the exact time of sleep during the day and night, bedtime, night wake up and other important sleep-related facts (Wiggs & Stores 2004).

Treatment: behavioural interventions and options for pharmacological therapy

Although sleep disorders in children with ASD occur in high prevalence, there are several treatment options that can be used to improve sleep. First of all, it is necessary to determine the type of sleep disorder and based on that to select the appropriate method. Preference is given to non-pharmacological treatment and when behavioural methods are not successful, pharmacological treatments may be considered.

Sleep hygiene is an essential treatment method. It includes several categories like: daytime and evening habits, bedtime routines and also sleep environment. In the context of sleeping hygiene it is important to follow these steps: during the day to avoid naps, avoid drinking caffeine drinks and also it could be appropriate to do more physical activities and exposure to the light. In contrary in the evening, there is a need to limit these activities, as well as there is a need to avoid use of electronics (Reynolds & Malow 2011). Generally, children with ASD are more sensitive to environmental stimuli. Optimum conditions for sleeping can be created by a silent and cold room with minimal light. It is important also to be careful regarding the fabric with which the child comes into contact like pajamas or bedding. Moreover, the child should have a stable sleeping routine, therefore all bedtime activities should be more or less the same and have the same time routine (Deliens *et al* 2015).

Behavioural interaction includes numerous interventions e.g. a visual plan with pictures of individual activities before bedtime, that is often well tolerated by children with ASD (Reynolds & Malow 2011). Nightmares can be treated with so-called scheduled wake-ups, usually 10–15 minutes before the child usually would have a nightmare. Over time, these dreams should disappear and no further intervention is needed (Gregory & Sadeh 2016). Also, to teach the child to fall asleep on his own is very important. Several studies have confirmed the effectiveness of this intervention (Moon *et al* 2011).

Melatonin has been shown to be one of the alternatives for sleep problems involving sleep initiation or a circadian shifts. Zee *et al* (2013) states that melatonin is particularly effective in patients with circadian rhythm disorders. The summary evidence for melatonin supplementation for sleep problems in ASD suggests significantly improved sleep duration and sleep onset latency compared to a placebo, and significantly improved daytime behaviours, with minimal side effects (Tye *et al* 2019). The administration of melatonin is depending on the age, sex and pubertal stage of the child and also forms (immediate vs. controlled release) and timing may vary (Deliens *et al* 2015). Melatonin is usually given at a dose of 1mg 30 minutes before bedtime, the dose could be increased up to 3mg. Several studies have shown an improvement in sleep latency. If melatonin is administered as a chronobiotic to correct circadian rhythm, lower doses of about 300ug 3 to 5 hours before sleep for at least 6 weeks are administered (Giannotti *et al* 2006). However, in one study, children suffered from sleep problems despite the use of melatonin. Therefore, it is strongly recommended that behavioural methods be applied prior to melatonin treatment (Lord 2019).

In addition to melatonin, in some cases, also other pharmacological treatments may be used, but there are just a few studies about their efficacy in children with ASD. Children with ASD often suffer from various psychiatric and neurological comorbidities for which they must take different medications. It is recommended to avoid drugs causing insomnia, e.g. antipsychotics and serotonin reuptake inhibitors and instead focus on those medications that promote sleep as a side effect (Reynolds & Malow 2011). Concering some types of medicines, e.g. benzodiazepines and diphenhydramine,

that are over-the-counter drugs, special attention is needed since they have been shown to have paradoxical and excitatory effect (Devnani & Hegde 2015). On the other hand, a positive effect of a cysteinyl-leukotriene receptor antagonist was observed, that has been found to be useful in the treatment for obstructive sleep apnoe (Goldbart *et al* 2012). Further, diphenylmethylsulfinyl-acetamide is helpful by treatment of excessive daytime sleepiness, which occurs in narcolepsy (Thorpy 2015).

Conclusion

The sleep disorders have a high prevalence in children with ASD. They increase the severity of core symptoms of ASD and present a serious problem for the child. Still, sleep problems in ASD require further investigation. There are only limited data concerning abnormalities in circadian regulation, especially in toddlers and preschoolers with ASD, because of small study samples and the information obtianed only from reports of parents (Karaivazoglou & Assimakopoulos 2018). It is desirable that future research studies involve larger samples of participants with ASD, take into consideration their age distribution and use a multi-method approach for the most accurate diagnosis of sleep disorder. Also, it is important to focus on aetiology of sleep disturbances, since identifying causes of sleep disorders is essential for treatment. Implementation of non-pharmacotherapeutic measures with limited and carefully managed pharmacotherapy are the cornerstone of management and they can help to improve the quality of life of children with ASD and also decrease the family distress.

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