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Neonatal irritable sleep-wake rhythm as a predictor of autism spectrum disorders

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ABSTRACT

Recently, it has been suggested that sleep problems in autism spectrum disorder (ASD) not only are associated symptoms, but may be deeply related to ASD pathogenesis. Common clinical practice relating to developmental disorders, has shown that parents of children with ASD have often stated that it is more difficult to raise children in the neonatal period because these children exhibit sleep problems. This study investigated the possibility that abnormal neonatal sleep-wake rhythms are related to future ASD development.

We administered questionnaires to assess parent(s) of children with ASD and controls. A retrospective analysis was conducted among 121 children with ASD (94 male and 27 female children) recruited from the K-Development Support Center for Children (K-ASD), 56 children with ASD (40 male and 16 female children) recruited from the H-Children's Sleep and Development Medical Research Center (H-ASD) and 203 children (104 male and 99 female children) recruited from four nursery schools in T-city (control).

Irritable/over-reactive types of sleep-wake rhythms that cause difficulty in raising children, such as 1) frequently waking up, 2) difficulty falling asleep, 3) short sleep hours, and 4) continuous crying and grumpiness, were observed more often in ASD groups than in the control group. Additionally, the number of the mothers who went to bed after midnight during pregnancy was higher in the ASD groups than in the control group.

Sleep-wake rhythm abnormalities in neonates may be considerable precursors to future development of ASD. Formation of ultradian and postnatal circadian rhythms should be given more attention when considering ASD development. Although this is a retrospective study, the results suggest that a prospective study regarding this issue may be important in understanding and discovering intervention areas that may contribute to preventing and/or properly treating ASD.

1. Introduction

Several genetic and environmental factors are likely to be involved in autism spectrum disorders (ASD). The prevalence of ASD has been increasing, and has become a serious "problems in children" in modern society (Boyle et al., 2011; Christensen et al., 2016; Sheldrick et al., 2018). However, the pathogenesis that underlies this condition and the cause(s) of this rapid increase remains unclear. In the last 20 years, we have focused on chronobiology formation, including the sleep-wake rhythm in ASD.

Chronobiology formation is deeply related to the relationship between the mother and fetus during pregnancy. This study presents new concepts for ASD in terms of chronobiology (Wimpory et al., 2002; Nicholas et al., 2007; Bourgeron, 2007; Tordjman et al., 2015; Geoffray et al., 2016).

Abnormal behaviors have been recognized in neonates with ASD.

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These behaviors include crying infrequently or not seeking human interaction or stimulation and/or conversely being intensely irritable and overreactive to any form of stimulation. The former is termed an "apathetic" or "under-reactive" type of neonate and the latter is termed an "irritable" or "over-reactive" type of neonate (Ornitz, 1973; Ornitz et al., 1983). Based on our preliminary observation, neonates of an apathetic/under-reactive type exhibited continuous sleep once they fell asleep, similar to unaffected children; contrastingly, those of the irritable/over-reactive type exhibited more frequent waking, difficulty falling asleep, short sleep amounts and continuous crying and grumpiness.

A neonate's daily life is mainly controlled by the ultradian cycle, with a sleep-wake rhythm of approximately 3 (Bueno and Menna-Barreto, 2016) and/or 4 h (Meier-Koll et al.,1978, Stephenson et al., 2012). The reported center of the ultradian rhythm is formed in the pons and medulla oblongata at 28–29 to 30–33 weeks of gestation (Wakayama et al., 1993; Fukushima et al., 2008). Additionally, the formation of the chronobiology circadian clock also starts in the fetal period (Rivkees, 1997; Mirmiran et al., 2003; Schreck et al., 2004; Serón-Ferré, 2007) and is almost complete by early childhood (Serón-Ferré et al., 2012); therefore, it is still immature in the neonatal period. From 20 to 22 weeks of gestation, circadian rhythms begin to form in each organ of the fetus (de Vries, 1987) but they are engrained with independent rhythms (Rivkees, 1997; Mirmiran et al., 2003; Schreck et al., 2004; Serón-Ferré et al., 2007).

A fetus may be under the control of the mother's circadian rhythm, similar to one of the organs while in the uterus, and following birth, postnatal integration of the scattered fetal circadian clocks into an adult-like circadian system is commanded by the suprachiasmatic nucleus (SCN) (Rivkees, 1997; Mirmiran et al., 2003; Serón-Ferré et al., 2007). This is the background of the approximately 3–4 h sleep-wake daily life rhythm in neonates according to the ultradian cycle (Meier-Koll et al., 1978; Rivkees, 1997; Stephenson et al., 2012), which is an important chronobiology rhythm, but there is no relationship between ultradian period and time of day (Stephenson et al., 2012).

Moreover, several studies have discussed chronobiology clock formation during the fetal period and the close relationship between the mother and fetus: maternal sleep rhythm (Serón-Ferré et al., 2007; Micheli et al., 2011; Reiter et al., 2014; Warland et al., 2018), and/or melatonin secretion (Yellon and Longo, 1988; Serón-Ferré et al., 2012; Mendez et al., 2012; Reiter et al., 2014; Nehme et al., 2019) and feeding (Weaver and Reppert, 1989; Nováková et al., 2010; Serón-Ferré et al., 2012). Reiter et al. (2014) highlighted the importance of maintaining a regular maternal light-dark and sleep-wake cycles to stabilize maternal and fetal circadian rhythms, which may be essential in proper chronobiology formation for both the mother and fetus. Generally, apathetic/under-reactive and irritable/over-reactive types of neonates may have immature or disrupted ultradian and circadian chronobiology formation during fetal development. The circadian rhythm is formed based on the ultradian rhythm after birth (Bueno and Menna-Barreto, 2016), therefor, neonatal sleep-wake rhythm should be considered an important factor in circadian rhythm formation and is fundamental for life-sustaining function (Miike et al., 2004; Lack and Wright, 2007; Tomoda, 2009; Bollinger and Schibler, 2014; Dittmar 2014).

Based on this information, this study investigated the relationship between the neonatal "apathetic/under-reactive" and/or "irritable/over-reactive" type sleep-wake rhythm abnormalities and the future development of ASD using a retrospective questionnaire survey, which may be useful in future ASD studies.

2. Materials and methods

2.1. Participants

We administered questionnaires to the parent(s) of children with ASD and controls. A retrospective analysis was conducted among 121 children with ASD (94 male and 27 female children) recruited from the K-Development Support Center for Children (K-ASD), 56 children with ASD (40 male and 16 female children) recruited from the H- Children's Sleep and Development Medical Research Center (H-ASD) and 203 children (104 male and 99 female children) recruited from four nursery schools in T-city (control) (Table 1). In the present study, the terms "apathetic" and "irritable" referred to "under reactive" and "over reactive" respectively. The study complies with the Declaration of Helsinki and was approved by the ethics committees of the H-Rehabilitation Central Hospital. All parents of children provided written informed consent prior to enrollment in the study. All analyses were performed in accordance with Ethical Guidelines for Epidemiological Research in Japan.

2.2. Questionnaire items

Maternal lifestyle during pregnancy.

- Bedtime hour and awakening hour: 1. regular and 2. irregular. (>2 h)
- Mealtime hour: 1. regular and 2. irregular. (>2 h)
- Sleep-onset time: 1. before midnight and 2. after midnight.
- Abnormal symptoms: 1. none and 2. diabetes, and 3. hypertension.
- Number of weeks at child's birth

We have no established reasons for choosing the abovementioned items, apart from the following information. Going to sleep before midnight is an important condition for ensuring adequate sleep by 6–7 am, because 8 a.m. is conventionally regarded as the time to start social activities in modern society.

According to our unpublished data, significant autonomic nervous symptoms appear if the sleeping/waking time and/or eating time fluctuate by > 90 min. Therefore, the adequate limit is assumed to be within 120 min.

2.3. Neonatal sleep pattern

The neonatal sleep patterns were as follows: 1. normal wake up every 3 h; 2. continuous sleep, >6 h: require less care; 3. keep waking up, wake up every 15–120 min; 4. difficulty in falling asleep, need >60 min; 5. short sleep hours, <8 h/day; and 6. crying too much and grumpiness. In the study, we indicated that children who had continuous sleep (condition 2.) were apathetic/under-reactive type neonates and those who kept waking up, had difficulty falling asleep, had short sleep hours, and cried too much and were grumpy (conditions 3–6) were irritable/over-reactive type neonates. In addition, questionnaires in the neonatal period were selected from the results of our preliminary study conducted in 2012 on 60 patients with ASD.

2.4. Status of parent(s) in the child-rearing years

The statuses of parents were as follows: 1. Slight fatigue; 2. fatigue related to trouble with the child's sleep; 3. exhaustion without sleep; 4.

Table 1
Characteristics of the subjects at the time of the study.

	Control		K-ASD		H-ASD	
Age (years old)	Male	Female	Male	Female	Male	Female
1	23	24			3	3
2	20	20	3	0	3	0
3	21	24	16	3	4	2
4	21	18	27	8	17	3
5	13	9	30	13	5	6
6	6	4	18	3	8	2
Total	104	99	94	27	40	16
Overall total	203		121		56	

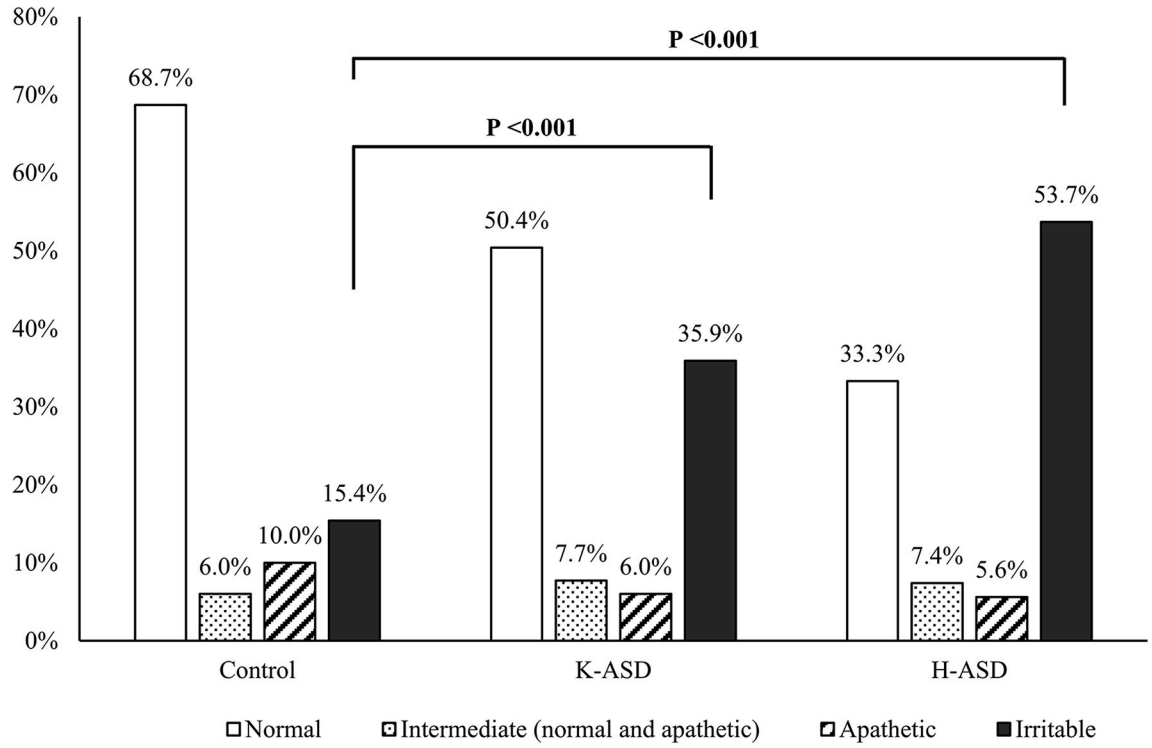

Fig. 1. Differences in the number of irritable-type neonates between the ASD and control groups.

depression; 5. Increased quarrels between partners; and 6. exhaustion of the surrounding family.

2.5. Statistical analyses

Fisher's exact test was used for comparison of the categorical variables. The association between sleep type and ASD was analyzed using multivariable logistic regression modeling. This association was measured as the odds ratio (OR) and 95% confidence intervals (95% CI) for the prevalence of ASD. Structural equation modeling was used to assess both direct and indirect associations among maternal lifestyle during pregnancy, neonatal sleep pattern, ASD development, and sleep status of parent(s) during the child-rearing years. The goodness-of-fit in the structural equation model was evaluated based on the following criteria: Bentler-Bonett Normed Fit Index (NFI) > 0.90, Bollen's incremental fit index (IFI) > 0.90, Tucker-Levis index (TLI) > 0.90, and root mean square error of approximation (RMSEA) < 0.05. A value of $P < 0.05$ was considered statistically significant. Multiple comparisons were corrected using Bonferroni's method, and P-values <0.05/n were considered statistically significant after correcting for the number of comparisons made.

3. Results

The characteristics of the study subjects at the time of the research are shown in Table 1. Fig. 1 shows the association between an irritable-type neonate and ASD. The number of irritable-type neonates was significantly higher in both the K-ASD and H-ASD groups compared to the control group ($P < 0.001$ and $P < 0.001$, respectively) (Fig. 1). Moreover, the number of irritable-type neonates was significantly higher in both the K-ASD and H-ASD groups than in the control group (OR [95% CI]: 3.17 [1.82–5.52] and 7.17 [3.54–14.52], respectively). However, the associations between the number of apathetic-type neonates and ASD were not observed (Fig. 1).

Next, we analyzed the differences in maternal lifestyle behaviors during pregnancy between ASD and control groups. The number of mothers who went to bed after midnight during pregnancy was significantly higher in the H-ASD group than in the control group ($P < 0.01$) (Fig. 2). Contrastingly, the numbers did not differ in the K-ASD and control groups ($P = 0.419$) (Fig. 2). Other maternal lifestyle behaviors during pregnancy did not differ between the ASD and control groups.

Figs. 3 and 4 show the differences in neonatal sleep patterns between the ASD and control groups. The number of infants who slept normally, kept waking up, had difficulty falling asleep, and cried too much and exhibit grumpiness were different between the K-ASD and control groups (Fig. 3). The numbers of infants who slept normally, kept waking up, exhibited difficulty falling asleep, exhibited short sleep hours and cried too much and exhibited grumpiness were significantly different between the H-ASD and control groups (Fig. 4).

Finally, we evaluated the relationships between maternal lifestyle during pregnancy, neonatal sleep pattern, ASD development and sleep status of the parent(s) during the child-rearing years. Fig. 5 shows the structural equation model used in the K-ASD and control groups. The NFI, IFI, TLI and RMSEA were 0.991, 1.024, 1.079 and < 0.001, respectively. Generally, these fitness statistics indicated a good fit for the structural equation model. Irregular eating patterns and going to bed

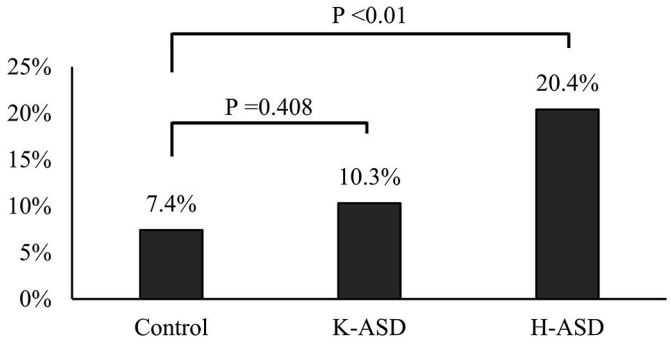

Fig. 2. The number of mothers who went to bed after midnight during pregnancy in the ASD and control groups.

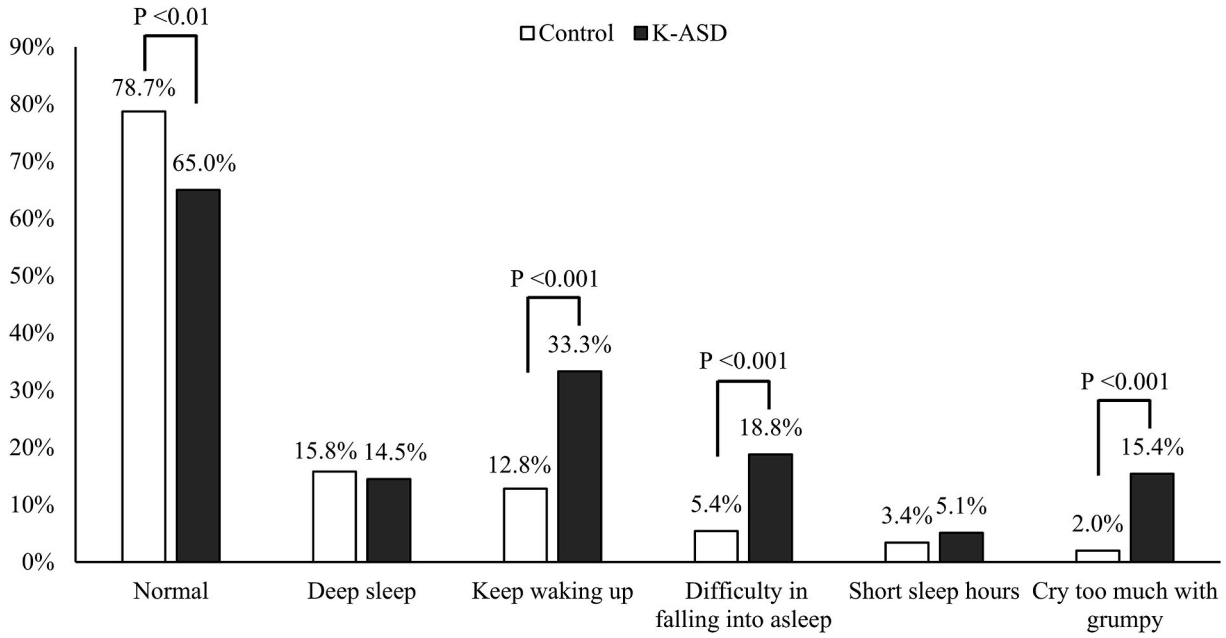

Fig. 3. Differences in neonatal sleep patterns between the K-ASD and control groups.

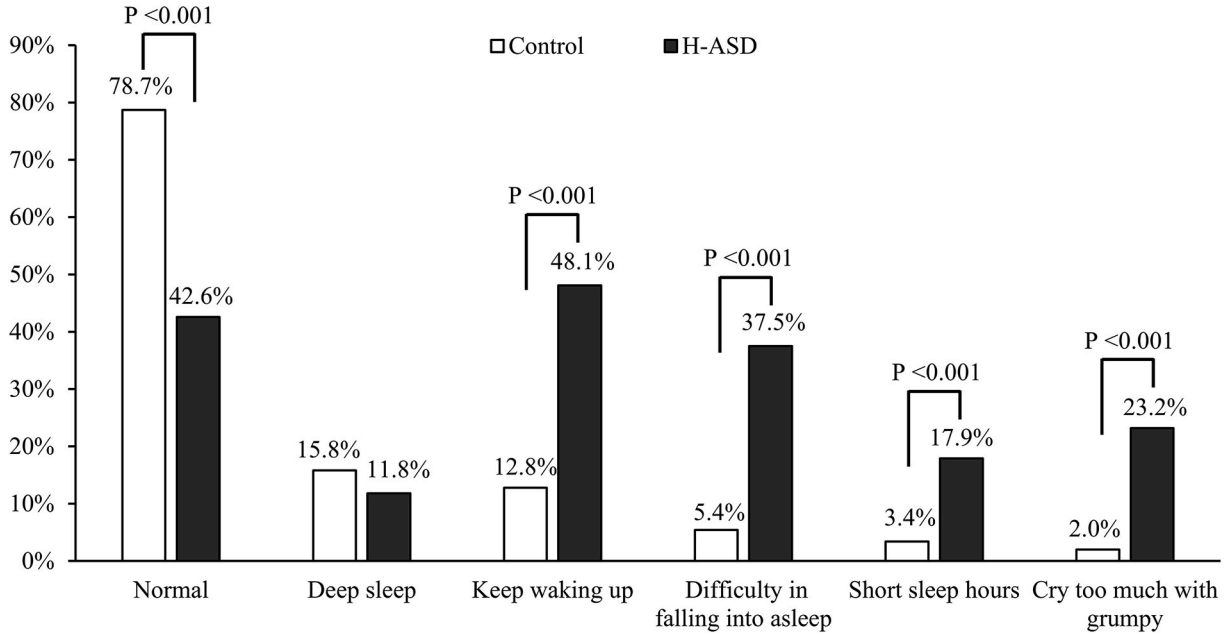

Fig. 4. Differences in neonatal sleep patterns between the H-ASD and control groups.

after midnight during pregnancy influenced the development of ASD indirectly by encouraging difficulty falling asleep during the neonatal period (Fig. 5). Moreover, ASD development was associated with fatigue related to trouble with the child's sleep and exhaustion of the parents without sleep (Fig. 5). Fig. 6 shows the structural equation model conducted in the H-ASD and control groups. The NFI, IFI, TLI and RMSEA were 0.965, 1.032, 1.064 and < 0.001, respectively, and these fitness statistics indicated a good fit for the structural equation model. Going to bed after midnight during pregnancy appeared to influence the development of ASD directly and indirectly through difficulty

falling asleep during the neonatal period (Fig. 6). Additionally, ASD development was associated with parents who were exhausted without sleep, those who were developing depression, and those with exhaustion of the surrounding family (Fig. 6). Furthermore, the risk of developing ASD was significantly greater at <35 weeks of gestation (OR, 24.67) compared to 35–36(0.32), 37–39 (1.11) and ≥40 (1.00) weeks of gestation in the H-ASD group (Table 2). However, maternal diabetes and hypertension during pregnancy were not associated with an increased risk of developing ASD.

4. Discussion

In our study, the irritable-type neonate that exhibited excessive crying was also recognized in approximately 16% of the controls; these neonates settled and decreased in number within 6 months (data not shown). Crying or irritability, also known as being unsettled, is commonly observed (Douglas and Hiscock, 2010) and reported in up to 20% (Hiscock and Jordan, 2004) of infants.

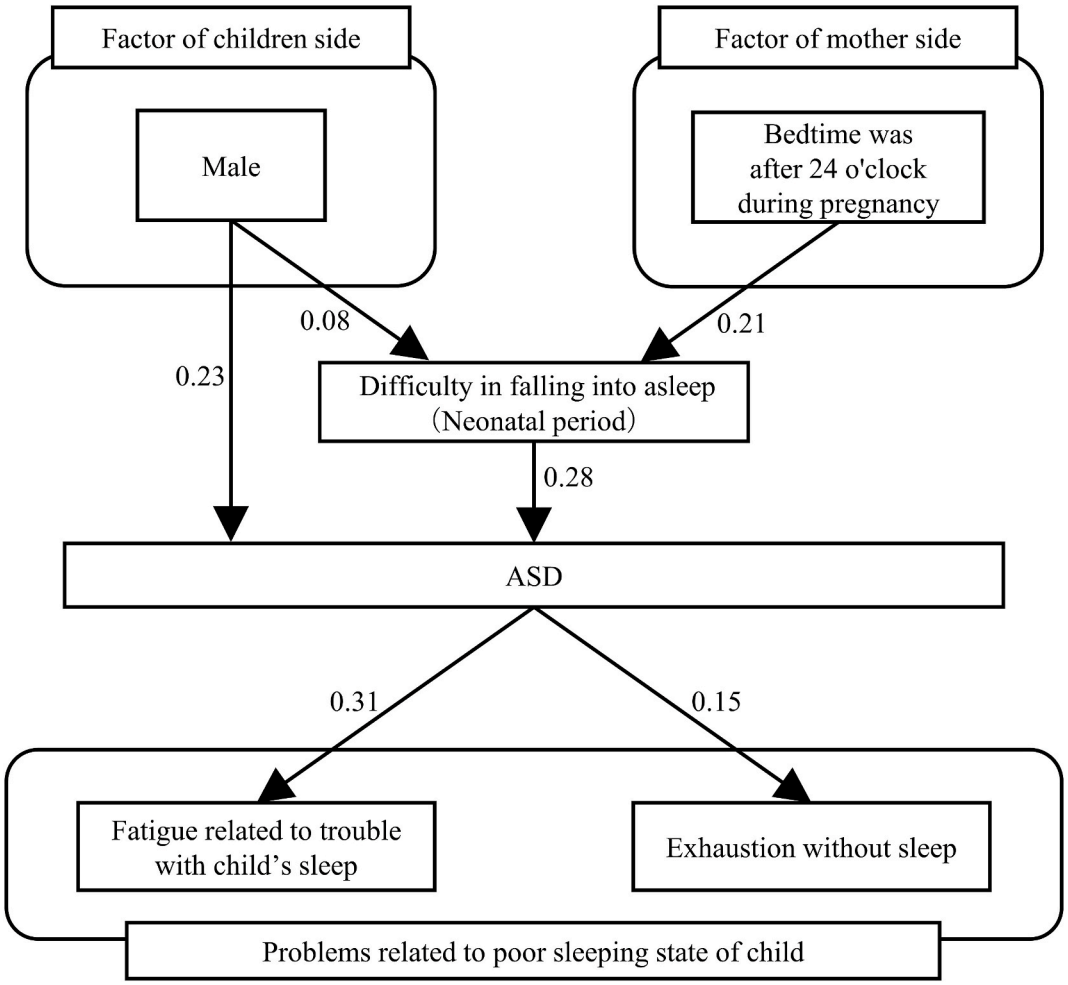

Fig. 5. Structural equation model used in the K-ASD and control groups.
Lines with numbers indicate significant paths with standardized partial regression coefficients ($P < 0.05$). Arrows represent an association between two factors. A positive value represents a positive correlation and a negative value represents a negative correlation. ASD, autism spectrum disorder.

Interestingly, the longitudinal observation of irritable infants showed differences such as an increase in the amount and intensity of crying and more disrupted sleep-wake rhythms, compared with non-irritable infants (Keefe MR et al., 1996. Hiscock and Jordan, 2004).

Excessive crying was also shown to be associated with increased risks for postnatal depression, long-term psychological disturbance and child abuse (Douglas and Hiscock, 2010).

In our study, sleep-wake rhythm abnormalities in the neonatal period suggest immature or disrupted formation of ultradian rhythm during the fetal period in the pons and medulla oblongata and asimultaneously circadian rhythm formation in the SCN mainly after birth (Wimpory et al., 2002; Nicholas et al., 2007; Bourgeron, 2007; Tordjman et al., 2015).

It has been reported that formation of the center regulating ultradian rhythms begins at 29–33weeks (Wakayama et al., 1993) and/or 28–30 weeks of gestation (Fukushima et al., 2008). Ultradian rhythm was divided into four groups by period: (group I, 5—30 min; group II、30–60 min; group III, 60–100 min; group IV, >100 min) (Wakayama et al., 1993). Changes in the characteristic values of ultradian components in group II, which seemed to be the clinically basic rhythm in neonates, showed that there were critical periods in the development of central nervous activity at 29 and 33 weeks of gestation. Immaturity of the ultradian rhythm center is considered one of the main causes of ultradian rhythm abnormalities, such as irritable-type. In this study, the risk of ASD development was significantly greater at <35 weeks (OR, 24.67) compared to 35–36 weeks (0.32), 37–39 (1.11) and ≥40 weeks (1.00) of gestation in the H-ASD group. Despite having no observed differences, the K-ASD group still generated an OR of 5.64, which suggests a tendency in this group that should not be ignored. Although prevalence estimates vary widely across studies, it has been reported, that extremely preterm (<26 weeks) (Johnson et al., 2010) and early preterm infants (Darcy-Mahoney et al., 2016; Harel-Gadassi et al., 2018) (<33 6/7 weeks) are at an increased risk of developing ASD.

Our findings suggest that maternal bedtime lifestyle is related to increased risk of the child being irritable-type neonates and possibly developing future ASD, especially in the H-ASD group. Although, no statistical abnormality was shown in the K-ASD group, going to bed after midnight during pregnancy appeared to influence the development of ASD directly and indirectly through difficulties in falling asleep in the irritable-type neonate. It has been reported that, maternal rhythms influence the fetus, and fetal rhythms feed back to the mother (via placenta). Disruption of this fetal-maternal interaction during gestation leads to the following: 1) disturbances in maternal and fetal circadian rhythms; 2) disappearance of circadian rhythms at the time of birth; 3) gestational period that is either too short or too long; and 4) delayed or impaired maturation of the circadian rhythms of the infant (Mirmiran and Lunshof, 1996). Additionally, disturbed sleep in pregnancy may also be associated with preterm birth (Strange et al., 2009), which induces an indirect cause of ASD development.

Thus, the results of our study of pregnant mothers suggested the necessity of a future study on the daily life, including bed and mealtime. In this study, sleep problems, including short sleep hours and/or sleep

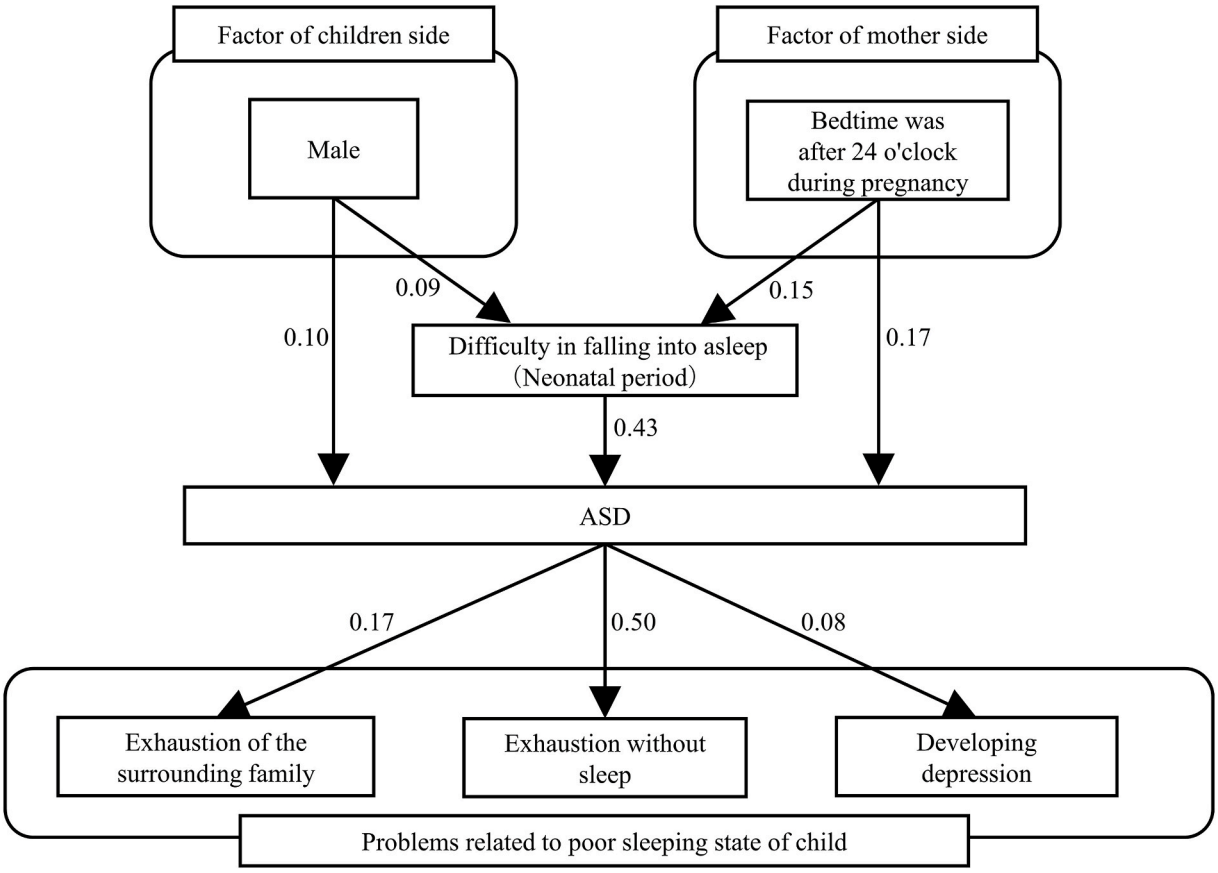

Fig. 6. Structural equation model used in the H-ASD and control groups. Lines with numbers indicate significant paths with standardized partial regression coefficients ($P < 0.05$). Arrows represent an association between two factors. A positive value represents a positive correlation and a negative value represents a negative correlation. ASD, autism spectrum disorder.

Table 2
The relationship between ASD prevalence and maternal gestational week.

Gestational week	Control	K-ASD				H-ASD			
	N (%)	N (%)	OR	95% CI	P	N (%)	OR	95% CI	P
40 weeks	74 (38.5)	42 (36.5)	1			18 (34.0)	1		
37–39 weeks	104 (54.2)	67 (58.3)	1.14	0.70–1.85	0.610	28 (52.8)	1.11	0.57–2.15	0.764
35–36 weeks	13 (6.8)	3 (2.6)	0.41	0.11–1.51	0.179	1 (1.9)	0.32	0.04–2.58	0.282
<35 weeks	1 (0.5)	3 (2.6)	5.29	0.53–52.44	0.155	6 (11.3)	24.67	2.79–2170.94	0.004

deprivation in both of the mother and neonate may induced lack of melatonin secretion (Huang et al., 2014; Chen et al., 2015; Touitou et al., 2017; Gao et al., 2019).

Recently, it was reported that, low parental melatonin levels could be one of the contributors to ASD and possibly intellectual disability etiology (Braam et al., 2018).

In fact, we realize that sleep-wake rhythm correction in ASD is often extremely effective in actual daily practice, especially when using melatonin (Tomoda et al. 1994, 1999), and recent studies also support the effectiveness of the therapy (Tordjman et al., 2015; Gringras et al., 2017; Gagnon and Godbout, 2018; Maras et al., 2018) with almost no side effects (Ninomiya et al., 2001).

Interestingly, it has been reported that, ultradian and circadian cycles, do not run independently, but constitute a system of connected oscillators even in the neonatal period (Meier-Koll et al.,1978; Freudigman and Thoman, 1994). A recent study reported the dual-oscillator theory, observed a marked bi-modal sleep-wake pattern, as evidenced by the appearance of a pronounced ~12-h component in the periodogram of the neonatal rats, and suggested the presence of two ~24-h components consistent with the dual-oscillator concept. Moreover, the authors claimed that the maturation of circadian organization of sleep-wake behavior precedes the expression of mature sleep homeostasis, in the Long–Evans rat strain (Frank et al., 2017).

These reports may also indicate the importance of the living environment after birth, including, feeding, (Löhr and Siegmund, 1999; Frank et al., 2017; Kinoshita. et al., 2018), lighting (Rivkees, 2007), warmth and contact behavior with affection (Frank et al., 2017).

It has been anticipated that consideration of circadian biology will become an increasingly important component of neonatal care (Rivkees, 2007) and also suggested that neonate's sleep characteristics during the first postnatal day provide uniquely sensitive indices of later neurobehavioral function (Freudigman and Thoman, 1993).

Children diagnosed with ASD more often showed a neonatal sleep status of irritability or over-reactivity, suggesting a strong relationship between the two conditions. Sleep-wake rhythm abnormalities in the neonatal period suggest that there is a failure of circadian rhythm, following ultradian rhythm formation and these abnormalities may be considered important information relating to early intervention with

possible prevention of ASD, and for research related to ASD.

In contrast, the apathetic type characteristics showed no relationship to ASD development. After a neonate has been managed, some cases of apathetic type later shift into an irritable type, and there are those who shift to a normal sleep/wake rhythm. The results suggested that the apathetic type is included in the normal sleep/wake rhythm, as "the sleeping child grows up", in addition to exhibiting an abnormal ultradian cycle.

It has also been known that, ASD has links to many biological clock functions, and it is more logical to understand and interpret it based on circadian rhythm and pineal gland function (melatonin). (Geoffray et al., 2016; Shomrat and Nesher, 2019).

There is a possibility that follow-up with irritable/over-reactive type neonates and intervention in correcting sleep-wake rhythm abnormalities at an appropriate time (Okun et al., 2011; Touchette et al., 2013) may prevent the subsequent onset of ASD.

5. Conclusion

Neonatal sleep-wake rhythm abnormalities, especially in irritable-type neonates, are important precursors for future ASD development. The findings of this study suggest that it is important to pay much more attention to the maternal role in fetal chronobiology formation and to circadian rhythm formation, which have crucial roles in child development, and protect health throughout human life. This finding provides useful information for the prophylactic treatment of ASD in the future. We hope this study offers a new direction for future ASD therapy, prevention and research.

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Ethical approval

The study complies with the Declaration of Helsinki and was approved by the ethics committees of the H-Rehabilitation Central Hospital. All analyses were performed in accordance with Ethical Guidelines for Epidemiological Research in Japan.

Informed consent

All parents of children provided written informed consent prior to enrollment in the study.

Declaration of competing interest

The authors have no conflicts of interest relevant to this manuscript to disclose.

CRediT authorship contribution statement

Teruhisa Miike: Conceptualization, Formal analysis, Writing - original draft, Writing - review & editing, Data curation. **Makiko Toyoura:** Formal analysis, Writing - original draft, Writing - review & editing. **Shiro Tonooka:** Writing - original draft, Writing - review & editing. **Yukuo Konishi:** Formal analysis, Writing - original draft, Writing - review & editing. **Kentaro Oniki:** Formal analysis, Writing - original draft, Writing - review & editing. **Junji Saruwatari:** Formal analysis, Writing - original draft, Writing - review & editing. **Seiki Tajima:** Formal analysis, Writing - original draft, Writing - review & editing. **Jun Kinoshita:** Writing - original draft, Writing - review & editing, Supervision. **Akio Nakai:** Formal analysis, Writing - original draft, Writing - review & editing. **Kiyoshi Kikuchi:** Formal analysis, Writing - original draft, Writing - review & editing.

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