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Original Article

Brain tumours result in sleep disorders in children and adolescents

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ABSTRACT

Background and objectives: Sleep disturbances are frequently reported in children with brain tumours. The objective of our cross-sectional study was to systematically examine sleep in these children. We hypothesised that children with tumours involving the sleep-wake-regulatory areas have an altered sleep-wake-regulation.

Methods: Sixty-one patients aged 0–18 years and with a diagnosis of a primary brain or cervical medullary tumour were included. They were categorised based upon tumour location into two groups – those affecting the sleep-wake regulatory regions, i.e. brain stem, basal forebrain, hypothalamus, thalamus, and posterior fossa compressing the brain stem and those that did not. Sleep history, questionnaire surveys, polysomnography, and multiple sleep latency test were used, as indicated clinically. Surveys included Pediatric Daytime Sleepiness Scale, Children's Sleep Habits Questionnaire, Strengths and Difficulties Questionnaire, and Pediatric Quality of Life Inventory, Multidimensional Fatigue Scale and Generic Core Scale.

Results: Patients with tumours involving the sleep-wake regulatory areas were sleepier/more fatigued ($p = 0.03$). Sleep apnoea was observed in 86% of all the patients and comorbid narcolepsy in 8%, without group differences ($p \geq 0.12$). Patients with tumours involving the sleep-wake-regulatory areas had more emotional problems ($p = 0.04$), were more affected by mental health problems ($p < 0.001$), and had poorer quality of life ($p \leq 0.03$).

Conclusions: Many children with brain tumours suffer from disturbed sleep, poor mental health, and low quality of life. We recommend that systematic sleep evaluation is included in their routine care along with psychological and social support.

1. Introduction

Wakefulness, sleep, and circadian rhythm are reciprocally regulated by interactions in neuropeptide-producing neuronal networks involving thalamus, hypothalamus, basal forebrain, and brain stem. Wakefulness results from maintained connectivity to cortex via activating signalling pathways, i.e. the ascending reticular activation system (ARAS). Neurons in ARAS are crucial in maintenance of behavioural arousal and consciousness. Sleep is derived from a reduction in cortical tone promoted by neurons in the ventro-lateral and median pre-optic nuclei of the hypothalamus, and sleep active neurons located in the basal forebrain and parafacial zone.

Abbreviations: Apnoea hypopnoea index, AHI; Attention Deficit Hyperactivity Disorder, ADHD; Body mass index, BMI; Multiple sleep latency test, MSLT; Neurofibromatosis type 1, NF1; Nonsteroidal anti-inflammatory drug, NSAID; Obstructive sleep apnoea, OSA; Rapid eye movement, REM; Non-rapid eye movement, NREM; Sleep-wake, SW; Standard deviation score, SDS.

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Additionally, there is a balance between the circadian drive to wakefulness and the sleep-promoting homeostatic drive [1]. Lesions or functional disturbances in this system lead to dysregulation in sleep and wakefulness. Tumour location, expansion, effects of surgery, or cranial irradiation can impair the sleep-wake (SW) regulatory systems, thereby affecting these regulatory processes or the mediating functions of the signalling pathways. Although sleep disturbances are frequently reported among children with brain tumours [2], there has been no risk stratification based upon anatomic location of the tumour. As a consequence, no management guidelines exist for sleep problems in this population. Many publications are case reports [3,4], and sleep disturbances are often assessed by questionnaires useful for screening, but insufficient for in-depth, qualitative assessment of SW-function [5,6].

The objective of this study was to systematically evaluate the homeostatic sleep regulation in children previously diagnosed with primary tumours of the brain and cervical medulla. We hypothesised that patients with tumours involving the SW-regulatory areas have altered SW-regulation as compared to children with tumours that do not affect these regions.

2. Material and methods

2.1. Subjects

Patients were recruited from the tertiary Paediatric Department, Rigshospitalet, Copenhagen, Denmark between June 2016 and January 2020. Custody holders and patients ≥18 years gave written informed consent before enrolment after full explanation of all procedures.

Inclusion criteria were patients aged 0–18 years at time of inclusion and previously diagnosed with a brain tumour or a tumour in the cervical medulla. Four patients were on active chemotherapy at the time of inclusion with no prospect of ending treatment during the investigation period.

Exclusion criteria were tumour diagnosis, surgical tumour intervention or radiotherapy within six months prior to inclusion. Insufficient substitution of pituitary hormone deficiencies within three months prior to inclusion was an exclusion criterion.

Three hundred and nine patients were identified, of whom 174 (56%) patients met the inclusion criteria. Sixty-one patients consented to participate and had a polysomnography performed, of which 54 (89%) had a subsequent multiple sleep latency test (MSLT). Questionnaires were obtained from 56 (92%) patients. The present study was part of a larger investigation, from which data on circadian function has been presented previously [7]. It was possible for the patients only to participate in parts of the project. Reasons for non-participation in 113 (65%) eligible patients: 20 thought the study program was too extensive, one was included in another study, four had no sleep complaints and therefore chose to abstain, 28 considered study participation but did not go further, 11 gave no explanation for not wanting to participate, and 49 did not respond to study invitation.

2.2. Baseline assessment

Medical records were obtained in all patients. Traveling across time zones ≤2 weeks before inclusion and during the investigation period was not allowed. None of the patients suffered from blindness without perception of light and form. Anthropometric measurements included height, weight, and body mass index (BMI).

2.3. Comorbidity, tumour classification and treatment

Information on comorbidity, pituitary insufficiencies, tumour pathology, imaging, and treatment were obtained from medical records. The tumours were categorised according to location into: 1) SW-regulatory areas [1], defined as involving one or more of the brain stem, basal forebrain, hypothalamus, thalamus, and posterior fossa tumours compressing the brain stem and 2) other areas. During the investigation period, all patients had either completed tumour therapy or had stable disease except one with tumour progression on active chemotherapy (Trametinib). Antidepressants, hypnotics, melatonin, and central nervous system stimulants for altered sleep or excessive daytime sleepiness were paused at least two weeks before the investigation.

2.4. Sleep-wake characteristics

Structured and thorough clinical sleep histories and evaluations for the diagnostics of paediatric sleep disorders [8] were obtained in all patients by LP supervised by PJ. Fatigue, sleepiness, and sleep attacks were defined as present if occurring one month before and at the time of investigation. The presence of cataplexy, sleep paralysis, and hypnagogic hallucinations were recorded if ever occurred in lifetime.

Sleep was assessed from one nightly polysomnography (starting from about 12 to 14 o'clock to the next morning) and performed in hospital or at home as some of the children were quite uncomfortable with hospitalisation and to endorse study participation. Equipment was applied in hospital by experienced neurophysiology assistants. Daytime sleepiness was obtained by an MSLT in hospital consisting of five scheduled naps starting in the morning (30 min rest and 45 min awake) with continuous electroencephalography, electrooculography, and submental electromyography recordings [9].

Nicolet (Nervus) EEG version 5.95.1.17 (Cephalon, Noerresundby, Denmark) or Domino version 2.9.0 (SOMNOmedics, Randersacker, Germany) were used for the electrophysiological recordings. Scorings were performed according to criteria set by the American Academy of Sleep Medicine [10,11]. Sleep stages, arousals, motor activity, and respiratory events were scored manually by experienced polysomnography technicians, supervised by PJ.

Rules for scoring respiratory events were provided by the American Academy of Sleep Medicine. Patients <18 years of age followed the paediatric scoring rules, and adult criteria were used for patients ≥18 years of age [12].

2.5. Questionnaires

The following questionnaires were used for assessment of sleep quality, fatigue, and mental health status: I) Pediatric Daytime Sleepiness Scale [13] measured daytime sleepiness in school aged children, where scores ≥15 indicated excessive daytime sleepiness [14]. As this questionnaire is commonly used in studies of sleep, it was included even though it is not validated in Danish. Two laypersons, one Danish native and fluent in English and the other one English native and fluent in Danish, double translated the questionnaire from English version into Danish; II) the Children's Sleep Habits Questionnaire [15] encompassed major medical and behavioural sleep disorders. Higher scores indicated disturbed sleep, and a total score above 41 suggested a paediatric sleep disorder in need for clinical referral; III) Strengths and Difficulties Questionnaire [16] assessed mental health in children aged ≥2 years and adolescents. It covered emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behaviour. An impact supplement measured the effect of emotional and behavioural problems on well-being and function. Higher scores indicated more problems, however, the opposite applied for prosocial behaviour. A problem score above 17 and an impact score above 3 were considered high

[17]; IV) Pediatric Quality of Life Inventory Multidimensional Fatigue Scale [18] covered three dimensions (general, sleep/rest, and cognitive fatigue). Higher scores indicated fewer problems, and scores ranging from about 75 to 90 have been reported in healthy children. Validated Danish versions were available from age ≥8 years; and V) Pediatric Quality of Life Inventory Generic Core Scales [19] where higher scores indicated better health-related quality of life, and scores of about 80–90 have been reported in healthy children [18].

2.6. Ethical approval

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by the local ethical committee (J.no. H-16014208) and the Danish Data Protection Agency (J.no. RH-2016-53, I-Suite no. 04449).

2.7. Statistical analyses

The 61 patients were divided into two groups according to tumour location (SW-regulatory areas versus other areas). Age and sex specific BMI standard deviation scores (SDS) were calculated according to national references [20]. As polysomnographic sleep variables and sleep architecture vary with age [9], the patients were divided into age-groups of 0–12 years and 13–18 years, when comparing the raw electrophysiological data. Since the overall sleep evaluation of the polysomnography and MSLT takes age into account, analyses of these were performed across the whole age range.

Between-group comparisons of continuous data were performed by Mann–Whitney's *U*-test. Categorical data were compared by two-tailed Fisher's exact test or the chi-squared test. Data were presented as frequency (percentage) or median (25th-75th percentiles). $P < 0.05$ was considered significant. All statistical analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., North Carolina, USA).

3. Results

3.1. Baseline assessment

Forty of 61 (66%) patients had tumours involving SW-regulatory areas, and 21 of 61 (34%) had tumours elsewhere. Their anthropometric profiles and sleep history are presented in Table 1.

3.2. Comorbidity, tumour classification and treatment

Tumour localisations and treatments are described in Fig. 1 and Table 2, respectively. Three patients with neurofibromatosis type 1 (NF1) were diagnosed with gigantism, two of whom also had hyperprolactinaemia. Six patients were treated for epilepsy, two of whom were also diagnosed with Attention Deficit Hyperactivity Disorder (ADHD). Two patients aged 15 and 17 years, respectively, were diagnosed with depression and treated with selective serotonin reuptake inhibitors before and during the investigation period, and two patients were diagnosed with autism.

3.3. Sleep-wake characteristics

Fifty-two (85%) patients had a video polysomnography performed in hospital. Nine (15%) patients had a polysomnography performed at home without video monitoring. Electrophysiological data are presented in Table 3. Sleep disorders were observed in nearly 90% of all the patients (Table 4), sleep apnoea being most frequent.

3.4. Sleep apnoea

The patients with sleep apnoea (obstructive, central and mixed sleep apnoea) ($n = 51$) were not significantly sleepier than those with apnoea hypopnoea index (AHI) < 1/h ($n = 8$) ($p = 0.67$). They had significantly higher median (25th-75th percentiles) BMI SDS (0.7 (−0.3 to +2.2)) than those with AHI < 1/h (−0.5 (−0.7 to +0.3)), $p = 0.03$. BMI SDS did not differ between patients with moderate-severe sleep apnoea ($n = 20$) (0.8 (−0.2 to +1.7)) and those with AHI < 5/h ($n = 39$) (0.4 (−0.6 to +2.1)), $p = 0.34$.

The prevalence of sleep apnoea (obstructive, central and mixed sleep apnoea; AHI ≥ 1/h and AHI ≥ 5/h, respectively) in patients with tumour involvement of the brain stem (five patients with brain stem tumours, seven with posterior fossa tumours compressing the brain stem, and one with tumour involvement of the fourth ventricle compressing the brain stem (Fig. 1)) did not differ significantly from those with tumours located elsewhere (all $p = 1.00$).

Six out of seven (86%) patients with NF1 (all with involvement of the SW-regulatory areas) had sleep apnoea of which one had severe obstructive sleep apnoea (OSA) (AHI 13/h). The last NF1 patient had an optic nerve glioma combined with severe neurofibromas of pharynx, rhino pharynx, thorax, and abdomen causing restrictive lung disease and severe OSA with hypoventilation and hypercapnia. Before inclusion, this patient was already being treated with nighttime bilevel positive airway pressure and continuous positive airway pressure thrice daily. The electrophysiological measurements while treated with bilevel positive airway pressure showed normal respiration and sleep. Neither exclusion of this patient nor exclusion of all the patients with NF1 from the electrophysiological analyses changed the overall results (Table 4).

3.5. Comorbid narcolepsy

In 5/61 (8%) of the patients, an organic hypersomnia syndrome was identified that was suspected to be narcolepsy [7]. 1) One boy previously treated with radical resection, ventriculoperitoneal shunt, and chemo- and radiotherapy of a medulloblastoma WHO IV in the posterior fossa with compression of the brain stem had developed severe cerebellar mutism syndrome. Two years post-surgery, he suffered from daytime sleepiness, sleep attacks, and fragmented sleep pattern with long wake periods during the night. The polysomnography showed long rapid eye movement (REM) sleep latency (5.4 h), decreased eye movements, REM sleep without atonia, and muscle twitches of limbs, body, and head without paroxysmal activity. He responded well to treatment with sodium oxybate. 2) One girl with panhypopituitarism after partial tumour resection, chemo-, and radiotherapy of a mixed malignant germ cell tumour responded well to treatment with methylphenidate. She also had OSA (AHI 13/h). 3) One boy with a stable cerebellar hemisphere pilocytic astrocytoma without involvement of the fourth ventricle received treatment with methylphenidate which reduced his daytime sleepiness and sleep attacks. He was also diagnosed with OSA (AHI 6/h). 4) One girl treated with three surgeries for a parieto-occipital pleomorphic xanthoastrocytoma complained of excessive daytime sleepiness which was supported by a short mean sleep latency of 6.8 min on the MSLT. She also had OSA (AHI 4/h). 5) One girl previously treated with partial resection, ventriculoperitoneal shunt, and chemotherapy for a hypothalamic-chiasmatic glioma tumour involving the pituitary region showed a

Table 1
Anthropometric profiles and sleep history in 61 paediatric patients with brain tumours categorised by 1) location involving one or more of the sleep-wake regulatory areas, i.e. the brain stem, basal forebrain, hypothalamus, thalamus and posterior fossa tumours compressing the brain stem and 2) other locations.

	Patients				
	Sleep-wake regulatory area		Other		p
	n		n		
Sex					0.42
Male	40	22 (55)	21	14 (67)	
Age at inclusion (year)	40	12.4 (7.9–16.0)	21	12.6 (8.6–17.1)	0.45
Age at diagnosis (year)	40	5.6 (2.2–8.8)	21	4.9 (3.1–9.8)	0.68
Time between diagnosis and inclusion (year)	40	5.3 (2.5–8.7)	21	4.2 (2.5–6.8)	0.85
Height for age SDS	40	−0.4 (−1.0–0.8)	21	−0.6 (−1.1–0.6)	0.74
Body Mass Index SDS	40	1.0 (−0.0–2.1)	21	−0.3 (−0.6–0.5)	**0.02**[a]
Sleepiness and/or fatigue	40	33 (83)	20	11 (55)	**0.03**[a]
Sleep attacks	40	3 (8)	21	1 (5)	1.00
Hypnagogic hallucinations	40	3 (8)	21	1 (5)	1.00
Sleep paralysis	40	1 (3)	21	1 (5)	1.00
Cataplexy	40	0 (0)	21	0 (0)	

SDS (standard deviation score). Data are given as numbers (%) or median (25th-75th percentiles).
[a] $p < 0.05$; group comparisons by Mann–Whitney U-test or Fisher's exact test.

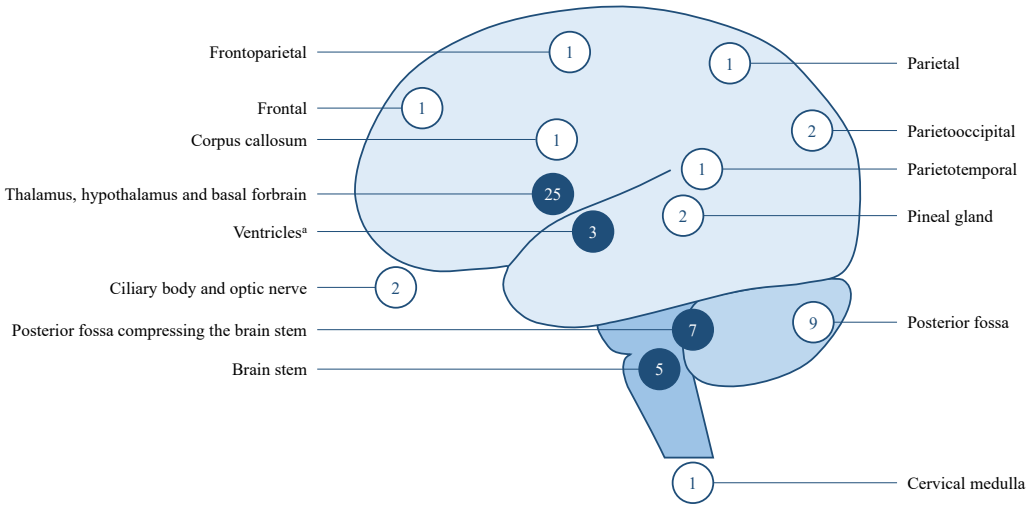

Fig. 1. Location of the brain tumours in 61 paediatric patients categorised by 1) location involving one or more of the sleep-wake regulatory areas, i.e. the brain stem, basal forebrain, hypothalamus, thalamus, and posterior fossa tumours compressing the brain stem (locations marked in dark shaded circles, numbers indicate patient numbers) and 2) other locations (locations marked in light shaded circles, numbers indicate patient numbers). [a] One patient with tumour involvement of the pituitary gland, one patient with tumour involvement of the basal ganglia and one patient with tumour involvement of the fourth ventricle with compression of the brain stem.

severely fragmented sleep pattern, day nap of 4 h that included REM sleep, and severe mixed sleep apnoea (AHI 87/h).

3.6. Parasomnia

Two patients were diagnosed with non-REM (NREM) parasomnia: 1) One boy with previous partial resection of a pilocytic astrocytoma in the cervical medulla. 2) One girl with previous partial resection of a ganglioglioma in corpus callosum and previously diagnosed with epilepsy. Antiepileptic drugs were discontinued four years before study enrolment without history of seizures within this period. The polysomnography showed three episodes of screaming and anxiety derived from NREM stage 2. Also, irregular body and limb movements were observed, and epileptic seizures could not be ruled out [21,22]. One boy was diagnosed with REM parasomnia, previously treated with partial resection for a diffuse astrocytoma involving the amygdala, hippocampus, thalamus, mesencephalon, and pons and currently treated with chemotherapy. He also suffered from intractable epilepsy, infantile autism, and ADHD. All diagnoses of parasomnia were confirmed by clinical history and polysomnographic findings, and none of these patients had a family history of parasomnia.

3.7. Restless legs syndrome

No patients were diagnosed with restless legs syndrome.

3.8. Questionnaires

Patients with tumours in the areas of the SW-regulatory system had significantly more complaints regarding sleep disordered breathing, emotional problems, and had a higher impact score suggesting that they were more affected by emotional and behavioural problems on well-being and function than those with tumours located elsewhere. Furthermore, they were more fatigued and had a lower health related quality of life (all $p \leq 0.04$) (Table 5).

4. Discussion

This is the first large systematic study of sleep disorders in an unselected group of children and adolescents with tumours in the

Table 2
Tumour treatment in 61 paediatric patients with brain tumours categorised by 1) location involving one or more of the sleep-wake regulatory areas, i.e. the brain stem, basal forebrain, hypothalamus, thalamus, and posterior fossa tumours compressing the brain stem and 2) other locations.

	Patients		
	Sleep-wake regulatory area, n = 40	Other, n = 21	p
	No. (%)	No. (%)	
Number of tumour surgeries			0.36
0	12 (30)	2 (10)	
1	15 (38)	11 (52)	
2	9 (23)	4 (19)	
3	2 (5)	3 (14)	
4	1 (3)	1 (5)	
6	1 (3)	0 (0)	
Ventriculo-peritoneal shunt at the time of investigation	12 (30)	1 (5)	**0.02**[b]
Radiotherapy, previous	8 (20)	9 (43)	0.08
Chemotherapy			
Previous[a]	18 (45)	9 (43)	1.00
Current	4 (10)	0 (0)	0.29
Dendritic Cell Vaccine at the time of investigation	0 (0)	1 (5)	0.34
Tumour progression	1 (3)	0 (0)	1.00
Pituitary insufficiency at the time of investigation			0.29
One axis	2 (5)	2 (10)	
Two axes	1 (3)	2 (10)	
Three axes	2 (5)	0 (0)	
Panhypopituitarism	4 (10)	0 (0)	
Pituitary hormone insufficiencies at the time of investigation			
Growth hormone	7 (18)	3 (14)	1.00
Adrenocorticotroph hormone	7 (18)	0 (0)	0.08
Thyroid stimulating hormone	7 (18)	3 (14)	1.00
Antidiuretic hormone	5 (13)	0 (0)	0.15
Gonadotrophins	4 (10)	0 (0)	0.29
Precocious puberty, previous or current	7 (18)	0 (0)	0.08
Medical treatment at the time of investigation			
Pituitary hormone replacement therapy	9 (23)	4 (19)	1.00
Precocious puberty hormone therapy	3 (8)	0 (0)	0.54
Cabergolin	2 (5)	0 (0)	0.54
Pegvisomant/Octreotide	3 (8)	0 (0)	0.54
Antiepileptic drugs	4 (10)	2 (10)	1.00
Analgesics (paracetamol, NSAID, tricyclic antidepressants)	9 (23)	0 (0)	**0.02**[b]
Antidepressants for depression	1 (3)	1 (5)	1.00
Methylphenidate for ADHD	0 (0)	1 (5)	0.34
Melatonin	3 (8)	1 (5)	1.00

NSAID (nonsteroidal anti-inflammatory drug), ADHD (attention deficit hyperactivity disorder). Data are given as numbers (%).
[a] More than six months prior inclusion.
[b] $p < 0.05$; group comparisons by Fisher's exact test or Chi–Square test.

brain and cervical medulla followed at a single tertiary University hospital. We observed sleep apnoea in 86% of the patients and comorbid narcolepsy in 8%. Patients with tumours involving the SW-regulatory areas were significantly sleepier and/or more fatigued than those with tumours in other areas with potential consequences for social performance and self-rated quality of life.

OSA was the most frequently observed sleep disorder in both patient groups and observed in about two-thirds of the included children. Even allowing for a possible selection bias, in that the participation rate in the study was 35%, this suggests a considerably higher occurrence of OSA in survivors of paediatric brain tumours than in the general population, where the estimated prevalence is 1–4% [23]. OSA is reported among patients with tumours of the suprasellar and hypothalamic region, posterior fossa, and cervical medulla, thus the pathophysiology is diverse [2,24]. Hypothalamic tumour involvement may cause postoperative weight gain and obesity [25] and thereby increase the risk of OSA. However, BMI was not clearly associated with sleep apnoea among our patients suggesting a structural or regulatory aetiology. Tumours involving the brain stem and posterior fossa may influence central chemoreceptors and ventilatory muscle control resulting in hypoventilation [26,27]. Nocturnal determination of carbon dioxide may help to identify hypoventilation in these children.

Children with NF1 are more likely to exhibit fatigue and sleep disturbances compared with unaffected siblings [28,29]. However, excluding the patients with NF1 from the analyses did not change the overall results.

Lesions involving the hypocretinergic systems or its projections may potentially result in narcolepsy. Narcolepsy type 1 is primarily due to an autoimmune destruction of the hypocretinergic neurons in the lateral hypothalamus and affects 0.03% of the general population [30]. Comorbid narcolepsy is reported in patients with suprasellar, sellar, parasellar, and hypothalamic tumours [2,4], and treatment with central stimulants in these patients may have positive effects [4]. We found five patients (8%) suspected of comorbid narcolepsy without symptoms of sleep paralysis, hypnagogic/hypnopompic hallucinations, or cataplexy. This can suggest an involvement of the hypocretin projections rather than the hypocretin secreting neurons *per se* [31]. Furthermore, we identified a high prevalence (n = 4) of sleep apnoea in these patients, which may be explained by several factors such as lesions to the brain and brain stem, structural/anatomic factors, obesity, and changes in the respiratory regulation [32]. As obstructive sleep apnoea and sleepiness may or may not be related [33], central hypersomnia in children with brain tumours needs to be considered independent of sleep apnoea.

Table 3
Electrophysiological findings in 61 paediatric patients aged 0–12 and 13–18 years, respectively, and with brain tumours categorised by 1) location involving one or more of the sleep-wake regulatory areas, i.e. the brain stem, basal forebrain, hypothalamus, thalamus, and posterior fossa tumours compressing the brain stem and 2) other locations.

Polysomnography	Patients aged 0–12 years					Patients aged 13–18 years				
	Sleep-wake regulatory area		Other		p	Sleep-wake regulatory area		Other		p
	n		n			n		n		
Total sleep time (h)	20	8.8 (7.9–9.4)	11	8.4 (7.8–9.1)	0.63	19	7.3 (5.6–8.4)	10	7.5 (6.9–9.4)	0.11
Sleep efficiency (%)	20	94 (87–96)	11	94 (90–97)	0.48	19	91 (86–96)	10	94 (88–97)	0.44
Sleep latency (min)	21	10 (5–23)	11	10 (8–24)	0.68	19	14 (4–32)	10	9 (5–21)	0.48
REM sleep latency (min)	21	118 (85–171)	11	82 (71–151)	0.25	19	73 (65–103)	10	80 (58–99)	0.95
Number of awakenings	20	14 (10–23)	11	9 (3–26)	0.09	19	14 (9–25)	10	14 (12–19)	0.87
Number of arousals	20	64 (50–130)	11	61 (41–79)	0.33	19	56 (41–97)	10	59 (50–105)	0.84
NREM 1 of total sleep time (%)	20	4 (1–6)	11	3 (2–4)	0.88	19	4 (2–5)	10	6 (4–8)	0.06
NREM 2 of total sleep time (%)	20	39 (34–43)	11	44 (31–49)	0.51	19	42 (40–50)	10	43 (40–44)	0.66
NREM 3 of total sleep time (%)	20	37 (30–41)	11	31 (24–38)	0.19	19	30 (23–39)	10	27 (22–33)	0.38
REM of total sleep time (%)	20	19 (16–25)	11	22 (20–27)	0.37	19	22 (18–25)	10	25 (23–27)	0.05
Wake after sleep onset (min)	20	27 (17–40)	11	23 (5–31)	0.15	19	15 (9–34)	10	16 (12–33)	0.44
Leg movement index (/h)	19	12 (8–18)	11	13 (7–17)	1.00	19	5 (4–11)	10	5 (3–12)	0.55
Oxygen desaturation index (/h)	16	2 (0–3)	9	2 (1–3)	0.98	19	2 (1–5)	10	3 (2–5)	0.93
AHI (/h)	19	2 (1–7)	11	3 (1–5)	0.43	19	5 (2–11)	10	4 (2–5)	0.34
Sleep apnoea type (AHI ≥1/h)					0.17					0.40
Obstructive	19	11 (58)	11	5 (45)		19	15 (79)	10	8 (80)	
Central	19	3 (16)	11	1 (9)		19	0 (0)	10	1 (10)	
Mixed	19	4 (21)	11	1 (9)		19	2 (11)	10	0 (0)	
Sleep apnoea type (AHI ≥5/h)					0.72					0.37
Obstructive	19	4 (21)	11	2 (18)		19	9 (47)	10	3 (30)	
Central	19	1 (5)	11	0 (0)		19	0 (0)	10	0 (0)	
Mixed	19	1 (5)	11	0 (0)		19	0 (0)	10	0 (0)	
Multiple sleep latency test										
Mean sleep latency (min)	16	20 (18–20)	9	20 (18–20)	0.69	19	16 (14–19)	10	15 (8–19)	0.36
Mean sleep latency ≤8 min	16	0 (0)	9	0 (0)	1.00	19	1 (5)	10	2 (20)	0.27
≥2/5 REM-sleep, 30 min/test	16	0 (0)	9	1 (11)	0.39	19	2 (11)	10	3 (30)	0.31
≥2/5 sleep-onset REM periods	16	0 (0)	9	1 (11)	0.39	19	1 (5)	10	1 (10)	1.00

REM (rapid eye movement), NREM (non-rapid eye movement), AHI (apnoea hypopnoea index). Data are given as numbers (%) or median (25th-75th percentiles). Group comparisons by Mann–Whitney U-test or Chi–Square test.

Table 4
Electrophysiological sleep evaluation in 61 paediatric patients with brain tumours categorised by 1) location involving one or more of the sleep-wake regulatory areas, i.e. the brain stem, basal forebrain, hypothalamus, thalamus, and posterior fossa tumours compressing the brain stem and 2) other locations.

Overall electrophysiological sleep evaluation	Patients				p
	Sleep-wake regulatory area		Other		
	n	No. (%)	n	No. (%)	
Normal sleep pattern including minimal changes[a,b]	40	4 (10)	21	3 (14)	0.68
Normal sleep pattern incl. minimal changes and AHI<5/h[a,b]	40	24 (60)	21	12 (57)	1.00
Sleep apnoea with AHI ≥1/h[c]	38	35 (92)	21	16 (76)	0.12
Sleep apnoea with AHI ≥5/h[c]	38	15 (39)	21	5 (24)	0.26
NREM parasomnia	40	0 (0)	21	2 (10)	0.12
REM parasomnia	40	1 (3)	21	0 (0)	1.00
Comorbid narcolepsy	40	3 (8)	21	2 (10)	1.00
Epilepsy	40	2 (5)	21	1 (5)	1.00
Abnormal micro and macro sleep	40	1 (3)	21	0 (0)	1.00

REM (rapid eye movement), NREM (non-rapid eye movement), AHI (apnoea hypopnoea index). Data are given as numbers (%). Group comparisons by Fisher's exact test.
[a] Minimal changes include background slowing.
[b] One patient with neurofibromatosis type 1 with a neurofibroma located in the sleep-wake-regulatory area was prior to inclusion diagnosed with severe obstructive sleep apnoea due to multiple extracranial fibromas. Electrophysiologic measurements while treated with bilevel positive airway pressure showed normal respiration and normal sleep.
[c] In two patients, respiratory events were not accessible.

Sleepiness and altered sleep architecture are also reported in patients with epilepsy, which may be explained by nocturnal seizures or interictal epileptiform activity during sleep leading to frequent arousals or side effects of antiepileptic drugs. On the other hand, sleep disorders can lead to worsening of seizure control. Improving sleep may optimise seizure control and have positive effect on quality of life in these patients and vice versa [34].

Patients with brain tumours may experience late effects from cranial radiotherapy such as fatigue and poorer quality of life [35]. However, due to the limited number of patients included, we have not subdivided the patients in accordance to radiotherapy treatment as this would require a differentiation of, e.g. photon versus proton treatment, doses (Gray), and involved CNS locations. About one-third of our patients were treated with radiotherapy, relatively more patients ($p = 0.08$) with tumours located outside the SW-regulatory areas had received this treatment, and two out of five patients with comorbid narcolepsy had been treated with radiotherapy.

Table 5
Questionnaires in 61 paediatric patients with brain tumours categorised by 1) location involving one or more of the sleep-wake regulatory areas, i.e. the brain stem, basal forebrain, hypothalamus, thalamus, and posterior fossa tumours compressing the brain stem and 2) other locations.

	Patients				
	Sleep-wake regulatory area		Other		
Pediatric Daytime Sleepiness Scale (age ≥6 years) Higher scores indicate daytime sleepiness	**n**		**N**		**P**
Daytime sleepiness, score range 0–32	33	14 (11–19)	17	13 (10–16)	0.54
Children's Sleep Habits Questionnaire (all ages) Higher scores indicate disturbed sleep					
Bedtime resistance, score range 6–18	33	7 (6–9)	17	6 (6–7)	0.27
Sleep onset delay, score range 1–3	36	2 (1–2)	17	1 (1–2)	0.67
Sleep duration, score range 3–9	32	5 (3–7)	16	4 (3–7)	0.61
Sleep anxiety, score range 4–12	31	4 (4–7)	17	4 (4–6)	0.22
Night waking, score range 3–9	32	5 (4–7)	14	4 (3–6)	0.11
Parasomnias, score range 7–21	28	8 (7–10)	14	8 (7–10)	0.67
Sleep disordered breathing, score range 3–9	31	4 (3–4)	15	3 (3–3)	**0.03**[a]
Daytime sleepiness, score range 8–24	29	13 (12–18)	13	12 (12–13)	0.37
Total score, score range 33–99	24	50 (43–56)	11	45 (38–49)	0.09
Strengths and Difficulties Questionnaire (age ≥2 years) Higher scores indicate more problems, however, higher scores of prosocial behaviour indicate fewer problems					
Total difficulties score (problem score), score range 0–40	37	12 (7–18)	17	12 (6–14)	0.22
Emotional problems, score range 0–10	37	4 (3–6)	18	2 (0–5)	**0.04**[a]
Conduct problems, score range 0–10	38	1 (0–2)	18	1 (0–1)	0.91
Hyperactivity, score range 0–10	38	4 (2–6)	18	4 (2–5)	0.85
Peer relationship problems, score range 0–10	38	3 (1–4)	17	2 (1–3)	0.06
Prosocial behaviour, score range 0–10	38	8 (6–10)	18	9 (8–10)	0.36
Impact score, score range 0–10	36	1 (0–3)	17	0 (0–0)	**<0.01**[a]
Pediatric Quality of Life Inventory, Multidimensional Fatigue Scale (age ≥8 years) Higher scores indicate fewer problems, score range 0–100					
General fatigue	25	63 (50–75)	15	83 (46–88)	**0.03**[a]
Sleep/Rest fatigue	25	50 (38–67)	15	67 (46–83)	0.08
Cognitive fatigue	25	54 (29–67)	15	71 (46–88)	**0.04**[a]
Total score	25	56 (42–69)	15	74 (53–85)	**0.03**[a]
Pediatric Quality of Life Inventory, Generic Core Scale (all ages) Higher scores indicate better health–related quality of life, score range 0–100					
Physical functioning	37	72 (47–88)	18	89 (78–97)	**0.01**[a]
Emotional functioning	37	63 (50–75)	18	75 (65–100)	**0.03**[a]
Social functioning	37	65 (40–80)	18	93 (65–100)	**0.01**[a]
School functioning	34	45 (25–55)	18	48 (40–75)	0.15
Psychosocial health summary score	37	57 (40–70)	18	75 (50–85)	**0.02**[a]
Total score	37	59 (46–75)	18	79 (55–87)	**0.01**[a]

Data are given as median (25th-75th percentiles).
[a] $p < 0.05$; group comparisons by Mann–Whitney U-test.

To our knowledge, this is the first study quantifying quality of life in children with brain tumours located in the SW-regulatory areas versus other locations. Questionnaires were completed either by caregivers or the patients themselves depending on their age or cognitive ability. Due to power limitations, these data were analysed collectively. Patients with brain tumours located in the SW-regulatory areas reported significantly lower health-related quality of life than the other patient group. Regardless of tumour location, the patients tended to be more fatigued and have poorer health-related quality of life than what has previously been reported in healthy children [18]. Patients with brain tumours face serious challenges to their quality of life such as side effects of treatment, sequelae secondary to focal neurologic deterioration, and sleep disturbances. Sleepiness and fatigue are frequently reported complaints in health-related quality of life studies in patients with brain tumours. Previous studies report that large brain tumours, tumours located in the right hemisphere, in the anterior region, and infratentorial tumours are correlated with poorer quality of life [36,37]. Furthermore, patients with tumours located in the SW-regulatory areas are more burdened with emotional problems than the other patient group. Poor or inadequate sleep may negatively affect mood; but conversely, the emotional problems can as well be a result of the tumour location itself due to the closely located anatomical structures engaged in SW-regulation and emotion regulation [1,38]. A limitation to the study is that we did not screen the patients for depression, as this may potentially affect sleep. Two-thirds of our patients had tumours located in the areas of the SW-regulation. This may reflect that patients experiencing altered sleep were more encouraged to participate in the study. However, it can also reflect that paediatric brain tumours have a predilection for the midline sites (57%) of which 60% are infratentorial [39]. In alignment with this, we found that 60% of the patients invited to participate in this study (n = 174) had tumours located in the SW-regulatory areas.

It is noteworthy that both our patient groups seemed sleepier/more fatigued and reported more disturbed sleep than what has previously been reported in healthy children [15,18] indicating that children with brain tumours regardless of location may suffer from sleep disturbances and disorders. Therefore, sleep evaluation should be included in the follow-up of children and adolescents

with brain tumours. However, the study refusal rate of 65% impairs our possibility to generalize as those experiencing sleep problems may have been more likely to participate. However, the time and energy required for study participation were quite extensive, which also contributed to study refusal in this population. For optimal assessment of polyphasic sleep and circadian function in these patients, polysomnography should preferably be of at least 24-h duration, although this may be difficult. We extended all recordings to about 18 h duration to obtain information about daytime sleep prior to the MSLT.

5. Conclusion

To our knowledge this is one of the largest systematic studies assessing sleep in children with tumours of the brain and cervical medulla. A large proportion of the children had OSA and/or narcolepsy which was regardless of location. We suggest that follow-up of children and adolescents with tumours of the brain and cervical medulla include systematic sleep evaluation as well as psychological, cognitive, and social support.

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Contributors' statement

Line Pickering contributed to study design, initiation of the project, recruitment of patients, data collection, analyses and management of the project, collection and assessment of structured clinical evaluation and electrophysiological data, verified the underlying data, contributed to the data interpretations, and writing of the manuscript.

Katharina M. Main contributed to study design, initiation of the project, verified the underlying data, contributed to the data interpretations, and writing of the manuscript.

Astrid Sehested and René Mathiasen contributed to study design, initiation of the project, recruitment of patients, verified the underlying data, contributed to the data interpretations, and writing of the manuscript.

Ulla Feldt-Rasmussen and Marianne Klose contributed to study design, data interpretations, and writing of the manuscript.

Suresh Kotagal contributed to the data interpretations and writing of the manuscript.

Poul J. Jennum contributed to study design, initiation of the project, collection and assessment of structured clinical evaluation and electrophysiological data, supervised the electrophysiological scorings and evaluations, verified the underlying data, contributed to the data interpretations, and writing of the manuscript.

All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Conflict of interest

None.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2021.09.016.

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