SLEEPJ, 2018, 1–7

doi: 10.1093/sleep/zsy009
Advance Access Publication Date: 6 January 2018
Original Article

ORIGINAL ARTICLE

Sleep findings in Brazilian children with congenital Zika syndrome

Luciana Pinato[1,*], Erlane M. Ribeiro[2,3], Rebeka F. P. Leite[2], Thayse F. Lopes[2], André L. S. Pessoa[2,5], Leila M. Guissoni Campos[4], Giovanna E. Piffer[4], Ana L. D. M. Souza[1] and Célia M. Giacheti[1]

[1]São Paulo State University – UNESP, Marilia, São Paulo, Brazil, [2]Albert Sabin Children's Hospital, Fortaleza, Ceará, Brazil, [3]Christus University Center, Fortaleza, Ceará, Brazil, [4]University of Marilia – UNIMAR, Marilia, São Paulo, Brazil and [5]State University of Ceará (UECE), Fortaleza, Ceará, Brazil
Work Performed: CAVIVER, a nongovernmental organization clinic in Fortaleza, Ceará, Brazil.

*Corresponding author. Luciana Pinato, Av. Hygino Muzzi Filho, 737, Mirante – Marília, São Paulo, Brazil. Email: lpinato@marilia.unesp.br.

Abstract

Study Objectives: Zika virus infection during pregnancy may result in congenital Zika syndrome (CZS), whose characteristics are being described.

Methods: The aim of the present study was to investigate the sleep characteristics of 136 infants and toddlers (88 with CZS and 48 with typical development [TD], age and gender matched, 60% girls and 40% boys in both groups) using the Brief Infant Sleep Questionnaire. The ages of children in both groups ranged from 5 to 24 months (CZS 15.9 ± 0.4 vs. TD 15.8 ± 1.0 months, $p = 0.90$).

Results: The results show that 34.1% of CZS and 2% of TD children were defined as poor sleepers, 15% of CZS and 2% of TD children remained awake at night for a period longer than 1 hr, and 24% of CZS and 2% of TD children slept less than 9 hr. The CZS group showed shorter total sleep time (CZS 11.24 ± 2.6 vs. TD 12.02 ± 1.9 hr, $p = 0.03$) and shorter nocturnal sleep duration than the TD group (CZS 8.2 ± 0.2 vs. TD 9.4 ± 0.2 hr, $p = 0.0002$). In contrast to the control group ($p = 0.02$, $r = -0.34$), in the CZS group, no correlation was found between age and nocturnal wakefulness. Future studies should explore these data in relation to the development and maturation of the central nervous system of these children.

Conclusions: Considering the well-known consequences of poor sleep quality on health in several populations, the presence of sleep disorders should be considered in CZS using multidisciplinary treatments.

Statement of Significance

To characterize clinical aspects in infants with congenital Zika syndrome (CZS), this study investigated the sleep patterns and the presence of sleep problems in 88 infants and toddlers with CZS using the Brief Infant Sleep Questionnaire. The data contribute to a better understanding of this syndrome and highlight that the diagnosis and treatment of sleep disorders should be considered in multidisciplinary therapy in this population. The causes and consequences of sleep disorders in these children should be explored in future studies.

Key words: neurodevelopment; Zika virus; microcephaly; sleep habits

Submitted: 2 September, 2017; **Revised:** 6 December, 2017

Introduction

The Zika virus, declared to be an emerging global health threat in 2016 [1], affects the fetal central nervous system during pregnancy, causing brain anomalies such as severe microcephaly with decreased cortical thickness and malformations, subcortical calcifications, ventriculomegaly, cerebellar and corpus callosum hypoplasia, delayed myelination, and peripheral alterations such as macular scarring and focal pigmentary retinal mottling [2, 6], which compose the congenital Zika syndrome (CZS) features.

The full spectrum of CZS and its consequences are still being described. Clinical features include irritability, convulsions, clonus, crying, epilepsy, dysphagia, neurodevelopmental cognitive and language disorders, motor disorders with congenital contractures, hypertonia, and extrapyramidal disturbances [5, 7, 8]. Although not yet characterized as one of the clinical symptoms of CZS, mothers of infants with CZS often complain of sleep problems in their children.

In fact, it is known that sleep problems are more frequent in children with developmental abnormalities [9–11]. The sleep–wake cycle is a complex phenomenon that depends on the integrity of various structures such as brainstem nuclei, reticular formation, thalamus, and hypothalamus, specifically the suprachiasmatic nucleus, pineal gland, and cortex [12–14]. Thus, several of the brain anomalies present in CZS could lead to a disruption in the sleep–wake cycle pattern.

In spite of this evidence, there is currently no literature about the biological and behavioral aspects of the sleep–wake cycle in this population. The only study to investigate sleep characteristics in patients with CZS showed abnormalities in electroencephalographic (EEG) recording patterns during spontaneous sleep, such as interictal epileptogenic activity and hypsarrhythmia, drawing attention to the importance of studying sleep in this population [15].

In addition to being an important marker of neurodevelopment [16, 17], sleep is a modulator of development, quality of life, cognitive performance, behavior, language, and learning as well as metabolic and immune systems [10, 11, 18, 19]. The severity of sleep disturbances is also reflected in the stress levels, health, and quality of life of parents, with negative consequences on the effectiveness of behavioral treatments as a result of reduced child performance and reduced parental ability to correctly apply treatment techniques and strategies [20–23].

The importance of the early characterization is that many of the negative repercussions of sleep disorders can be reversed when these children are submitted to interventions to minimize and/or remedy such problems [24].

Considering the lack of information about sleep in these children for multidisciplinary professionals, the aim of the present study was to investigate sleep characteristics of children with CZS with the use of a sleep evaluation questionnaire.

Methods

This study is part of a multidisciplinary research project approved by the Ethics Committee in Research of the Albert Sabin Children's Hospital, Fortaleza, Ceará, Brazil (protocol number 1.743.023). The results of this research project have been published in several studies in recent years [25–29].

Since 2016, more than 200 infants with CZS were referred by Albert Sabin Children's Hospital and by state health services to the CAVIVER, a nongovernmental organization clinic in Fortaleza, Ceará, Brazil, that promotes multidisciplinary therapy for children. Some of the patients, who were present at the last two family support meetings, were invited to participate in the present study, and 88 accepted.

Mothers or legal guardians of 136 infants and toddlers (with CSZ or with typical development [TD]) that participated in this study signed informed consent forms prior to answering the sleep questionnaire.

A total of 70.4% of the mothers in the CZS group (24.3 ± 5.9 years old) were infected by the Zika virus in the first, 22.2% in the second, and 3.7% in the third trimester of gestation. The socioeconomic status of the families included 68% in category E (less than two basic salaries), 18% in category D (between two and four basic salaries), and 14% in category C (between four and 10 basic salaries), following the socioeconomic stratification criteria of the Brazilian Institute of Geography and Statistics (IBGE). In 2017, the basic salary in Brazil was 937.00 Brazilian real (BRL) or 291.18 American dollars (USD).

The indicators of sleep disturbances of the mothers were obtained from the Pittsburgh Sleep Quality Index (PSQI). The PSQI is a self-rated questionnaire that assesses sleep quality and disturbances over a 1 month time interval and probes clinically important and patient-relevant symptoms in the areas of sleep quality and quantity. The PSQI consists of 19 self-rated items divided into seven subscales: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. Each subscale is rated from 0 to 3, with a higher score indicating a more severe sleep complaint. The summed score of the seven subscales yields a single global score that represents the patient's overall sleep experience; a lower total score reflects a better quality of sleep. A global PSQI score greater than 5 is an indication that the person has great difficulties in at least two components of sleep quality or moderate difficulties in more than three components of sleep quality [30].

The ages of the infants and toddlers with CZS (CZS group, $N = 88$) ranged from 5 to 24 months, and the inclusion criterion of this group was the diagnosis of CZS. Approximately 5.5% of this group were preterm, and 94.5% were full term. The mean ± standard deviation (*SD*) of cephalic perimeter was 29.7 ± 2.1 cm (range, 25–32 cm), birth weight, 2,699 ± 483 g, and stature, 45.2 ± 3 cm. Seventy-seven percent of the CZS group children had an epilepsy diagnosis. Data about medication use in the CZS children are described in Table 1; more than 78% of the CZS group used some type of medication, and 65.9% of them used drugs that may cause side effects such as sedation or drowsiness.

After the CZS group was assembled, infants and toddlers with TD, with no history of neuropsychomotor developmental abnormalities and an absence of brain injuries, genetic syndromes, congenital malformations, and hearing or visual impairments, paired by age (CZS 15.9 ± 0.4 vs. TD 15.8 ± 1.0 months, $t(134) = 0.11$, $p = 0.90$), gender (CZS 59.1% girls and 40.9% boys; TD 60.4% girls and 39.6% boys), and socioeconomic status (control group, 62% in the category E, 20% in D, and 18% in C) to the CZS group were recruited as a comparison group. The TD group was recruited from people familiar with the CZS group's own families or by the team involved in the project using advertisements

on parenting websites and other related-media channels. Data collection from the control group was performed the week after the collection from the CZS group. More than 100 parents of infants and toddlers with TD were invited to participate, and 48 accepted. Thus, for both groups, the sample size was determined by convenience.

Data collection from the CZS group was performed in December 2016 and in July 2017, to compare the data of children at two time points with an interval of 6 months. The data of 88 infants and toddlers were collected at the first time point, and the data of 15 of these infants and toddlers were collected at both time points. The mothers of infants and toddlers with CZS responded to the Brief Infant Sleep Questionnaire (BISQ), a tool for screening sleep disorders in infants and toddlers (0–3 years).

The BISQ version used was translated into Brazilian Portuguese [31] and included questions that addressed the following variables: nocturnal sleep duration (between the hours of 07:00 pm and 07:00 am), daytime sleep duration (between the hours of 07:00 am and 07:00 pm), number of night wakings, duration of wakefulness during the night hours (10:00 pm to 06:00 am), nocturnal sleep-onset time, settling time (latency to falling asleep for the night), method of sleeping, location of sleeping, preferred body position to sleep, age, and gender. The criteria for defining whether a child has a sleep disorder included the following: the child wakes up more than three times at night; the child remains awake for more than 1 hr at night; or the total sleep time is less than 9 hr.

In addition to the calculation of the percentage of children with indications of a sleep disorder, the percentages of sleep location and sleep behaviors, data are also presented as the mean ± *SD* for the comparative statistical analyses of sleep duration, bedtime routine components, and night waking. Complementarily, both groups were subdivided by semesters in the age groups, from 0 to 6, 6.1 to 12, 12.1 to 18, and 18.1 to 24 months.

The comparisons between groups (CZS vs. TD) were analyzed by t tests when only one parameter was analyzed or by an analysis of variance (ANOVA) when several parameters were analyzed; statistical significance was defined as $p \leq 0.05$. The correlations between sleep and age were analyzed using Spearman's correlation test.

Table 1. Medication influencing sleep in CZS group

Baclofen† (4 individuals)	Oxybutynin† (1individual)
Clonazepam† (4 individuals)	Passionflower† (3individuals)
Domperidone (8 individuals)	Phenobarbital† (8 individuals)
Doxazosin† (1 individual)	Ranitidine† (6 individuals)
Levetiracetam† (6 individuals)	Valproate† (19 individuals)
Nitrazepam† (4 individuals)	Vigabatrin† (5 individuals)

CZS = congenital Zika syndrome; *N* = 88.
†This medication causes drowsiness.

Results

The BISQ sleep pattern analysis showed that 34.1% of children with CZS were defined as poor sleepers, 3.5% had more than three awakenings at night, 15% remained awake at night for a period longer than 1 hr, and 24% had less than 9 hr of total sleep time (total hours of day and night sleep). In the TD group, 2% of children were defined as poor sleepers, no child presented more than three awakenings at night, 2% stayed awake at night for a period longer than 1 hr, and 2% had less than 9 hr of total sleep time.

When only nocturnal sleep duration was analyzed, 51% of the CZS group and 20.8% of the TD group presented less than 9 hr of sleep.

The CZS group showed lower total sleep time [CZS 11.24 ± 2.6 vs. TD 12.02 ± 1.9 hr, t (134) = 1.8, p = 0.03; Figure 1A] and lower nocturnal sleep duration than the TD group [CZS 8.2 ± 0.2 vs. TD 9.4 ± 0.2 hr, t (134) = 3.8, p = 0.0002; Figure 1B]. There was no difference between groups in daytime sleep duration [CZS, 3.1 ± 2.0 vs. TD, 2.6 ± 1.5, t (134) = 1.47, p = 0.14; Figure 1C].

When the average number of night wakings (Figure 2A) and the duration of nocturnal wakefulness (min) (Figure 2B) were analyzed, there were no differences between the groups, although the CZS group had greater heterogeneity and higher individual values (up to 700 min) of the duration of nocturnal wakefulness (Figure 2B).

The CZS group had a longer settling time or sleep latency (min) than the TD group (CZS, 49.7 ± 70.1 vs. TD, 25.3 ± 16.6, p = 0.02; Figure 2C). The average nocturnal sleep-onset time was later for the CZS group (CZS, 22.35 ± 1.7 vs. TD, 21.47 ± 1.18, p = 0.04), who presented greater heterogeneity, with some children having sleep-onset time after 24 hr (Figure 2D).

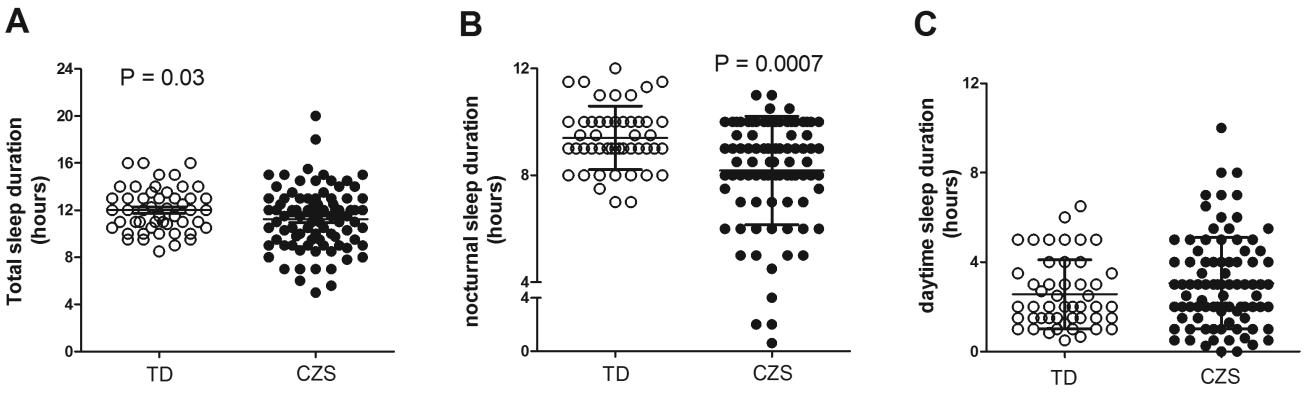

Figure 1. Sleep duration (hr) of children with CZS, *N* = 88 and those with TD, *N* = 48. The white circles represent the children in the TD group, and the black circles represent the children in the CZS group. (A) The horizontal bars represent the mean ± *SD* of total sleep time (day and night). (B) The mean ± *SD* of sleep duration at night time (07:00 pm–07:00 am) is shown. (C) The mean ± *SD* of sleep duration at daytime (07:00 am–07:00 pm) is shown.

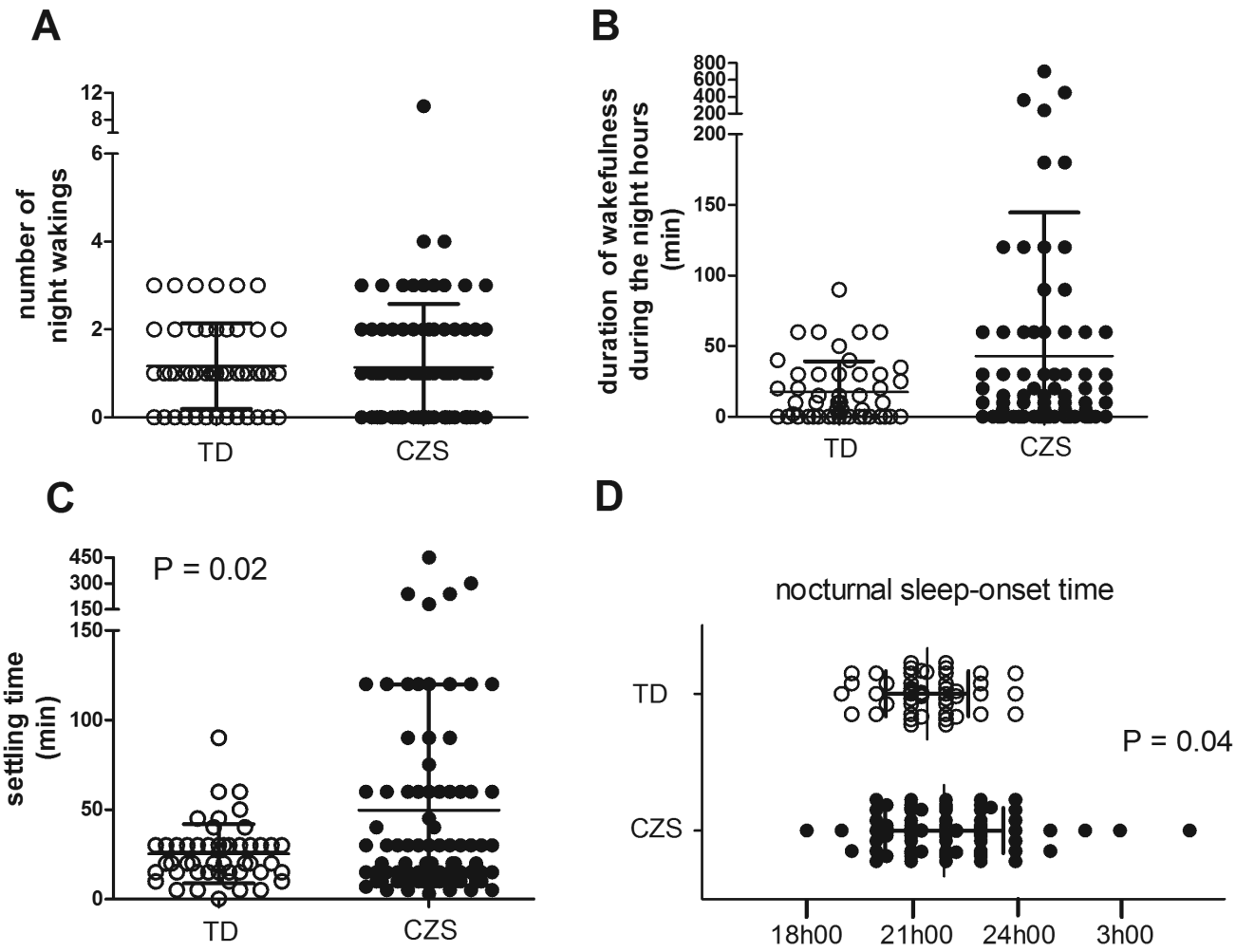

Figure 2. Sleep patterns of children with CZS, *N* = 88 and those with TD, *N* = 48. The white circles represent the children in the TD group, and the black circles represent the children in the CZS group. (A) The horizontal bars show the mean ± *SD* of the number of night awakenings. (B) The mean ± *SD* of the duration of nocturnal wakefulness in minutes (min) is shown. (C) The mean ± *SD* of the settling time or sleep latency in minutes (min) is shown. (D) The mean ± *SD* of nocturnal sleep-onset time is shown.

There were no differences between genders in the sleep parameters analyzed. The analysis of CZS and TD groups subdivided by age in semesters (0 to 6; 6.1 to 12; 12.1 to 18; and 18.1 to 24 months) showed that CZS and TD groups differed in daytime sleep duration in the 0–6 month subgroup; in addition, daytime sleep decreased significantly with age from children in the first (5.8 ± 1.6 hr) to children in the second semester of life (2.2 ± 2.2 hr, $p = 0.01$) in the CZS group (Figure 3B).

When a group of children with CZS was analyzed twice over an interval of one semester, 46.6% showed an increase in total sleep duration, 33.4% did not change, and 20% showed a decrease in the total sleep duration.

The correlation analysis between the sleep parameters and the age of the children showed that in the TD group, the nocturnal wakefulness presented a negative correlation with age ($p = 0.02$, $r = -0.34$; Figure 4A). Interestingly, in the CZS group, no correlation was found between age and nocturnal wakefulness ($p = 0.13$) or other sleep parameters (Figure 4B).

In the TD group, most of the infants (52.2%) slept in a crib in the parents' room; 30.4% were reportedly sleeping in a separate crib in a separate room, whereas 17.4% were reported to be sleeping in their parents' bed. In the CZS group, there was no

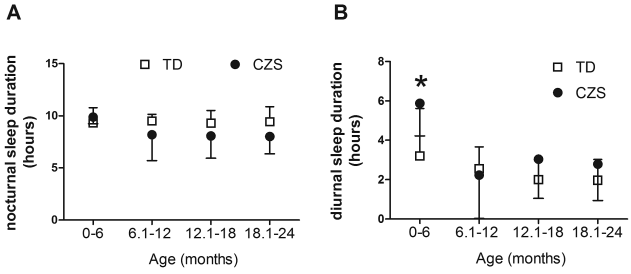

Figure 3. Sleep parameters of children with CZS, *N* = 88 and those with TD, *N* = 48, compared by age. (A) and (B), respectively, show the mean ± *SD* of nocturnal sleep duration (between 07:00 pm and 07:00 am) and diurnal sleep duration (between 07:00 am and 07:00 pm) by semester (0 to 6; 6.1 to 12; 1 to 18; and 18.1 to 24 months). The white squares represent the children in the TD group, and the black circles represent the children in the CZS group.

difference between the percentage of infants that slept in a crib in the parents' room (48.7%) and those sleeping in their parents' bed (47.5%). Just 3.8% of the CZS infants were reportedly sleeping in a separate crib in a separate room.

Almost one-third of the children with TD (34.8%) were soothed to sleep while being fed, one-third (34.8%) fell asleep

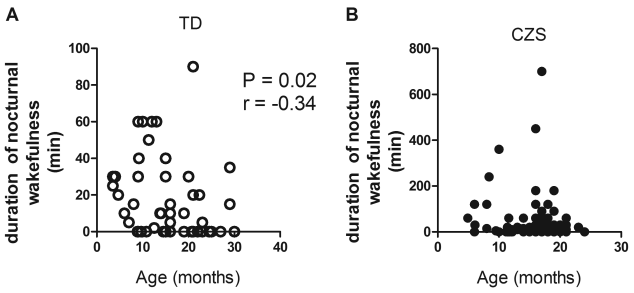

Figure 4. Correlations between the duration of nocturnal wakefulness in minutes (min) and age in the TD, N = 48 (A) and children with CZS, N = 88 (B) groups. The open circles represent the children in the TD group, and the closed circles represent the children in the CZS group.

alone in the crib, and one-third (30.4%) while being rocked. In the CZS group, 55% of children were soothed to sleep while being rocked. The second most common method of falling asleep in the CZS group was alone in the crib (23.7%), followed by falling asleep while being fed (21.3%).

Regarding the mothers' concern about the sleep patterns of the children, 13.7% of the mothers of the TD group considered their child's sleep a minor problem and none of them considered their child's sleep to be a severe problem. In the CZS group, 20% of the mothers considered their child's sleep to be a minor problem and 42% considered their child's sleep to be a severe problem.

The analysis of the mothers' sleep quality showed that 70.6% of the mothers of the CZS group and 20% of the mothers of the controls had an indication of great difficulties in at least two components of sleep quality or moderate difficulties in more than three components of sleep quality (Pittsburgh score: CZS 8.0 ± 4.9 vs. control 3.8 ± 2.7, $p = 0.0087$).

Discussion

Although infant sleep problems are among the most prevalent problems presented to paediatricians and other child-care professionals [32], to the best of our knowledge, this is the first study to screen sleep disorders in a population of infants and toddlers with CZS.

We have found that 34.1% of this population was defined as poor sleepers. Approximately 24% of the children with CZS sleep less than 9 hr of total sleep time (total hours of day and night sleep). These percentages are high, even for infants, in whom it is expected that the sleep–wake cycle is not yet consolidated, at least before the first year of life [33]. In the core *FOXG1* syndrome, which consists of postnatal microcephaly, severe mental retardation, absence of language, dyskinesia, and corpus callosum hypogenesis, sleep was disrupted from infancy in at least 8/11 children, with frequent nighttime waking [34].

The prevalence of sleep disorders varies between 5% and 40% in typically developing individuals [35]. In Table 2, we describe the results of the present study and the results from the literature using the same questionnaire. Some aspects are quite variable because of differences in health conditions and cultural aspects, but infants and toddlers with CZS presented lower nocturnal sleep duration, later sleep-onset time, and longer sleep latency than most of the other children.

However, it is worth emphasizing that this number may still be an underestimation since, in the present study, 65.9% of individuals used drugs that can mask sleep disorders as they may cause side effects such as sedation or drowsiness (Table 1).

In normal conditions, the mechanisms involved in the circadian cycle of sleep and wakefulness are present even before birth, starting at the 18–20th week of gestation, and are generated in the anterior hypothalamus, specifically in the suprachiasmatic nucleus, as well as other diencephalic areas and the brainstem [12, 13]. After birth, this circadian cycle remains generated endogenously but is also modulated by exogenous factors such as light [12–14, 36].

The fact that the CZS group showed lower total sleep time and lower nocturnal sleep duration than the TD group highlights the importance of this aspect in the life quality of children and their families. Sleep deprivation has a negative impact on the pattern of neurogenesis, synaptic plasticity, cognitive performance, behavior, breathing, neuronal development, and blood pressure, contributing to increased morbidity of patients [37].

These children are not developing the expected relationship between sleep and growth that in a normal situation includes brain growth [38]. In children with TD, a progression in the maturation of the circadian system and sleep–wake cycle is expected, but the infants and toddlers with CZS did not succeed in achieving this maturation and their sleep continues to be fragmented; for example, 3.5% had more than three awakenings at night and 15% remain awake at night for a period longer than 1 hr. Although in the TD group the nocturnal wakefulness presented a negative correlation with age, in the CZS group this did not occur. These multiple and/or prolonged night wakings are considered to be a frequent sleep problem during early childhood [39].

The CZS group had a longer settling time or sleep latency (min) than the TD group. The average nocturnal sleep-onset time was later for the CZS group, which presented greater heterogeneity, with some children having sleep-onset times after 24 hr. Sleep latency is modulated by the hormone melatonin, which marks the dark phase for the body, influencing human circadian timing and acting as a sleep modulator by opening the circadian "sleep gate" [40]. In normal conditions, the secretion of melatonin by the pineal gland develops after the second month of life [17, 36], but this was not described in this population. The possible causes of sleep disorders in patients with CZS should be explored in a future study.

In addition to the causes, the consequences of these sleep problems should also be studied, since if not treated, these night-waking problems are persistent [41, 42] and lead to consequences in children's behavior [11, 14, 18, 42] and neurobehavioral functioning [10]. Sleep problems in early childhood can also result in parental stress and psychopathological conditions [20, 43, 44], which can be observed in the present study since 42% of mothers assumed that the sleep of their children represents a severe problem.

The finding of sleep disorders in more than 30% of children with CZS opens a new perspective to explore this aspect in relation to the development and maturation of the central nervous system of these children [45].

Numerous studies have shown that infant sleep disorders are treatable, with high success rates [46, 47] in attenuating their negative implications for infants and their parents. Therefore, considering the well-known consequences of poor sleep quality on general health in several populations, the presence of sleep disorders in this population should be considered in multidisciplinary treatments.

Table 2. Brief Infant Sleep Questionnaire (BISQ) measures in the present study and in the literature

Study	Population	Settling time (hr) Mean ± SD Min–Max	Sleep-onset time (hr) Mean ± SD Min–Max	Nocturnal sleep duration (hr) Mean ± SD Min–Max	Daytime sleep duration (hr) Mean ± SD Min–Max	Total sleep duration (hr) Mean ± SD Min–Max	Night wakings n° Mean ± SD Min–Max	Nocturnal wakefulness (hr) Mean ± SD Min–Max	Severe sleep problem rating, %
Sadeh, 2004	Infants and toddlers 0–3 years		20.6 ± 1.1 18.7–24.0	9.35 ± 1.40 4–12	2.25 ± 0.79 0.3–4	11.61 ± 1.57 7–15.5	3.21 ± 2.47 0–12	0.65 ± 0.64 0–3.5	34.3%
Sadeh, 2004	Clinical infants and toddlers 0–3 years	0.48 ± 0.31		8.91 ± 1.65	2.16 ± 0.78		4.98 ± 2.38	1.05 ± 0.73	
Sadeh, 2004	Control infants and toddlers 5–26 months	0.38 ± 0.33		9.67 ± 1.08	2.32 ± 0.79		1.83 ± 1.45	0.34 ± 0.34	
Mindell et al., 2009	American infants 7–18 months	0.34 ± 0.25		9.6 ± 1.36	2.5 ± 1.08		1.5 ± 0.89	0.39 ± 0.43	1.6
Mindell et al., 2017	Asian infants and toddlers 0–36 months		21.26 ± 1.25	9.19 ± 1.49	3.11 ± 1.78	12.31 ± 2.17	1.69 ± 1.36		
Mindell et al., 2017	Caucasian infants and toddlers 0–36 months		20.25 ± 1.26	10.01 ± 1.57	3.01 ± 1.77	13.02 ± 2.01	1.13 ± 1.15		
Present study	Brazilian typical developmental infants and toddlers 0–24 months	0.42 ± 0.28 0–1.5	21.47 ± 1.18 19.0–24.0	9.4 ± 1.2 7.0–12.0	3.1 ± 2.0	11.24 ± 2.6	1.17 ± 0.97	0.12 ± 0.05	2.0
Present study	Brazilian CZS infants and toddlers 0–24 months	0.83 ± 1.17 0.05–7.5	22.35 ± 1.7 18.0–5.0	8.2 ± 2.0 0.6–11.0	2.6 ± 1.5	12.02 ± 1.9	1.14 ± 1.45	0.71 ± 0,16	34.1

CZS = congenital Zika syndrome.

Acknowledgments

We thank the families of children with congenital Zika syndrome for allowing us to learn from their children.

Funding

This work was supported by FAPESP (11/51495-4) funding grant to L.P.

Notes

Conflict of interest statement. None declared.

References

1. World Health Organization. WHO Statement on the First Meeting of the International Health Regulations (2005) (IHR 2005) Emergency Committee on Zika Virus and Observed Increase in Neurological Disorders and Neonatal Malformations; 2016. http://www.who.int/mediacen-tre/news/statements/2016/1st-emergency-commit-tee-zika/en/.
2. Cragan JD, *et al*. Baseline prevalence of birth defects associated with congenital Zika virus infection – Massachusetts, North Carolina, and Atlanta, Georgia, 2013-2014. *MMWR Morb Mortal Wkly Rep*. 2017; **66**(8): 219–222.
3. de Fatima Vasco Aragao M, *et al*. Clinical features and neuroimaging (CT and MRI) findings in presumed Zika virus related congenital infection and microcephaly: retrospective case series study. *BMJ*. 2016; **353**: i1901.
4. Hazin AN, *et al*.; Microcephaly Epidemic Research Group. Computed tomographic findings in microcephaly associated with Zika virus. *N Engl J Med*. 2016; **374**(22): 2193–2195.
5. Moore CA, *et al*. Characterizing the pattern of anomalies in congenital Zika syndrome for pediatric clinicians. *JAMA Pediatr*. 2017; **171**(3): 288–295.
6. Oliveira Melo AS, *et al*. Zika virus intrauterine infection causes fetal brain abnormality and microcephaly: tip of the iceberg? *Ultrasound Obstet Gynecol*. 2016; **47**(1): 6–7.
7. Moura da Silva AA, *et al*. Early growth and neurologic outcomes of infants with probable congenital Zika virus syndrome. *Emerg Infect Dis*. 2016; **22**: 1953–1956.
8. Ozkurt Z, *et al*. Global alert: Zika virus-an emerging arbovirus. *Eurasian J Med*. 2017; **49**(2): 142–147.
9. Galland BC, *et al*. Anticipatory guidance to prevent infant sleep problems within a randomised controlled trial: infant, maternal and partner outcomes at 6 months of age. *BMJ Open*. 2017; **7**(5): e014908.
10. Santoro SD, *et al*. Correlations between behavior, memory, sleep-wake and melatonin in Williams-Beuren syndrome. *Physiol Behav*. 2016; **159**: 14–19.
11. Fadini CC, *et al*. Influence of sleep disorders on the behavior of individuals with autism spectrum disorder. *Front Hum Neurosci*. 2015; **9**: 347.
12. Horner RL, *et al*. Brain circuitry controlling sleep and wakefulness. *Continuum (Minneap Minn)*. 2017; **23**(4, Sleep Neurology): 955–972.
13. Kahn A, *et al*. Normal sleep architecture in infants and children. *J Clin Neurophysiol*. 1996; **13**(3): 184–197.
14. Zuculo GM, *et al*. Melatonin and circadian rhythms in autism: case report. *Chronobiol Int*. 2017; **34**(4): 527–530.

15. Carvalho MD, *et al*. Sleep EEG patterns in infants with congenital Zika virus syndrome. *Clin Neurophysiol*. 2017; **128**(1): 204–214.
16. Nunes ML, *et al*. Maturational changes of neonatal electroencephalogram: a comparison between intra uterine and extra uterine development. *Clin Neurophysiol*. 2014; **125**(6): 1121–1128.
17. Hoppenbrouwers T, *et al*.; CHIME Study Group. Sleep architecture in term and preterm infants beyond the neonatal period: the influence of gestational age, steroids, and ventilatory support. *Sleep*. 2005; **28**(11): 1428–1436.
18. Zuculo GM, *et al*. Correlation between sleep and quality of life in cerebral palsy. *Codas*. 2014; **26**(6): 447–456.
19. O'Brien LM, *et al*. Sleep pressure correlates of cognitive and behavioral morbidity in snoring children. *Sleep*. 2004; **27**(2): 279–282.
20. Gelman VS, *et al*. Wellbeing of mothers with children exhibiting sleep disturbance. *Aust J Psychol*. 2001; **53**: 18–22.
21. Malow BA, *et al*. Characterizing sleep in children with autism spectrum disorders: a multidimensional approach. *Sleep*. 2006; **29**(12): 1563–1571.
22. Meltzer LJ, *et al*. Sleep in young children with asthma and their parents. *J Child Health Care*. 2017; **21**(3): 301–311.
23. Smith L, *et al*. A qualitative study of how preschoolers' problematic sleep impacts mothers. *Behav Sleep Med*. 2017; **26**: 1–13.
24. Sadeh A, *et al*. Sleep, neurobehavioral functioning, and behavior problems in school-age children. *Child Dev*. 2002; **73**(2): 405–417.
25. van der Linden V, *et al*. Description of 13 infants born during October 2015-January 2016 with congenital Zika virus infection without microcephaly at birth – Brazil. *MMWR Morb Mortal Wkly Rep*. 2016; **65**(47): 1343–1348.
26. Del Campo M, *et al*.; Zika Embryopathy Task Force-Brazilian Society of Medical Genetics ZETF-SBGM. The phenotypic spectrum of congenital Zika syndrome. *Am J Med Genet A*. 2017; **173**(4): 841–857.
27. Jucá E, *et al*. Hydrocephalus associated to congenital Zika syndrome: does shunting improve clinical features? *Childs Nerv Syst*. 2017; **34**(1): 101–106.
28. Moore CA, *et al*. Characterizing the pattern of anomalies in congenital Zika syndrome for pediatric clinicians. *JAMA Pediatr*. 2017; **171**(3): 288–295.
29. Verçosa I, *et al*. The visual system in infants with microcephaly related to presumed congenital Zika syndrome. *J AAPOS*. 2017; **21**(4): 300–304.e1.
30. Bertolazi AN, *et al*. Validation of the Brazilian Portuguese version of the Pittsburgh Sleep Quality Index. *Sleep Med*. 2011; **12**(1): 70–75.
31. Nunes ML, *et al*. BISQ Questionnaire for infant sleep assessment: translation into Brazilian Portuguese. *Sleep Sci*. 2012; **5**(3): 89–91.
32. Owens JA. The practice of pediatric sleep medicine: results of a community survey. *Pediatrics*. 2001; **108**(3): E51.
33. Anders TF, *et al*. Sleeping through the night: a developmental perspective. *Pediatrics*. 1992; **90**(4): 554–560.
34. Kortüm F, *et al*. The core FOXG1 syndrome phenotype consists of postnatal microcephaly, severe mental retardation, absent language, dyskinesia, and corpus callosum hypogenesis. *J Med Genet*. 2011; **48**(6): 396–406.
35. Ivanenko A, *et al*. Classification and epidemiology of sleep disorders. *Child Adolesc Psychiatr Clin N Am*. 2009; **18**(4): 839–848.
36. Begum Ea, *et al*. Emergence of physiological rhythmicity in term and preterm neonates in a neonatal intensive care unit. *J Circadian Rhythms*. 2006; **4**: 11.
37. Peever JH, *et al*. Why do we sleep? In: Lavigne G, Sessle B, Choinière M, Soja P, eds. *Sleep and Pain*. Seattle: IASP Press; 2007: 1–8.
38. Montemitro MD, *et al*. Maturation of spontaneous arousals in healthy infants. *Sleep*. 2008; **31**(1): 47–54.
39. Armstrong KL, *et al*. The sleep patterns of normal children. *Med J Aust*. 1994; **161**(3): 202–206.
40. Pandi-Perumal SR, *et al*. Physiological effects of melatonin: role of melatonin receptors and signal transduction pathways. *Prog Neurobiol*. 2008; **85**(3): 335–353.
41. Zuckerman B, *et al*. Sleep problems in early childhood: continuities, predictive factors, and behavioral correlates. *Pediatrics*. 1987; **80**(5): 664–671.
42. Kataria S, *et al*. Persistence of sleep disturbances in preschool children. *J Pediatr*. 1987; **110**(4): 642–646.
43. Urfer-Maurer N, *et al*. The association of mothers' and fathers' insomnia symptoms with school-aged children's sleep assessed by parent report and in-home sleep-electroencephalography. *Sleep Med*. 2017; **38**: 64–70.
44. Mindell JA, *et al*. A nightly bedtime routine: impact on sleep in young children and maternal mood. *Sleep*. 2009; **32**(5): 599–606.
45. Bonan KC, *et al*. Sleep deprivation, pain and prematurity: a review study. *Arq Neuropsiquiatr*. 2015; **73**(2): 147–154.
46. Kuhn BR, *et al*. Interventions for infant and toddler sleep disturbance: a review. *Child Fam Behav Ther*. 2000; **22**: 33–50.
47. Owens LJ, *et al*. REVIEW ARTICLE: Behavioural and cognitive-behavioural interventions for sleep disorders in infants and children: A review. *Sleep Med Rev*. 1999; **3**(4): 281–302.