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Sleep problems and impact of obstructive hydrocephalus in newly diagnosed pediatric brain tumor patients

Eva Hooft van Huijsduijnen [a,1], Marita Partanen [a,2], Martha Grootenhuis [a,3], Eelco Hoving [a,4], Myrthe Nuijts [b,5], Raphaële van Litsenburg [a,*,6]

[a] Princess Máxima Center for Pediatric Oncology, Utrecht, the Netherlands
[b] Department of Ophthalmology, University Medical Centre Utrecht, Utrecht, the Netherlands

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ABSTRACT

Background: Pediatric brain tumor patients are at risk of developing sleep problems. Previous studies were conducted in longer-term survivors or without comprehensive sleep evaluations, therefore it remains unclear whether and when problems arise. Insights can facilitate timely interventions. The aim is to examine sleep problems and contributing factors shortly after diagnosis.
Methods: Children 6–16 years with a primary brain tumor (diagnosed ≤3 months) were recruited for a prospective study. Sleep was measured at home using wrist-worn actigraphy and questionnaires (PROMIS Sleep Disturbance and Sleep Related Impairment, self- and parent-reports). Mean PROMIS scores, prevalence of sleep problems (established by cut-off scores) and actigraphic outcomes were compared to norms (t-test, chi-square, linear regression). Risk factors were explored with multivariable linear regression models.
Results: Sixty-nine children (68% male, mean age 11.6 ± 2.8 years, 53 ± 28 days after diagnosis) participated. Parents reported more child sleep disturbances (mean T = 53.7, $P < .01$) compared to norms. Rates of self- and parent-reported severe sleep disturbances were elevated (11% versus 5% in norms, $P < .04$). Parents also reported higher rates of moderate child sleep disturbance (31%) and sleep related impairment (42%) than norms (25%, $P < .03$). Actigraphy was comparable to healthy controls. Obstructive hydrocephalus was associated with longer sleep times (B=41.04, 95%CI 11.41;70.68) and shorter time since diagnosis with self-reported sleep disturbances (B=−.11, 95%CI −0.19;−0.03).
Conclusion: Sleep problems are more frequently reported shortly after pediatric brain tumor diagnosis, compared to healthy controls. Attention for sleep around brain tumor diagnosis and impact of obstructive hydrocephalus is important, as sleep is vital for recovery and health-related quality of life.

1. Introduction

Sleep problems are known to be highly prevalent in pediatric cancer patients and can be caused by biological and/or psychosocial factors such as treatment toxicity, pain, and anxiety [1,2]. In the short term, sleep problems can lead to distress, cognitive problems, and lower quality of life in pediatric cancer patients [2–4]. In the long term, resulting from studies in the general population, sleep problems are associated with obesity, cardiovascular disease and lower life expectancy [2]. Sleep also plays a critical role in neuroimmune function and neuronal recovery in pediatric cancer patients. Moreover, fragmented sleep has increasingly been linked to tumor growth in mice [5–7]. Children with a brain tumor are especially prone to develop sleep problems. Neurosurgery, cranial radiation therapy and hypothalamic

* Correspondence to: Princess Máxima Center for Pediatric Oncology, 3720 AC Bilthoven, PO box 113, Utrecht, the Netherlands.
E-mail address: r.r.l.vanlitsenburg@prinsesmaximacentrum.nl (R. van Litsenburg).
[1] Orcid ID: 0000–0002-8519–4785
[2] Orcid ID: 0000–0003-1018–9778
[3] Orcid ID: 0000–0002-9632–248X
[4] Orcid ID: 0000–0002-5587–0439
[5] Orcid ID: 0000–0002-6362–0122
[6] Orcid ID: 0000–0003-1779–6159

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damage may further contribute to the onset of disturbances in sleeping patterns [1,8].

Currently, little is known about the prevalence and extent of sleep problems of children with a brain tumor, in an early stage of their disease. Previous studies have mainly focused on patients with all types of cancer diagnoses, causing heterogeneity, or included only patients with hematologic malignancies, the most common type of pediatric cancer [9]. In addition, most studies focus on sleep during survivorship. Multiple physical, psychological, and therapeutic factors related to the period around diagnosis may impact sleep, such as high levels of distress or the requirement of one or multiple hospitalizations, which are characterized by frequent nightly awakenings [10]. Poor sleeping habits and maladaptive strategies may emerge in this period and persist over the course of the disease. Lastly, sleep is most often assessed by questionnaires only, which provide information on sleep behaviors and consequences of disrupted sleep. However, questionnaires do not measure sleep duration and sleep efficiency, and do not correlate well with polysomnography, the gold standard for measuring sleep [11]. Some questionnaire studies only assess parent-reported sleep, which inherently poses some reporting bias. Using several modes of sleep assessment is important as it provides complementary information and contributes to our understanding of sleep [11–14].

Sleep in the early phases of treatment in pediatric brain tumor patients has thus far not been studied comprehensively, despite strong recommendations by researchers and clinicians [5,14–16]. Identifying which children are at risk is important, to provide effective, targeted sleep interventions in a timely manner, aiming to improve long-term negative health outcomes associated with poor sleep. In adult cancer patients, non-pharmacological interventions such as cognitive behavioural therapy have shown favorable results reducing sleep problems [17,18]. In contrast, in hospitalized children with central nervous system tumors, a multicomponent sleep intervention modestly improved sleep outcomes [19]. Therefore, more insight into disrupted sleep and contributing factors in the earliest phase after brain tumor diagnosis is needed.

We performed a prospective, observational study into sleep within three months after primary pediatric brain tumor diagnosis. Our aim was to describe sleep estimates, patient- and parent-reported sleep problems and daytime consequences, and biological and psychological risk factors for poor sleep. This study is part of a larger longitudinal study into sleep, post-traumatic stress, and neurocognitive functioning (SuSPeCT-study).

2. Materials and methods

2.1. Participants and procedures

The Princess Máxima Center for Pediatric Oncology is a Dutch center where pediatric oncology care is centralized. A small number of low grade brain tumor patients, requiring neurosurgery only, are treated in former pediatric oncology centers. Between January 2019 and October 2021 all patients treated for a primary brain tumor were eligible if they were 6–16 years old, spoke Dutch sufficiently, had no pre-existing developmental delay and were not receiving end-of-life care. All children and parents provided written informed consent. Sleep assessments took place one to three months after hospital entry. All assessments took place when the child slept at home. This study was approved by the Clinical Research Committee of the Princess Maxima Center and confirmed subsequently by the Medical Research Ethics Committee of the University Medical Center Utrecht.

2.1.1. Demographic and medical information

Children's demographic and medical information were abstracted from medical records. Parents provided sociodemographic information through a general survey. Information was provided on pre-existing sleep problems, use of sleep medications, daytime naps and whether they slept at home or in the hospital.

2.1.2. Sleep questionnaires

Subjective sleep was assessed with two eight-item questionnaires (both self-report and proxy-report) from the Patient-Reported Outcomes Measurement Information System (PROMIS) [20].

The Pediatric Sleep Disturbance shortform assesses satisfaction with sleep, including difficulties and concerns with falling asleep and staying asleep. The Pediatric Sleep Related Impairment shortform focusses on perceptions associated with sleep problems, such as impaired alertness, tiredness and sleepiness during usual waking hours. Both questionnaires assess sleep over the past seven days, and are generic rather than disease-specific. Strong internal consistency reliability and clinical validiy were demonstrated [21]. Raw scores are rescaled into T-scores (mean=50, standard deviation (SD)= 10). Cut-off points for moderate (75–94th percentile) and severe ($\geq$ 95th percentile) sleep problems were used [22].

2.1.3. Actigraphic measures

Sleep estimates were assessed using a wrist-worn actigraph (type wGT3XBT, Pensacola, FL). This device registers the occurrence and the intensity of arm movements and distinguishes the wake state from sleep. This low-cost measurement has been validated against polysomnography, and is well-tolerated during this intense stage of cancer therapy [23]. Participants were instructed to wear the actigraph for seven days and seven nights and keep a sleep log, to facilitate correct interpretation of the data.

Actigraphy software ActiLife (version 6.13.4, Sadeh algorithm) was used to process sleep outcomes (Table 1). To obtain reliable actigraphic measures, a minimum of five recorded nights was required [24]. Norm data of 47 healthy Dutch children were used to compare actigraphic sleep outcomes [25]. Actigraphic data of the healthy control participants were collected one year before this study; control participants were in the same age range and their average age did not differ from study participants ($P = 0.26$).

2.1.4. Statistical analysis

Baseline characteristics were descriptively reported. T-tests and chi-square tests were used to examine potential differences in age, sex and tumor location between participants and non-participants (active/passive refusal), and between participants and patients who were not approached (due to severe illness or logistical issues).

To examine differences in reported sleep between participants and healthy children, PROMIS scores were compared to a norm score of 50, using one-sided t-tests. The percentage moderate and severe sleep problems was described by using questionnaire-specific cut-offs [22] and compared to the general population with non-parametric chi-square tests.

Linear regression models were used for comparing actigraphic sleep estimates between participants and healthy children. Regression models were adjusted for age [25].

Risk factors were explored with linear regression models.

Table 1
Actigraphic sleep estimates.

Sleep estimate	Definition
Sleep efficiency (SE)	Ratio between the time spent in bed and the total sleep time
Sleep onset latency (SOL)	Number of minutes between bedtime and onset of sleep
Wake after sleep onset (WASO)	Number of minutes awake after the onset of sleep
Total sleep time (TST)	Number of minutes sleeping during the time spent in bed
Total time spent in bed (TIB)	Number of minutes spent in bed
Number of awakenings (NA)	Total number of awakenings

Demographic (age, sex, highest parental educational level) and medical variables relevant for sleep outcomes were examined with univariable analyses. Medical variables were: tumor location (supratentorial midline versus other locations); treatment (neurosurgery, start of chemotherapy or radiotherapy before assessment); comorbidites (hormone deficiency, epilepsy, obstructive hydrocephalus); time since diagnosis; body mass index. Variables with a *P*-value of < .10 were subsequently added to a multivariable model.

P-values of < 0.05 were considered significant. All analyses were carried out with IBM SPSS Statistics version 26.0.0.1.

3. Results

3.1. Demographic and medical information

In total, 69 (75%) children consented to the study; details of participant enrollment are described in Fig. 1. Baseline characteristics of the participants and non-participants are described in Table 2. Of the children with supratentorial midline tumors (N = 26, 38%), fifteen children (22%) had a tumor in the pituitary region, and none of the children had a tumor in the hypothalamus. Pre-existing sleep problems were reported by the parents of seven (10%) participants. During the assessment, six (9%) participants took daytime naps, two (3%) participants used melatonin and all actigraphy assessments took place when the children slept at home.

3.1.1. Sleep questionnaires

Compared to norm data, parents reported significantly more child sleep disturbances (mean T = 53.7, *P* < .01; Table 3). This was not reported by children themselves (mean T = 50.6, *P* = .64). Sleep Related Impairment was not compared to norms as the data was not normally distributed.

Severe sleep disturbance was experienced by 11% of the children compared to 5% in the general population, according to both parent- and self-reports (*P* = 0.03 and *P* = .04, respectively). Moderate sleep disturbance was also frequently reported by parents: 31% compared to 20% in the general population (*P* = .03). Rates of severe sleep related impairment were not significantly elevated. However, moderate sleep related impairment was more prevalent according to parents (42% vs 20%, *P* < .01).

3.1.2. Actigraphic sleep estimates

There were no statistical differences between participants and controls (Table 4). Based on the sleeplog, participants' bedtime (mean 21:36) was 30 min later, compared to controls (*P* = 0.04). Also, participants' wake time (mean 07:57) was 32 min later, compared to controls (*P* < 0.001).

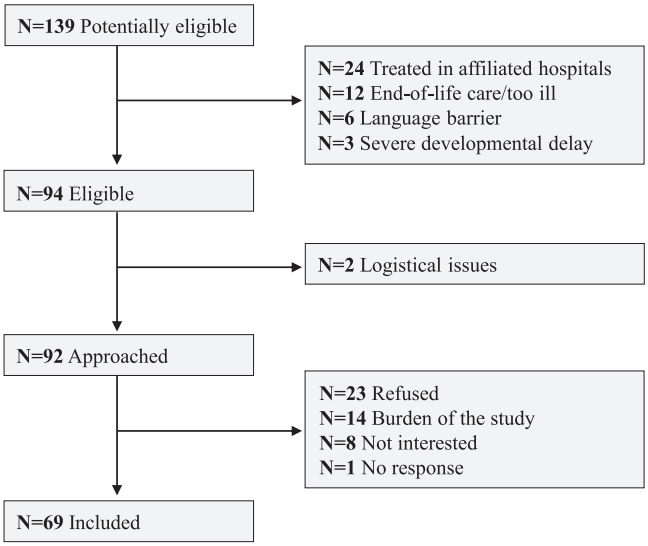

Fig. 1. Flowchart of participant enrollment.

Table 2
Baseline characteristics of participants.

	Study participants (N = 69)	Non-participants (N = 23), *P*-value[3]	Not approached (N = 14), *P*-value[3]
Child variables			
Male sex, N (%)	47 (68%)	14 (61%), *P* = .52	8 (57%), *P* = .44
Age at assessment, mean years (SD)	11.6 (2.8)	11.1 (4.3), *P* = .76	9.9 (2.3), *P* = .08
Time since diagnosis, mean days (SD)	53 (28)		
Body Mass Index, mean (SD)	18.7 (3.7)		
Parental education level[1]			
Low-Middle N (%)	33 (51%)		
High, N (%)	32 (49%)		
Medical variables			
Tumor type			
Low grade glioma, N (%)	33 (48%)		
Germ cell tumor, N (%)	10 (15%)		
Craniopharyngioma, N (%)	9 (13%)		
High grade glioma, N (%)	6 (8%)		
Medulloblastoma, N (%)	6 (8%)		
Ependymoma, N (%)	2 (3%)		
Other, N (%)[2]	3 (4%)		
Tumor location			
Posterior fossa, N (%)	29 (42%)	8 (35%), *P* = .54	6 (43%), *P* = .95
Supratentorial medial structures, N (%)	26 (38%)	5 (22%), *P* = .16	5 (36%), *P* = .89
Cerebral lobes, N (%)	14 (20%)	10 (44%), *P* = .03 *	3 (21%), *P* = .92
Started treatment			
Neurosurgery, N (%)	63 (91%)		
Started chemotherapy, N (%)	12 (17%)		
Started radiotherapy, N (%)	13 (19%)		
Proton therapy, N (%)	5 (7%)		
Photon therapy, N (%)	8 (12%)		
Obstructive hydrocephalus, N (%)	33 (48%)		
Hormone deficiency, N (%)	18 (26%)		
Epilepsy, N (%)	9 (13%)		

[1]Low = no education, primary school, lower secondary education; middle = upper secondary education, preuniversity education, intermediate vocational education; high = higher vocational education, university.
[2]ATRT (N = 1), plexus tumor (N = 1), meningioma (N = 1).
[3]Compared to participant group.
*Statistically significant

3.1.3. Risk factors

Univariable analyses for risk factors are presented in Tables S1 and S2. Multivariable analyses (Tables 5 and 6) showed that shorter time after diagnosis (B=−.11, 95%CI −.19;−.03, *P* = <.01) remained the only independent significant determinant for self-reported sleep disturbance. Younger age remained associated with longer sleep onset latency (B=−1.73, 95%CI −3.12;−.35, *P* = .02), more total sleeping time (B=−8.63, 95%CI −14.00;−3.26, *P* < .01) and more time in bed

Table 3
Patient- and parent-reported child sleep and prevalence of sleep problems.

	T-score[1]		Moderate sleep problems		Severe sleep problems		Any sleep problem	
	Mean (SD) or median [IQR]	*P*-value[2]	N (%)	*P*-value[3]	N (%)	*P*-value[4]	N (%)	*P*-value[5]
Self-report (n = 53)								
Sleep Disturbance	50.6 (9.5)	0.64	8 (15%)	0.37	6 (11%)	**0.04**	14 (26%)	0.81
Sleep Related Impairment	49.7 [40.1 – 54.2]	-	7 (13%)	0.22	3 (6%)	0.83	10 (19%)	0.30
Proxy-report (n = 65)								
Sleep Disturbance	53.7 (10.0)	**<0.01**	20 (31%)	**0.03**	7 (11%)	**0.03**	27 (42%)	**<0.01**
Sleep Related Impairment	57.1 [37.9 – 61.8]	-	27 (42%)	**<0.01**	5 (8%)	0.32	32 (49%)	**<0.01**

Abbreviations: SD = standard deviation, IQR = interquartile range.
Significant *P*-values are bold.
[1]Higher scores indicate more sleep problems
[2]Compared to norm population (mean=50, SD=10)
[3]Compared to percentage of moderate sleep problems in the norm population (20%)
[4]Compared to percentage of severe sleep problems in the norm population (5%)
[5]Compared to percentage of sleep problems (moderate or severe) in the norm population (25%)

Table 4
Differences in actigraphic sleep estimates between participants and healthy controls.

	Participants (n = 53) Mean (SD)	Control group (n = 47) Mean (SD)	B (95% CI)	*P*-value
SE (%)	79.0 (7.1)	77.8 (7.3)	-1.1 (−3.9 to 1.8)	0.47
SOL (min)	20.7 (14.8)	25.9 (15.4)	4.2 (−1.6 to 10.1)	0.15
WASO (min)	107.3 (39.7)	113.9 (45.5)	4.5 (−12.2 to 21.2)	0.60
TST (min)	480.9 (58.9)	479.1 (48.0)	-7.8 (−26.9 to 11.3)	0.42
TIB (min)	608.9 (55.0)	618.6 (56.7)	.8 (−15.3 to 16.9)	0.92
NA (N)	28.6 (6.9)	28.6 (6.2)	-.3 (−3.0 to 2.3)	0.80

Abbreviations: SE = sleep efficiency, SOL = sleep onset latency, WASO = wake after sleep onset,
TST = total sleep time, TIB = total time spent in bed, NA = number of awakenings, min = minutes.
Models were adjusted for age.
Significant values are in bold.

(B=−10.59, 95%CI −15.33;−5.85, $P < .01$). Finally, history of an obstructive hydrocephalus was independently associated with longer sleeping times (B=41.04, 95%CI 11.41;70.68, $P < .01$).

Children with prior obstructive hydrocephalus slept on average 21 min longer (TST), and fell asleep 10 min sooner (SOL), compared to controls. In contrast, children without obstructive hydrocephalus slept on average 12 min shorter, and fell asleep equally fast compared to controls. On average, children with obstructive hydrocephalus went to bed 42 min later and rose 53 min later than the control group. Lastly, when corrected for age, the mean difference in TST with and without obstructive hydrocephalus was 41 min. Differences in age between the hydrocephalus and no hydrocephalus group were however not significant.

Body mass index, parental education level, start of chemotherapy, hormone deficiency and epilepsy were not significantly associated with any of the sleep outcomes.

4. Discussion

The results of this unique prospective nationwide cohort study of children with a recently diagnosed brain tumor demonstrate a higher prevalence of parent-reported sleep problems compared to a control group. Children more often reported severe sleep disturbances compared to healthy peers, but not more moderate sleep disturbances. Actigraphic sleep outcomes were not different from healthy controls. Shorter time since diagnosis was associated with more sleep disturbances and obstructive hydrocephalus was associated with longer sleep duration and shorter time to fall asleep.

We found high rates of parent-reported child sleep disturbance and sleep related impairment, with up to half of the parents reporting moderate or severe problems. Children themselves frequently reported severe sleep disturbances, especially more shortly after brain tumor diagnosis. These findings are consistent with our expectations, indicating sleep problems are experienced regularly and already at the earliest phase of cancer treatment, possibly arising as a result of factors such as distress and neurological damage. In children with ALL, high rates of sleep problems have also been reported in the first period after

Table 5
Multivariable regression models of risk factors for patient- and parent reported sleep outcomes.

Questionnaires, B (95% CI)				
	PROMIS Sleep Disturbance Self-report	PROMIS Sleep Related Impairment Self-report	PROMIS Sleep Disturbance Proxy-report	PROMIS Sleep Related Impairment Proxy-report
Time since diagnosis	**-0.11** *	-	-0.07	-
Continuous	**(−0.19 to −0.03)**		(−0.16 to 0.02)	
Tumor location	-3.56	-	-	-
Suprat. midline vs. others	(−8.74 to 1.62)			
Started radiotherapy[1]	-	-	-4.60	-
Yes vs. no			(−10.96 to 1.76)	

Only variables with a P-value of < .10 in univariable analyses (see Supplementary material) were added to the multivariable model.
[1]Proton and photon radiation therapy grouped together
*Statistically significant ($P < 0.01$)

Table 6
Multivariable regression models of risk factors for actigraphic sleep outcomes.

Actigraphic outcomes, B (95% CI)						
	SE	SOL	WASO	TST	TIB	NA
Age	-	**-1.73** *	-	**-8.63** * *	**-10.59** * *	-
Continuous		**(−3.12 to −0.35)**		**(−14.00 to −3.26)**	**(−15.33 to −5.85)**	
Neurosurgery	-	-	-	-	-	4.68
Yes vs. no						(−1.26 to 10.61)
Started radiotherapy[1]	-	-	-	-	-	3.63
Yes vs. no						(−1.37 to 8.64)
Obstr. hydrocephalus	-	-7.28	-	**41.04** * *	-	-
Yes vs. no		(−14.93 to 0.37)		**(11.41 – 70.68)**		

Only variables with a P-value of < .10 in univariable analyses (see Supplementary material) were added to the multivariable model.
Abbreviations: SE = sleep efficiency, SOL = sleep onset latency, TST = total sleep time, TIB = total time in bed, NA = number of awakenings, suprat. = supratentorial, obstr. = obstructive.
[1]Proton and photon radiation therapy grouped together
* Statistically significant ($P < 0.05$)
* * Statistically significant ($P < 0.01$)

diagnosis [26]. Interestingly, although parents reported high rates of sleep related impairments, children did not report this and on average their scores did not differ from the general population.

Differences in self- and proxy-report are common in pediatric research and may be explained by several factors [26–28]. Firstly, children may underreport symptoms. This can be the result of "response shift", meaning symptoms are judged differently during cancer treatment than how they would be judged before diagnosis [29]. It could also be that neurocognitive-, stress- and sleep disturbances impact children's' capability of adequately recalling sleep experiences [30]. Second, parents may overreport symptoms due to feelings of stress and concern. Earlier research suggests that parental distress, parental sleep problems and parenting problems are related to parent reported child sleep [26]. Hence, differences in self- and proxy-reports emphasize the importance of using both types when measuring sleep, as they may provide complementary information.

We hypothesized that actigraphic outcomes would show lower sleep estimates compared to age-matched, healthy controls, due to the physical/psychosocial stressors associated with the period following brain tumor diagnosis. This was not seen in the overall group, however, it is important to note that sleep was measured at home. Sleep during hospitalization may have been impaired, as shown in previous studies [31]. Also, compared to controls, children without obstructive hydrocephalus slept shorter, and children with obstructive hydrocephalus slept longer and had shorter sleep onset times. Impact of obstructive hydrocephalus was not seen in earlier research amongst CNS tumor survivors [32] and is not previously investigated in any research into recently diagnosed pediatric brain tumor patients. Possibly, children with obstructive hydrocephalus are more ill and/or tired and therefore require more sleep to support physical recovery [5,33,34]. This is in line with comparable research in children with acute lymphoblastic leukemia (ALL), who showed longer sleeping times than healthy peers [26]. Another explanation could be poorer sleep quality, for example due to more sleep fragmentation with a destruction of the hypocretin system, biological clock or breathing disorders. The total group had later bed times and later rising times, possibly because they were all not going to school, however, this was particularly seen in children with obstructive hydrocephalus and could be related to altered sleep-wake rhythms.

Nevertheless, overall participant and control group sleep estimates were comparable. This study sample was however almost entirely assessed during the Covid-19 pandemic, while data of the control group were collected before. Possibly, children slept better during the pandemic, as due to lockdowns they were staying at home with limited social interactions and thus less exposed to stimuli [35]. In the healthy population, it was found that people with insomnia complaints experienced clinically meaningful alleviations of symptoms during the pandemic [36]. Lastly, sleep may be influenced by substantial efforts and strategies of parents, such as co-sleeping and comforting activities, as illustrated in parents of children with ALL [37]. Possibly, as parents put in a great deal of energy, parents do report sleep problems in their child, and yet these efforts seem relatively effective in terms of child sleep duration. This may also explain the different outcomes in parental reported sleep problems and actigraphy and has been described before in children with ALL [26].

Generally, little research has been done with actigraphy and children with cancer during treatment. However, sleep problems are well described and measured amongst brain tumor survivors [8,14,32]. Toxic treatments effects such as radiation therapy or endocrine disturbances may lead to those sleep problems at a later stage. Longitudinal data from this current study should provide more insight into this matter [8,38].

This study has several limitations. Although the participant group is relatively large for pediatric brain tumor research, there may not have been enough power to demonstrate sleep problems or specific predictors. In addition, not all children participated in all actigraphic sleep measurements, due to treatment toxicity or study burden, increasing the risk of participation bias. Subsequently, even though participants were recruited from a national pediatric oncology hospital, specific tumor groups were underrepresented which may have lead to selection bias. Not invited for study participation were twenty-four children with low grade tumors, primarily treated in affiliated hospitals, and twelve children with high grade tumors, receiving palliative care. Finally, it would have been interesting to be informed on parental sleep, as previous work has shown the association between child and parents sleep in the first phases after a childhood cancer diagnosis [39].

Actigraphy measures movement which is a well validated tool, but does not measure sleep phases (light, deep and REM sleep). Also, possible shifted circadian rhythms or inconsistent bedtimes are not reflected in the actual number of minutes asleep as reported here, but may still contribute to fatigue [4,5,40]. Future research should explore sleep phases and rhythms to gain more insight into sleep quality. Lastly, previous research suggested more knowledge of parents on sleep hygiene benefits child sleep, therefore education and support for parents may be an interesting intervention for future research [41,42].

5. Conclusion

Sleep problems in children with a brain tumor are frequently reported in the first three months after brain tumor diagnosis, particularly sooner after diagnosis. History of obstructive hydrocephalus was related to longer sleeping times. Clinicians should be attentive to sleep problems and provide psycho-education on healthy sleep as part of regular care, as chronic problems may induce serious, negative consequences in this already vulnerable group. Systematic sleep monitoring with patient-reported outcomes is an important tool in early recognition of sleep

problems. Increasing our understanding of sleep is of major importance because sleep is vital for recovery and health-related quality of life.

5.1. Statements and declarations

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- *Authors' contributions.* All authors contributed to the study conception and design. Conceptualization: MG, RvL, MP, EHvH. Funding acquisition: MG. Data collection: EHvH, MN. Analyses: EHvH, RvL. Writing original draft: EHvH. Writing-reviewing and editing: RL, MP, MG, EH, MN. All authors read and approved the final manuscript.
- *Ethics approval.* This is an observational study. The UMC Utrecht Research Ethics Committee has confirmed that no ethical approval is required.
- *Concent to participate.* Written informed consent was obtained from all individual participants included in the study.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejcped.2023.100124.

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