REVIEW ARTICLE

A Systematic Review Assessing the Impact of Surgery on Sleep Disturbances in Craniopharyngioma

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Abstract

Introduction: Craniopharyngiomas (CP) are rare benign brain tumors associated with high morbidity due to their proximity to important structures. Surgical resection is key to treatment but carries significant risk due to iatrogenic hypothalamic injury. The hypothalamus plays a vital role in the regulation of the sleep-wake cycle. Therefore, damage due to the Craniopharyngioma or surgery could result in sleep disturbances, negatively affecting health outcomes and quality of life. This systematic review aimed to evaluate sleep in patients both pre- and postsurgery to try and define the role of surgery on sleep disturbances, which may enable better management of patients by guiding surgical decision-making.

Methods: A systematic review was performed using Medline, Embase, and Scopus. Inclusion criteria were articles that described sleep disturbances pre- and/or postsurgery in craniopharyngioma. Eleven studies were included. Critical appraisal showed a high risk of bias. The data extracted were unsuitable for meta-analysis, but the weighted prevalence of sleep disturbances was calculated and compared.

Results: No statistical difference was found between the weighted prevalence of sleep disturbances pre- vs postsurgery. Combined findings of individual studies displayed no clear patterns of differences in sleep disturbances pre- to postsurgery. The most common sleep disturbances were excessive daytime sleepiness (EDS)/somnolence. Limitations of studies included a lack of control groups, insufficient statistical analysis, and small sample sizes.

Conclusion: The findings of this review suggest that sleep disturbances are not different pre- to postsurgery. However, the strength of this conclusion is limited by the quality of the evidence included, highlighting the need for more suitably designed primary research in this area.

Systematic review registration: http://www.crd.york.ac.uk/PROSPERO, identifier CRD42023469112.

Keywords: Adamantinous, Brain tumor, Hypothalamic injury, Neurosurgery, Obstructive sleep apnea, Papillary, Pituitary, Rathke cleft.

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Introduction

Craniopharyngiomas (CP) are embryonic malformations affecting the sellar/para sellar regions of the brain.[1] These rare, benign tumors develop in around 0.5–2 million people each year and have a bimodal age distribution, with 30–50% of all cases presenting during childhood and adolescence.[1] Clinical manifestations of CP are most often non-specific symptoms of raised intracranial pressure, e.g., nausea and headache, followed by visual impairments and endocrine disorders.[2] Despite their low-grade histological classification, the morbidity of CP is often high, due to the proximity of the tumor to important structures in the brain, such as the hypothalamus.[1] Damage to the hypothalamus can occur directly due to tumor growth, causing specific symptoms at diagnosis, or due to treatment of the tumor, causing long-term consequences.[3]

Treatment-induced hypothalamic injury is often the result of surgical resection of the tumor.[3] There is debate regarding the optimal surgical strategy, with the choice between gross total resection (GTR) and subtotal resection (STR) usually being made on a case-by-case basis. GTR is associated with higher postoperative morbidity due to damage to structures such as the hypothalamus but carries a lower recurrence risk compared with STR. Because of this, STR is seldom used alone and is often combined with radiotherapy to reduce recurrence rates similar to those for GTR.[4] Irrespective of radiotherapy use, surgery remains a pivotal component of CP treatment, but the risk of surgery-induced injury can significantly impair the quality of life of survivors.[4,5] Alternatively, surgery can bring about favorable outcomes by helping to alleviate symptoms due to the mass effect of the tumor.[6] For example, studies show that symptoms such as impaired vision can be improved following surgery.[7,8]

The hypothalamus is a structure that sits in the ventral brain and works in conjunction with the pituitary gland to secrete hormones as part of the hypothalamic-pituitary axis.[9] As well as its endocrine role, the hypothalamus is key in regulating vital

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bodily functions such as appetite, thirst, and body temperature.[9] Damage to the hypothalamus can manifest as disturbances in homeostatic functions and/or endocrine abnormalities, such as growth impairment and amenorrhea.[9,10]

Another important, yet often overlooked, symptom of hypothalamic damage in CP is sleep disturbance, possibly due to damage of the suprachiasmatic nucleus of the hypothalamus.[11] This structure is termed the master circadian pacemaker as it regulates most circadian rhythms in the body including sleep-wake cycles. It receives input from the photosensitive ganglion cells in the retina and projects to structures such as the pineal gland to regulate melatonin production, mediating sleep and wakefulness.[12] Sleep is fundamental for almost every part of physical and mental health, with sleep disturbances having negative impacts on cardiovascular, immune, and metabolic health, contributing to overall morbidity and mortality.[13] It is therefore important to identify and treat CP patients with sleep problems to improve clinical outcomes for these patients.

Sleep disturbances such as somnolence, narcolepsy, and sleep-disordered breathing have been reported throughout the literature as negative consequences of CP both before and after treatment. However, it is not clear to what extent these are due to a mass effect caused by the tumor or due to surgical management. A recent systematic review analyzed sleep disturbances in the pediatric CP population and found a high prevalence of disturbances, mainly postsurgery.[14] For example, they found that excessive daytime sleepiness (EDS) occurs at rates between 14 and 35% post-treatment.[14] These authors suggested that research aimed at examining sleep before and after treatment would be beneficial to compare types and severity of sleep disturbances, to better clarify the underlying pathogenic mechanisms of sleep disturbance.[14] The present systematic review aims to assess sleep disturbances in CP patients pre- and postsurgery, to examine the potential role of surgery-induced injury or postsurgical improvement on sleep in these populations. This information may help guide surgical decision-making, helping to improve health outcomes and quality of life for CP patients.

Objective

To establish the role of surgical management of CP on sleep disorders

Methods

The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO CRD42023469112). This systematic literature review was undertaken in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) statement.[15]

Search Strategy

A systematic literature search of Medline (1946 – October 2023), Embase (1947 – October 2023), and SCOPUS (1946 – October 2023) electronic databases was conducted on October 10, 2023, using the following search keywords:

"craniopharyngioma" AND "sleep disorder*" OR "sleep qualit*" OR "sleep paralys*" OR "sleep apnea" OR "circadian rhythm*" OR "Sleep-wake transition disorder*" OR "sleep*" OR "REM" OR "sleep aid*" OR "chronotherapy" OR "sleep deprivation" OR "obstructive sleep apnea*" OR "sleep initiation and maintenance disorder*" OR "sleep latenc*" OR "sleep hygien*" OR "sleep bruxism" OR "polysomnography" OR "apnea" OR "hypocretin" OR "orexin*" OR "excessive daytime sleep*" OR "somnolence" OR "hypersomnolence*" OR "hypersomnia*" OR "narcolepsy" OR "fatigue*" OR "melatonin" OR "sleep disturbance*."

Medical subject headings (MeSH) were used where appropriate.

Selection Criteria

Inclusion criteria were studies that described sleep disturbances in patients with CP before/after surgical intervention or both. No date limits were set.

Exclusion criteria were (a) studies not written in the English language; (b) case reports/series, review articles, book chapters, and conference abstracts; (c) studies where radiotherapy was included in treatment; (d) studies where no differentiation was made between patients who had and had not undergone surgical intervention; (e) studies where no differentiation was made between CP and other brain tumors; (f) studies where the only sleep-related outcome was "fatigue" due to heterogeneity of definitions and causes.

Duplicates were removed by one researcher (JN). Two researchers (JN, PD) independently reviewed the titles and abstracts of the retrieved articles, applying the inclusion and exclusion criteria. One the researcher reviewed the full texts of the remaining articles to determine eligibility for inclusion (JN). Another researcher was consulted for conflicts (PN).

Data Extraction and Synthesis

Studies that were identified as meeting the inclusion criteria underwent independent data extraction. Data extraction included study author, study year, study title, journal, study design, study period, sample size, ages of patients, patient sex, patient weight/body mass index (BMI), tumor characteristics, surgical status and characteristics, time of measurement and follow-up periods, endocrine function status, hormone replacement therapy, sleep measures and outcomes, and types of sleep disturbances.

Critical Appraisal

All included studies were independently and critically appraised using Clinical Appraisal Skills Programme (CASP) checklists.[16,17]

Data Analysis

Meta analysis was not possible due to the heterogeneity of studies and study designs. The weighted prevalence of sleep disorders was calculated for studies that reported number of patients who experienced sleep disturbances for pre- and postsurgery only. Note that even though Honegger et al.[18] analyzed sleep both pre- and postsurgery, the number of patients who experienced a sleep disturbance was only reported for presurgical data. Therefore, this study was included in the weighted prevalence calculations for presurgery. Weighted prevalence of sleep disturbances were calculated using the formula:

$$\left(\frac{\textit{Number of patients with sleep disturbances}}{\textit{Total number of patients}} \times 100\right) \times \left(\frac{\textit{Total number of patients in study}}{\textit{Total number of patients in all pre - or postsurgical studies}}\right)$$

Weighted prevalence across studies was not normally distributed (Shapiro–Wilk $p > 0.05$), so a nonparametric test (Mann–Whitney *U*) was used to compare weighted prevalence scores between pre- and postsurgery papers (only data from papers that denoted number of patients with sleep disturbances presurgery alone and postsurgery alone was used. Papers that analyzed sleep both pre- and postsurgery and denoted the number of sleep disturbances in patients for both conditions were not included in these statistics as they are not independent samples). Statistical significance accepted at $p < 0.05$. Data were analyzed using SPSS-29 (IBM, NY, USA). Foschi et al.[19] described multiple sleep disturbances, but only "pathological sleep efficiency" was included in the data analysis as this was the main outcome of the paper. The whole cohort of 115 patients was included in the analysis for Muller et al.,[20] rather than the sub-cohort of 10 patients.

Results

The systematic search identified 1095 publications, of which 11 were included in the review (Fig. 1).[15] Critical appraisal of the included publications is shown in Table 1 (case-control) and Table 2 (cohort). In studies where only presurgical data were extracted, questions 3, 6a, and 6b were marked "not applicable (N/A)" as exposure to surgery and follow-up were irrelevant. Overall, the risk of bias across all studies included in this review is high. The main reasons for this across all studies included insufficient information regarding the method of cohort recruitment, exposure (surgery) inadequately described, subjective outcome measures, insufficient follow-up, confounding factors, a lack of statistical analysis, and small sample sizes. Table 3 reports the main characteristics of the studies included in this review.

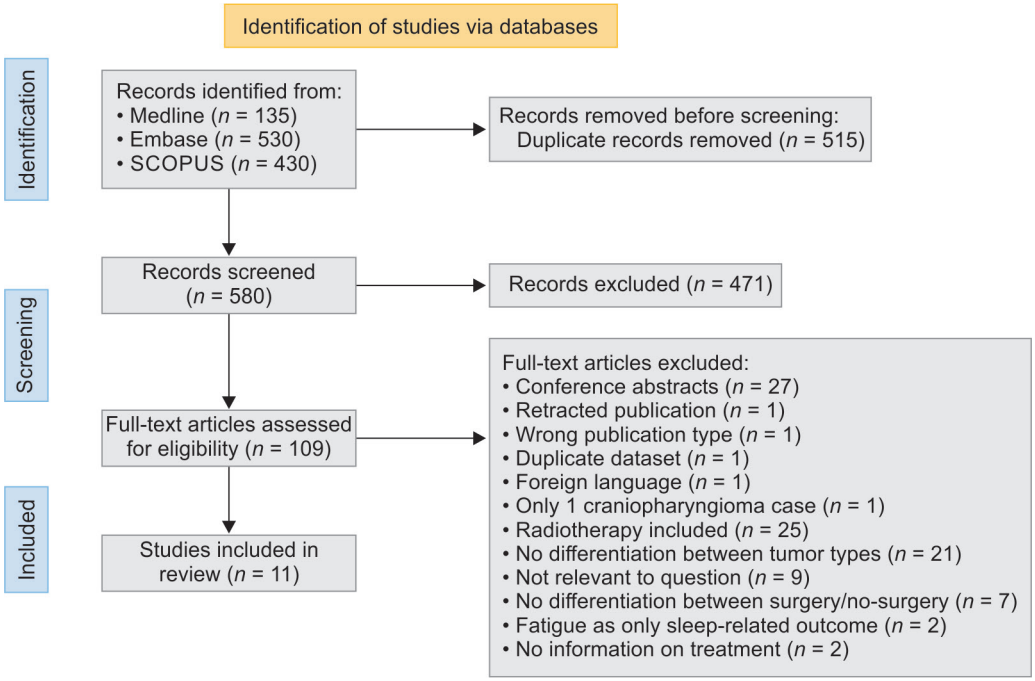

Fig. 1: PRISMA flow diagram of search results

Table 1: Clinical appraisal skills programme checklist for critical appraisal of case-control studies*

		Lee et al. 2023[21]	*Muller et al. 2006*[20]	*O'Gorman et al. 2010*[22]
1.	Did the study address a clearly focused issue?	N	Y	Y
2.	Did the authors use an appropriate method to answer their question?	Y	Y	Y
3.	Were the cases recruited in an acceptable way?	CT	CT	Y
4.	Were the controls selected in an acceptable way?	Y	N	Y
5.	Was the exposure accurately measured to minimize bias?	N	N	N
6a.	Aside from the experimental intervention, were the groups treated equally?	Y	Y	N
6b.	Have the authors taken account of the potential confounding factors in the design and/or in their analysis?	N	N	Y
8.	Were the results precise?	Y	CT	CT
9.	Do you believe the results?	CT	CT	Y
10.	Can the results be applied to the local population?	CT	CT	CT
11.	Do the results of this study fit with other available evidence?	Y	Y	Y

*CT, can't tell; N/A, not applicable; N, no; Y, yes

Table 2: Clinical appraisal skills programme checklist for critical appraisal of cohort studies*

	Foschi et al. 2017[19]	*Guo et al. 2019*[23]	*Guo et al. 2023*[3]	*Honegger et al. 1998*[18]	*Kalapurakal et al. 2003*[24]	*Larijani et al. 2004*[25]	*Pascual et al. 2019*[26]	*Qi et al. 2012*[27]
1. Did the study address a clearly focused issue?	Y	Y	Y	N	N	N	Y	Y
2. Was the cohort recruited in an acceptable way?	Y	N	Y	N	N	N	Y	N
3. Was the exposure accurately measured to minimize bias?	CT	N	N/A	N	N	CT	N/A	N/A
4. Was the outcome accurately measured to minimize bias?	Y	N	N	N	N	CT	CT	N
5a. Have the authors identified all important confounding factors?	N	N	N	N	N	N	N	N
5b. Have the authors taken account of the confounding factors in the design and/or analysis?	N	N	N	N	N	N	N	N
6a. Was the follow-up of subjects complete enough?	Y	Y	N/A	N	Y	Y	N/A	N/A
6b. Was the follow-up of subjects long enough?	Y	N	N/A	N	CT	CT	N/A	N/A
8. Were the results precise?	CT	CT	CT	CT	CT	CT	CT	CT
9. Do you believe the results?	Y	CT	CT	CT	CT	CT	CT	CT
10. Can the results be applied to the local population?	CT	CT	CT	CT	CT	CT	CT	CT
11. Do the results of this study fit with other available evidence?	Y	Y	Y	Y	Y	N	Y	Y
12. Are there implications of this study for practice?	N	N	N	N	N	N	Y	N

*CT, can't tell; N/A, not applicable; N, No; Y, yes

All included articles assessed sleep in adult and/or pediatric CP patients presurgery, postsurgery, or both.[20,22] Dates of publication ranged from 1998 to 2023. Study designs included case-control and cohort studies. Five studies included pediatric CP only[23,27] and three studies included adult CP only. Three studies included both adult and pediatric CP patients,[25,26] of which two studies did not differentiate results between ages;[3,25] therefore, it was not possible to differentiate results of this review by age group. Pituitary hormone dysfunction (PHD) was found in variable frequency. GTR had a relatively high prevalence of PHD compared to STR. Most of the patients had hormone replacement therapy at the time of sleep analysis.

As radiotherapy was an exclusion criterion in this systematic review, only the presurgical information was used from Guo et al.[3] as, in the postsurgical group, patients received radiotherapy alongside surgical intervention. Similarly, Larijani et al.[25] looked at two postsurgical groups but only the group without adjuvant radiotherapy was included in this review.

There was a discrepancy in the number of patients who experienced somnolence in Pascual et al.[26] The authors reported the clinical symptoms at diagnosis for each patient individually in Table 1 of their study. From this table, we identified 92 patients with pathologically verified CP and out of these, 41 patients (44.6%) had a clinical symptom of somnolence. However, when the data are summarized in Table 2, it was reported that 43 patients (46.7%) had a clinical symptom of somnolence. We have used the reported figure of 46.7% in the analysis.

The corresponding author from Foschi et al.[19] was consulted via email regarding queries and discrepancies in their data (see Appendix 1 for details).

Sleep Disturbances

A number of sleep disturbances were reported throughout the literature including excessive EDS, hypersomnia, somnolence, obstructive sleep apnea (OSA), periodic limb movement disorder (PLMD), secondary narcolepsy, sleep-wake cycle disorders, and insomnia. Some studies did not specify type.[3,18,23,24] The ways in which sleep was assessed included subjective measures, e.g., Epworth Sleepiness Scale (ESS), Sleep Disturbance Scale for Children (SDSC), Pittsburgh Sleep Quality Index (PSQI), Nottingham Health Profile (NHP), and objective measures, e.g., polysomnography (PSG), mean sleep latency test (MSLT), and 24-hour sleep-wake cycle recording.

Presurgery

Six studies assessed sleep in CP patients presurgery; three were presurgery only, and three compared patients pre- and postsurgery. Data on the number and type of sleep disturbance reported and how long presurgery they were measured are displayed in Table 4 for studies assessing sleep presurgery only.

Table 3: Characteristics of studies including study design, patient demographics, surgical details, tumor details, hormone deficiencies, and replacement and sleep outcomes

Ref.	*Study design**	*CP (n)*	*Age (yrs)*	*M/F (n)*	*Pre/ postsurgery*	*GTR or STR†*	*ACP/ PCP§ (n)*	*Hypothalamic injury*	*Hormone deficiencies*	*Hormone replacement*	*Obesity‖ (%)*	*Sleep measures¶*	*Main sleep-related results*	*Type of sleep disturbance*
Foschi et al. 2017[19]	C	10	48	4/6	Both	GTR 80% STR 20%	5/5	Anterior hypothalamus involved in all cases and posterior hypothalamus involved in 50% cases	Hypothyroidism: presurgery 10%, postsurgery 90%	Measurements taken after hormone replacement therapy	Presurgery: 0	24-hour sleep-wake cycle recording, nocturnal cardio-respiratory monitoring, number of diurnal naps	Sleep efficiency pathological (<85%) in 8 patients presurgery and improved in 4/8 patients postsurgery	Pathological sleep efficiency Abnormal REM latency
									Hypogonadism: presurgery 40%, postsurgery 30%		Postsurgery: 30		REM latency abnormal in 5 patients (increased in 4 patients and reduced in 1 patient) presurgery and normalized in 3/5 patients postsurgery.	Obstructive sleep apnea Daytime drowsiness
									Diabetes insipidus: 0% presurgery, 70% postsurgery				7 patients had 1–3 diurnal NREM naps lasting a mean of 35 ± 14 min presurgery. 9 patients had 2–6 diurnal NREM naps lasting a mean of 53 ± 27 min postsurgery. Daytime drowsiness increased postsurgery. 2 patients showed pathological number of periodic limb movements of sleep per hour presurgery. No information postsurgery. 2 patients had 5 or over sleep-related obstructive apnea's per hour presurgery. No information postsurgery	Period limb movement disorder

(Contd...)

Table 3: *(Contd...)*

Ref.	*Study design**	*CP (n)*	*Age (yrs)*	*M/F (n)*	*Pre/ postsurgery*	*GTR or STR†*	*ACP/ PCP§ (n)*	*Hypothalamic injury*	*Hormone deficiencies*	*Hormone replacement*	*Obesity‖ (%)*	*Sleep measures¶*	*Main sleep-related results*	*Type of sleep disturbance*
Guo et al. 2019[23]	CC	185	8.73 ± 3.12	96/89	Both	–	–	–	Diabetes Insipidus: presurgery 26.49%, postsurgery 44.86% Adrenocortical hypofunction: presurgery 18.38%, postsurgery 43.78% Central hypothyroidism: presurgery 20%, postsurgery 50.27% Impaired growth hormone-Insulin-like growth factor 1 axis: presurgery 47.03%, postsurgery 57.3% Hyperprolactinemia: presurgery 28.11%, postsurgery 20.54%	Not specified	Presurgery: 17.8 Postsurgery: 25.4	ESS	Number of patients with sleeping disorders: – Mass effect in situ (presurgery): 3 – After neurosurgery: 5 No significant differences in sleeping disorders between groups	Sleep rhythm disturbance Somnolence
Guo et al. 2023[3]	C	742	6 – 44	421/ 321	Pre	N/A	617/125	–	Impaired hypothalamus-pituitary-adrenal axis presurgery 19.7% Impaired hypothalamus-pituitary-thyroid axis presurgery 24.8% Growth hormone deficiency presurgery 24.8% Impaired hypothalamus-pituitary-gonad axis presurgery 37.8% Hyperprolactinemia presurgery 35.2% Diabetes insipidus presurgery 24%	Not specified	19.1	SDSC (<18yrs) or PSQI (>18yrs)	36/742 (4.9%) had a sleep disorder	Not specified

(Contd...)

Table 3: *(Contd...)*

Ref.	*Study design**	*CP (n)*	*Age (yrs)*	*M/F (n)*	*Pre/ postsurgery*	*GTR or STR†*	*ACP/ PCP§ (n)*	*Hypothalamic injury*	*Hormone deficiencies*	*Hormone replacement*	*Obesity‖ (%)*	*Sleep measures¶*	*Main sleep-related results*	*Type of sleep disturbance*
Honegger et al.1998[18]	C	13	17–76	4/9	Both	GTR 62% STR 23%	–	–	At time of evaluation, adrenal and thyroid axes were either normal or under sufficient replacement therapy		N/A	NHP	Sleep impairment on NHP (10 participants): Pre-op: 20% Post-op: 8%	Not specified
Kalapurakal et al. 2003[24]	C	25	1–15	14/11	Post	GTR 76% STR 24%	–	9 patients had tumors with extension into hypothalamic region	100% developed panhypopituitarism postsurgery	Supplementation of all pituitary hormones (including 1-deamino, vasopressin, cortisol, thyroxine, growth hormone and sex hormones)	32	N/A	3/25 (12%) had "sleep-disorder" as a complication of primary surgery	Not specified
Larijani et al. 2004[25]	C	68	4–48	–	Post	STR 100%	–	–	Diabetes insipidus in 75% of patients as an early complication of post partial resection Panhypopituitarism in 28% patients as a late complication of post partial resection	Not specified	3.1	N/A	3/68 patients had insomnia as late postsurgical complication	Insomnia
Lee et al. 2003[21]	CC	29	48 ± 12.77	16/13	Post	–	–	All patients had significant hypothalamic damage compared with controls	Not specified	Not specified	100	PSQI	No significant difference between PSQI scores for CP patients vs controls	Poor sleep quality
Muller et al. 2006[20]	CC	Whole cohort: 115 Sub-group: 10	Age at surgery: 6.2–15.6 *Age at study: 11–32*	5/5	Post	–	–	–	All patients had complete pituitary deficiency	All patients received adequate endocrine substitution	100	ESS, PSG, MSLT, Horne-Osberg scale	Whole cohort: 35/115 childhood CP patients had ESS>10 (severe daytime sleepiness) Sub-group: 10 obese CP patients (9 with ESS>10 and 1 control with ESS<10) and 1 obese astrocytoma patient with ESS>10 (control) were	Severe daytime sleepiness Narcolepsy Hypersomnia Obstructive sleep apnea

(Contd...)

Table 3: *(Contd...)*

Ref.	*Study design**	*CP (n)*	*Age (yrs)*	*M/F (n)*	*Pre/ postsurgery*	*GTR or STR†*	*ACP/ PCP§ (n)*	*Hypothalamic injury*	*Hormone deficiencies*	*Hormone replacement*	*Obesity‖ (%)*	*Sleep measures¶*	*Main sleep-related results*	*Type of sleep disturbance*
													analyzed for sleep disturbances: – 3/10 CP patients had secondary narcolepsy – 3/10 CP patients had hypersomnia – 2/10 CP patients had obstructive sleep apnea	
O'Gorman et al. 2010[22]	CC	15	10–21	7/8	Post	–	–	All patients had evidence of hypothalamic damage	Subjects had multiple pituitary hormonal insufficiencies	All patients received adequate replacement therapies including: 93% patients treated with desmopressin for diabetes insipidus, 93% treated with hydrocortisone, 93% treated with levothyroxine, 53% treated with growth hormone (of the 47% untreated, 71% had normal growth hormone and 29% had completed growth), 33% treated for hypogonadotropic hypogonadism	100	PSG	Sleep-onset latency was significantly lower in CP patients compared to controls (CP patients fell asleep quicker) Obstructive-apnea-hypopnea index was significantly higher in CP patients compared to controls. 6 CP patients had moderate or severe OSA (5 or more obstructive apnea episodes per hour) Sleep disordered breathing was increased in adolescents with craniopharyngioma-related obesity compared with body mass index (BMI)-matched controls	Moderate/ severe obstructive sleep a
Pascual et al. 2019[26]	C	92	3–60	45/47	Pre	N/A	67/10	Strong adherences to hypothalamus demonstrated in 63% cases	Endocrine deficits (76.1%) Diabetes insipidus (37%) Hypothalamic disturbances (38%)	Not specified	40.2	N/A	43 (46.7%) patients had somnolence at diagnosis Somnolence (p <0.001) highest rate in infundibulo-tuberal & third ventricular CPs	Somnolence

(Contd...)

Table 3: *(Contd...)*

Ref.	Study design*	CP (n)	Age (yrs)	M/F (n)	Pre/ postsurgery	GTR or STR†	ACP/ PCP§ (n)	Hypothalamic injury	Hormone deficiencies	Hormone replacement	Obesity‖ (%)	Sleep measures¶	Main sleep-related results	Type of sleep disturbance
Qi et al. 2012[27]	C	81 (group A = infra-diaphragmatic sellar tumors; group B = 3rd ventricular floor tumors)	A: 8.26 ± 4.02 B: 9.1 ± 3.83	A: 23/11 B: 26/21	Pre	N/A	–	3rd ventricular floor tumors usually involved hypothalamus	Adrenocorticotropic hormone deficiency 54.8% (A) and 31.5% (B) Thyroid stimulating hormone deficiency 67.6% (A), 53.2% (B) Growth hormone deficiency 100% (A), 94.7% (B) Diabetes insipidus 47.1% (A), 17% (B)	Not specified	32.6 (A) 5.8 (B)	N/A	Somnolence (3.7%) was relatively rare and randomly detected in both groups at presentation	Somnolence

Data provided as mean ± standard deviation where applicable. – Information not given; *Study design: C, cohort; CC, case-control; §ACP, adamantinomatous craniopharyngioma; †GTR, gross total resection; ¶ESS, epworth sleepiness scale; ‖Obesity reported as percentage of patients in study classified as obese or body mass index > 30 kg/m^2; MSLT, mean sleep latency test; NHP, nottingham health profile; PCP, papillary craniopharyngioma; PSG, polysomnography; PSQI, Pittsburgh sleep quality index; SDSC, sleep disturbance scale for children; STR, subtotal resection

Postsurgery

Eight studies assessed sleep in CP patients postsurgery; five were postsurgery only, and three compared patients pre- and postsurgery. Data on the number and type of sleep disturbance reported and how long postsurgery they were measured are displayed in Table 4 for studies assessing sleep postsurgery only.

Pre- and Postsurgery Comparisons

Four studies compared sleep in patients pre- and postsurgery. All studies used the same patients and the same methods of measuring sleep before and after surgery. The main findings of these studies are seen in Table 5.

Prevalence, study weighting, and weighted prevalence of sleep disturbances in CP patients presurgery and postsurgery are displayed in (Supplementary Material, Table 1). Combined prevalence across all studies included was 9.41 and 21.08% for pre- and postsurgery, respectively. There was no significant difference in weighted prevalence scores between pre- and postsurgical data ($p = 0.561$).

Discussion

The aim of this review was to evaluate sleep disturbances in CP patients pre- and postsurgery. Only four studies in this review made this comparison, so studies that assessed sleep only pre- and only postsurgery were also included, but these provide weaker evidence due to the lack of control/comparison groups. No significant difference between the weighted prevalence of sleep disturbances in CP patients pre- vs postsurgery was found. This may suggest that surgery does not consistently cause hypothalamic damage leading to sleep disturbances, or that if the CP tumor extends into the hypothalamus presurgery, then surgery does not improve sleep outcomes. However, the strength of this conclusion is severely limited by several factors. Firstly, the analysis relies on comparisons made between cohorts who may not be representative of one another due to a variety of confounding factors. These include the presence of hypothalamic injury, BMI, time of measurement before/after surgery, age, and histological subtype. Also, most studies in this review assessed sleep as a secondary outcome and used subjective measures that rely on self-report, which might not report sleep as accurately as objective measures and are more prone to bias.

The combined findings of the four individual studies that compared sleep pre- and postsurgery displayed no clear patterns in terms of sleep disturbances. Some studies reported improvement in sleep postsurgery, while others reported the opposite or no effect, which supports our statistical analysis of no overall difference pre- to postsurgery. However, these studies all display strengths and weaknesses which must be taken into consideration. Guo et al.[23] was the highest-weighted study in this group, with 185 participants compared to a total of 88 participants across the other three studies. Guo et al.[23] found no statistical difference between sleep disturbances pre- and postsurgery, which supports the comparison of weighted prevalence in this review. However, sleep was measured subjectively (ESS) by Guo et al.[23] Conversely, Foschi et al[19] was the only study in this cohort to measure sleep objectively and found improvement in sleep efficiency postsurgery but worsening of daytime drowsiness. However, these authors had a very small sample size and performed no statistical analysis. Small sample sizes used in many of the studies make results more susceptible to confounding by other variables and lack of statistical analysis prevents the drawing of solid conclusions.

Table 4: Sleep disturbances reported in studies that analyzed sleep in CP patients presurgery only and postsurgery only

Pre/postsurgery	*Study*	*Time of sleep measurement presurgery*	*Type of sleep disturbances reported (number of patients/total number of CP patients)*
Presurgery only	Guo et al. 2023[3]	Information not given	Not specified (36/742)
	Pascual et al. 2019[26]	Information not given	Somnolence (43/92)
	Qi et al. 2012[27]	Information not given	Somnolence (3/81)
Postsurgery only	Kalapurakal et al. 2002[24]	Information not given	Not specified (3/10)
	Lee et al. 2003[21]	40.67 ± 25.87 months	Poor sleep quality (*/29)
	Muller et al. 2006[20]	8.76 ± 4.49 years (since first surgery)	Whole cohort: Severe daytime sleepiness; (35/?115)
	O'Gorman et al. 2010[22]	Information not given	Sub-group: Secondary narcolepsy (3/10); hypersomnia (3/10); obstructive sleep apnea (2/10)
			Moderate/severe obstructive sleep apnea (6/15)
	Larijani et al. 2004[25]	1 month – 13 years (mean = 56.4 months)	Insomnia (3/68)

Data provided as range and/or mean ± standard deviation. *no information given

Table 5: Sleep disturbances reported in studies that analyzed CP patients presurgery and postsurgery

Study	*Time of sleep measurement presurgery/postsurgery*	*Type of sleep disturbances reported presurgery (number of patients/ total number of CP patients)*	*Type of sleep disturbances reported postsurgery (number of patients/ total number of CP patients)*	*Comparison of sleep pre- vs postsurgery*
Foschi et al. 2017[19]	Days and nights before surgery/65–431 days (mean = 233 days)	Pathological sleep efficiency (8/10); abnormal REM latency (5/10); daytime drowsiness (7/10); OSA (2/10); pathological number of periodic limb movements (2/10)	Pathological sleep efficiency (4/10); abnormal REM latency (2/10); daytime drowsiness (9/10)	4/8 patients showed improvements in sleep efficiency postsurgery REM latency normalized in 3/5 patients postsurgery Daytime drowsiness increased postsurgery
Guo et al. 2019[23]	Within 1 month of surgery /14 ± 3 days	3/185 (Sleep rhythm disturbance (2/185); somnolence (1/185)]	5/185 [Sleep rhythm disturbances (4/185); not specified (1/185)]	Overall number of patients with sleep disorders increased from 3/185 patients to 5/185 patients after neurosurgery but not statistically significant Sleep rhythm disturbances increased from 2/185 patients to 4/185 patients
Honegger et al. 1998[18]	Information not given/ 3 months	Not specified (5/10)	Not specified (not specified/10)	Sleep impairment (%) on Nottingham Health Profile (NHP) decreased from 20 to 8% postsurgery indicating improvement in sleep postsurgery Five patients reported a sleep problem presurgery. No information on how many patients reported a sleep problem postsurgery

Somnolence, hypersomnolence, and EDS were the most frequently reported sleep disturbances in both pre- and postsurgical CP patients.[27] While these terms all have slightly different definitions, they all share symptoms of excessive tiredness, particularly during waking hours.[28] Somnolence was measured subjectively in many of the studies and often was the only sleep outcome reported. This may provide some explanation on why it was reported most commonly, as it may be more easily detected or reported compared with other sleep disturbances that need objective measurements for diagnosis. Somnolence was described in 4/6 of the studies that assessed sleep presurgery. However, the amount of patients experiencing this differed between studies, with an apparent relationship with age. The studies in this review may suggest that adults are more likely to present with somnolence at diagnosis than children. Pediatric cohorts reported a lower prevalence of somnolence presurgery (3.7%,[27] 0.05%[23]) than

adults (70%).[19] A potential reason for this difference may be that children present more frequently with the adamantinomatous (ACP) CP subtype, while the papillary (PCP) form occurs more often in adults.[29] Hypothalamic dysfunction is higher in patients with PCP than ACP,[3] indicating a higher risk of sleep disturbance, possibly because PCP originates mainly in the suprasellar region, where the hypothalamus resides, while ACP originates in the sellar region.[3]

Somnolence/EDS was also the most frequently reported sleep disturbance in studies looking at postsurgical CP patients (reported in 2/6 studies), alongside OSA, which is a potential cause of somnolence. OSA was reported in 2/6 studies postsurgery and 1/6 studies presurgery. However, only one of these papers compared sleep both before and after surgery and only reported OSA presurgery, despite a mean increase in BMI after surgery. Obesity is a well-known risk factor for OSA in the general population,[30] but O'Gorman et al.[22] found that OSA was significantly more frequent in CP patients with hypothalamic obesity (HO) postsurgery than BMI-matched controls.[22] These findings are consistent with other studies suggesting patients with HO have a higher risk of OSA than those with obesity due to other etiology.[31,32] This indicates a direct role of hypothalamic damage in the development of OSA in CP patients, which does not appear to be different depending on whether due to mass effect from the tumor or surgical injury. For OSA, other causes for somnolence may include poor/insufficient sleep and disorders of the sleep-wake cycle such as narcolepsy,[33] the latter of which was reported in patients postsurgery by Muller et al.[20] Secondary narcolepsy occurs due to damage to hypothalamic neurons producing/transmitting orexin, a neuropeptide important in regulating sleep and wakefulness,[34] so the findings from this study may suggest a specific role of surgery in inducing this damage. However, this study was limited by having only 10 participants, 1 unmatched control, and no comparison to presurgical data, so it is not possible to confidently make this conclusion.

Other sleep problems were also reported in the studies included in this review, some of which have been previously mentioned in the literature as consequences of CP or its treatment.[14,35] These included sleep rhythm disturbances, with no significant difference found in frequency between pre- and postsurgery.[23] Problems with sleep quality were also seen postsurgery in one study[21] and sleep scores NHP seemed to improve postsurgery in another study.[18] However, two other sleep disturbances were mentioned that are not as commonly reported; PLMD and insomnia. PLMD was seen presurgery in two patients in Foschi et al.[19] PLMD appears to be related to restless leg syndrome (RLS) and previous research found that if the A11 nucleus of the posterior hypothalamus, a major source of dopamine for the spinal cord, is lesioned then the development of an RLS-like phenotype can occur in mice.[36–38] Considering 50% of the patients in Foschi et al.[19] had posterior hypothalamic involvement of the tumor, this may provide an explanation for why PLMD was seen in this study. However, this disturbance was not reported postsurgery and it is unlikely that surgery would have reversed any hypothalamic damage. Therefore, this brings into question possible confounding factors such as physical inactivity, smoking, or obesity, which all increase the risk of PLMD.[39] Similarly, insomnia was only reported in one study postsurgery.[25] Insomnia has been reported in survivors of other childhood brain tumors, potentially due to disruption of the ventrolateral preoptic nucleus located in the hypothalamus.[34] Hence, it is possible that surgery-induced hypothalamic injury could explain this finding. However, this is less likely considering that surgical management was STR, which is associated with a lower risk of damage.[5] It was also reported as a "late postsurgical complication," and sleep disturbances frequently occur in patients postoperatively, irrespective of type of surgery.[40,41] Therefore, it is difficult to determine to what extent the results are confounded by the act of surgery itself rather than specifically the iatrogenic hypothalamic damage done by the surgery. The same may be true for other studies in this review, particularly those where measurements were only taken days/months presurgery[19,23] and postsurgery.[18,23]

Hypothalamic damage is thought to be the most important factor in determining sleep disturbances in CP patients,[11] which may be due to the tumor or due to surgery. However, studies that demonstrated hypothalamic damage in patients found varying results in terms of sleep.[19,21,22]

This may have been due to variation in other factors that affect sleep, or due to differences in the extent and/or location of hypothalamic damage. For example, in two studies where postsurgical hypothalamic damage was present, one study found that sleep outcomes were significantly worse in CP patients compared to controls,[22] but the other study found no significant difference in sleep outcomes between CP patients and controls.[21] The exact location of hypothalamic damage and extent of surgical resection is not clear in either paper, which may have provided insight into the precise mechanisms of sleep disturbances and reasons for conflicting results between papers. In contrast, Foschi et al.[19] demonstrated that 50% of patients had tumors located at the posterior hypothalamus, the location of the suprachiasmatic nucleus which is critical for sleep,[12] and reported a high prevalence of sleep disorders presurgery. Additionally, there was an apparent worsening of overall sleep disorders postsurgery when a GTR method was used in the majority of patients, which has been predicted to cause further damage in patients with hypothalamic-invading tumors.[5] Many studies did not report the extent of hypothalamic damage or the extent of surgical resection, which makes it difficult to assess the precise role of hypothalamic injury on sleep disturbances. It is possible that when predicting adverse outcomes, one needs to consider that preoperative grading to define the exact location of hypothalamic damage is more important than simply just the presence or absence of damage. This may suggest a need to refine the already existing grading system to improve clinical outcomes both pre- and postsurgery.[42]

To conclude, this review suggests that surgery does not increase the risk of sleep disturbance in CP patients based on weighted prevalence calculations and a lack of clear differences in individual studies comparing sleep pre- and postsurgery. However, the quality of the literature is not strong enough to make any firm conclusions, with many limitations mentioned throughout. This highlights the need for more suitably designed studies, with adequate sample sizes that quantify sleep disturbances pre- vs postsurgery, with self-reported measurements supported by objective assessment of sleep quality, and measurements preferably taken at diagnosis/early stages in the disease followed by months-years postsurgery.[43,44] It would also be useful to assess the location of the tumor and the extent of hypothalamic damage pre- and postsurgery to improve knowledge of mechanisms contributing to sleep disturbances. Additionally, future research could focus on the effect of radiotherapy on sleep, as it is becoming more frequent in addition to surgery in CP treatment, and there is already a plethora of primary studies evaluating its use. Radiotherapy may carry its own consequences on sleep, hence it would be useful to examine

sleep pre- and posttreatment in CP where radiotherapy is used and assess if there are any differences to the current review.

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Supplementary Materials

All the supplementary materials are available online on the website of www.ijsm.in/journalDetails/IJSM.

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Appendix 1

The corresponding author from Foschi et al. was consulted via email regarding queries and discrepancies in their data. There were queries regarding a duplicate dataset with this paper and another paper identified during the screening process, and the number of males and females was reported differently in each paper. In this communication, the author confirmed that the two papers contained the same dataset and confirmed the correct number of females and males used for their study. The number of males and females is correctly reported in this systematic review (Table 3) as 4 and 6, respectively. The other paper was excluded for the reason of a duplicate dataset. The author was also consulted regarding discrepancies between results, e.g., the results state that all patients developed hypothyroidism and diabetes insipidus postsurgery yet Table 1 in their paper reported hypothyroidism and diabetes insipidus in 90 and 70%, respectively. The author did not respond so the values in Table 1 were extracted and used in this review.