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Sleep disturbance and delirium in patients with acromegaly in the early postoperative period after transsphenoidal pituitary surgery

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Abstract

Sleep disturbance is a common comorbidity among patients with acromegaly [patients with growth hormone (GH)-secreting tumor] due to somatotropic axis change and sleep apnea. However, no previous studies exist concerning sleep disturbance and delirium in the early postoperative period in patients with acromegaly undergoing transsphenoidal tumor surgery. Herein, we aimed to compare the incidence of postoperative sleep disturbance and delirium in the early postoperative period between patients with GH-secreting and nonfunctioning pituitary tumors.

We retrospectively reviewed the medical records of 1286 patients (969 with nonfunctioning and 317 with GH-secreting tumors) without history of psychological disease and sedative or antipsychotic use. We examined the use of antipsychotics/sedatives and findings of psychology consultation within the first postoperative week. Only patients with sleep disturbance noted in medical records were considered to have postoperative sleep disturbance. Patients with an Intensive Care Delirium Screening Checklist score of 4 or more were considered to have postoperative delirium.

The incidence of postoperative sleep disturbance was higher in the GH-secreting group than in the nonfunctioning tumor group (2/969 [0.2%] vs 6/317 [1.9%]; $P = .004$; odds ratio = 9.328 [95% confidence interval, 1.873–46.452]). Univariable regression analysis showed that only diagnosis (GH-secreting tumor or nonfunctioning tumor) was a risk factor for sleep disturbance, and not sex, age, body mass index, American Society of Anesthesiologists physical status score, surgery duration, anesthesia duration, anesthesia type, tumor size, cavernous sinus invasion, or bleeding. The incidence of postoperative delirium was comparable between the 2 groups (6/969 [0.6%] vs 0/317 [0%]; $P = .346$).

Patients with acromegaly showed increased incidence of sleep disturbance than those with nonfunctioning tumors in the early postoperative period after transsphenoidal tumor surgery. A prospective study evaluating sleep quality in patients with GH-secreting tumors in the early postoperative period could be conducted based on our findings.

Abbreviations: ASA = American Society of Anesthesiologists, GH = growth hormone, IGF-1 = insulin-like growth factor 1, REM = rapid eye movement.

Keywords: early postoperative sleep disturbance, growth hormone secreting tumor, transsphenoidal pituitary surgery

1. Introduction

General anesthesia and surgery can change the circadian rhythm of melatonin secretion, and this change may cause sleep disturbance and delirium in the postoperative period.[1] Especially within the first 3 postoperative days, sleep is highly fragmented by easy arousal, but the sleep patterns gradually return to normal.[2] Sleep in the first and second postoperative nights is characterized by reduced total sleep time and markedly decreased rapid eye movement (REM) and slow-wave sleep. However, rebound REM sleep with increased density appears in the middle of the first postoperative week[3,4] and could possibly be associated with episodic hypoxemia and hemodynamic instability.[5] Sleep disturbance could also be related to postoperative delirium, a risk factor for prolonged hospital stay, cognitive dysfunction, and poor activities of daily living after surgery.[6,7]

Previous studies have focused on quality of life impairments in patients with pituitary adenoma, the most frequently encountered tumor in the pituitary gland.[8] Sleep disturbance is prevalent among patients with pituitary adenoma and is an important factor contributing to quality of life impairment.[9,10] In particular, the relationship between sleep and the somatotropic axis, including growth hormone (GH) secretion, has been demonstrated.[11] Sleep disturbance is a common comorbidity

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among patients with acromegaly (i.e., those with GH-secreting tumor) due to hormonal imbalance and sleep apnea.[10] Even among patients treated for acromegaly, sleep quality was reduced compared with that of normal controls.[12] Irreversible change in the upper airway could be responsible for the sleep disturbance in these patients long after the condition has been cured.[10,12] A few studies have reported the association between insulin-like growth factor 1 (IGF-1) and delirium, but the results were inconsistent.[13–16]

There are no previous studies on sleep disturbance and delirium in the early postoperative period in patients with acromegaly undergoing transsphenoidal tumor surgery. In this retrospective study, we aimed to compare the incidence of postoperative sleep disturbance and delirium in the first postoperative week between patients with GH-secreting tumors and patients with nonfunctioning tumors.

2. Methods

2.1. Study population and data collection

The study protocol was approved by the institutional review board of the Yonsei University Health System, Seoul, South Korea (#4-2018-0473). This study was conducted in accordance with the ethical guidelines of the Helsinki Declaration. The requirement of informed consent from the patients was waived owing to the retrospective design of the study.

We queried our electronic medical records database for cases of transsphenoidal pituitary surgery for GH-secreting or nonfunctioning tumors under general anesthesia at a university hospital between January 1, 2013, and February 28, 2018. The exclusion criteria were age <18 years, history of radiotherapy or medical treatment for pituitary tumor, preoperative diagnosis of psychological disease, including sleep disturbance, preoperative history of sedative or antipsychotic drug use, Cushing disease, hypopituitarism, prolactinoma, craniopharyngioma, abnormal thyroid function test, and insufficient medical data.

To determine the incidence of postoperative sleep disturbance and delirium, we investigated the use of alprazolam, zolpidem, and quetiapine, which are the drugs most commonly prescribed as sedatives by neurosurgeons in our institution, and the need for postoperative psychological consultation within the first postoperative week. Only those patients who clearly stated having sleep disturbance such as reduced total sleep time or fragmented sleep by easy arousal in progress notes, consultation notes, or nursing records were considered to have postoperative sleep disturbance. The patients were diagnosed with postoperative delirium by a psychiatrist based on an Intensive Care Delirium Screening Checklist (ICDSC) score of 4 or more. Two investigators independently reviewed all medical records. We compared postoperative sedative use and incidence of sleep disturbance and delirium between patients with nonfunctioning tumors and patients with GH-secreting tumors. We also compared serum IGF-1 levels before and 3 days after the surgery in the GH-secreting tumor group.

2.2. Statistical analysis

Descriptive data are presented as mean values ± SD. For intergroup comparisons, Chi-square test or Fisher exact test was used for categorical variables and Student *t*-test or Wilcoxon-Mann–Whitney test was used for continuous variables. The effect sizes were calculated according to Cohen W, and an effect size less than 0.1 was considered to have sufficient power to detect differences between the 2 groups. Factors that affected postoperative sleep disturbance were determined by univariable and multivariable regression analysis. The regression analysis included variables such as diagnosis (GH-secreting tumor or nonfunctioning tumor), sex, age, body mass index (BMI), American Society of Anesthesiologists (ASA) physical status, duration of surgery, duration of anesthesia, type of anesthesia (inhalation anesthesia vs total intravenous anesthesia), tumor size, cavernous sinus invasion, and bleeding. All statistical analyses were performed using SPSS Statistics 23 (IBM SPSS Statistics for Windows, IBM Corp, Armonk, NY).

3. Results

A total of 1286 patients, comprising 969 with nonfunctioning tumors and 317 with GH-secreting tumors, were included in this study (Fig. 1). The proportion of female patients was higher in the nonfunctioning tumor group than that in the GH-secreting tumor group. Although the nonfunctioning group included 284 patients with ASA classification 1, all patients in the GH-secreting tumor group had ASA classification of more than 2; therefore, there was a difference in severity between the 2 groups. Especially, the prevalence of hypertension and diabetes mellitus was higher in the GH-secreting tumor group than that in the nonfunctioning tumor group (Table 1).

3.1. Postoperative sleep disturbance and delirium

The incidence of postoperative sleep disturbance was higher in the GH-secreting tumor group than that in the nonfunctioning tumor group (2/969 [0.2%] vs 6/317 [1.9%]; $P = .004$; odds ratio [OR] = 9.328 [95% confidence interval (95% CI),1.873–46.452]; effect size = .08; Table 2). Six of the eight patients with sleep disturbance had used alprazolam, zolpidem, or quetiapine at least once within the first postoperative week. The seventh patient underwent psychiatric consultation for insomnia on the first postoperative day, and the eighth patient complained of difficulty falling asleep and easy arousal for 3 postoperative nights (Table 3).

The incidence of postoperative delirium was comparable between the 2 groups. Of the 969 patients in the nonfunctioning tumor group, 6 were diagnosed with postoperative delirium, while none of the 317 patients in the GH-secreting tumor group were diagnosed with postoperative delirium (6/969 [0.6%] vs 0/317 [0%]; $P = .346$; effect size = .026). Six patients with delirium in this study presented with restlessness, agitation, hallucinations, or delusions and had an ICDSC score of 4 or more.

3.2. Postoperative sedative use

There was no significant difference in postoperative sedative use between the nonfunctioning tumor and the GH-secreting tumor groups (16/969 [1.7%] vs 9/317 [2.8%]; $P = .238$; OR = 1.740 [95% CI, 0.761–3.978]); effect size = .031; Table 2).

3.3. Serum IGF-1 level

In the GH-secreting tumor group, serum IGF-1 level measured 3 days after the surgery was significantly lower than that observed preoperatively (336.40 ± 133.96 vs 688.37 [223.58]; $P < .001$). Reduction in IGF-1 was also observed in patients with postoperative sleep disturbance (Table 3).

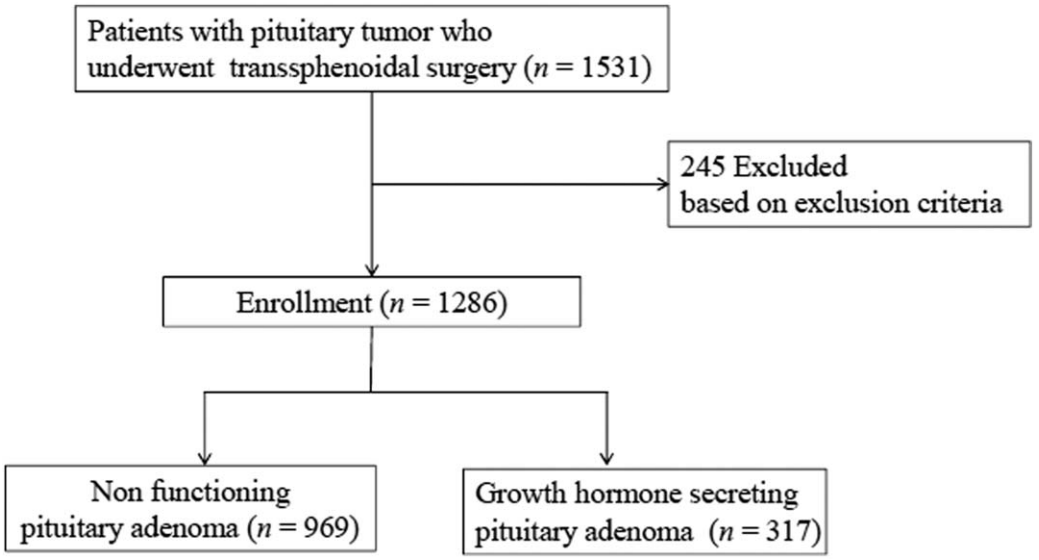

Figure 1. Flowchart of patient selection.

3.4. Factors that affected postoperative sleep disturbance

Only the diagnosis (GH-secreting tumor or nonfunctioning tumor) was found to be a risk factor for sleep disturbance in univariable regression analysis, and not sex, age, BMI, ASA physical status score, duration of surgery, duration of anesthesia, type of anesthesia (inhalation anesthesia vs total intravenous anesthesia), tumor size, cavernous sinus invasion, or bleeding. Along with the diagnosis, variables which were different between the 2 groups such as sex, age, BMI, ASA physical status score, and duration of anesthesia were included in the multivariable analysis. Multivariable regression model also showed that the diagnosis (GH-secreting tumor or nonfunctioning tumor) was the only factor that affected the incidence of sleep disturbance (Table 4).

Table 1

Patient demographics in this study.

	Nonfunctioning tumor (N = 969)	GH-secreting tumor (N = 317)	*P*
Age, yr	46.68 ± 13.87	44.06 ± 12.09	.001
Sex (male/female)	362/607	147/170	.004
Height, cm	164.45 ± 8.34	168.27 ± 10.11	<.001
Weight, kg	65.77 ± 12.85	71.62 ± 14.15	<.001
BMI	24.23 ± 3.82	25.14 ± 3.48	<.001
ASA (1/2/3/4)	284/558/123/4	0/261/55/1	<.001
Hypertension	198 (20.4%)	102 (32.2%)	<.001
Diabetes mellitus	79 (8.2%)	74 (23.3%)	<.001
Coronary artery disease	23 (2.4%)	4 (1.3%)	.231
Duration of surgery, min	181.19 ± 78.34	206.10 ± 94.64	.002
Duration of anesthesia, min	273.80 ± 89.41	291.95 ± 100.76	.002
Tumor size (> 1 cm)	871 (89.9%)	275 (86.8%)	.120
Sinus invasion	372 (38.3%)	128 (40.4%)	.528
Bleeding, mL	238.65 ± 267.69	265.87 ± 249.16	.110

Data are presented as mean ± standard deviation for continuous variables and count (percentage) for categorical variables.

ASA = American Society of Anesthesiologists, BMI = body mass index, GH = growth hormone.

4. Discussion

This is the first study to demonstrate that, in patients undergoing transsphenoidal surgery, the incidence of sleep disturbance in the early postoperative period is higher among patients with GH-secreting pituitary tumors than among those with nonfunctioning pituitary tumors. Univariable regression analysis showed that only the diagnosis (GH-secreting tumor or nonfunctioning tumor) was a significant risk factor for postoperative sleep disturbance. Although only patients with nonfunctioning pituitary tumors developed delirium, the difference between the groups was not significant.

Acromegaly is a chronic disease that results from excess secretion of GH, mostly caused by pituitary adenoma. GH is produced in the somatotrophs of the anterior pituitary gland and stimulates cell growth and proliferation in several major organs, both directly and through the release of IGF-1. IGF-1 is produced primarily in the liver by stimulation of GH and has growth-promoting effects on numerous organs together with GH. It is well known that GH secretion increases during sleep.[17] In particular, the onset of nocturnal sleep is a potent stimulator of GH secretion[18] and secretion increases during slow-wave sleep (also known as deep sleep) compared with that during REM- and stage 1 and stage 2 sleep.[19,20]

Table 2

Differences in the incidence of postoperative sleep disturbance, delirium, and antipsychotic use between the groups with nonfunctioning tumors and GH-secreting tumors.

	Nonfunctioning tumor (N = 969)	GH-secreting tumor (N = 317)	*P*	OR (95% CI)
Sleep disturbance	2 (0.2%)	6 (1.9%)	.004	9.328 (1.87–46.45)
Delirium	6 (0.6%)	0 (0%)	.346	
Sedative use	16 (1.7%)	9 (2.8%)	.238	1.740 (0.76–3.98)

Data are presented as count (percentage).

CI = confidence interval, GH = growth hormone, OR = odds ratio.

Table 3

Characteristics of patients with postoperative sleep disturbance.

Patient number	Sex/age	Preoperative IGF-1, μg/L	POD 3 IGF-1, μg/L	Treatment
GH 1	F/56	494	242	Zolpidem 6.25 mg (from operative day through POD 2), 10 mg (from POD 3 to POD 4)
GH 2	F/56	321	108	Quetiapine 6.25 mg (operative day)
GH 3	F/49	420	256	Consultation for sleep disturbance (POD 1), no medication
GH 4	F/62	501	100	Alprazolam 0.25 mg (POD 6)
GH 5	F/42	590	327	Nursing records showed that the patient complained of sleep disturbance (from the operative day through POD 2), no medication
GH 6	F/39	—	—	Zolpidem 12.5 mg (POD 4), zolpidem 12.5 mg + alprazolam 0.25 mg (POD 5)
NF 1	F/31	—	—	Zolpidem 10 mg (POD 6)
NF 2	M/56	—	—	Quetiapine 25 mg (from operative day to POD 2)

F = female, GH = patients with growth hormone secreting tumors, IGF-1 = insulin like growth factor 1, M = male, NF = patients with nonfunctioning tumors, POD = postoperative day.

In the patients with GH-secreting tumors in this study, early postoperative IGF-1 levels did not reduce to within the normal range, but were significantly decreased compared with the preoperative levels, which was consistent with the result of a previous study.[21] GH secretion reaches its peak immediately after sleep onset and is highly correlated to slow-wave sleep.[11,17–20,22] Therefore, abrupt reduction in GH could possibly be responsible for postoperative sleep disturbance. Normal IGF-1 values vary with age and sex and do not fluctuate during the day; therefore, IGF-1 level measurement is used as a screening test for acromegaly. The normalized IGF-1 level is also used as one of the criteria of controlled GH status after the treatment of acromegaly.[23] In a previous study, IGF-1 levels had returned to normal within the first week after surgery for GH-secreting tumor removal.[21] GH deficiency is associated with poor sleep quality and daytime sleepiness.[24,25] In patients with GH deficiency after successful treatment of acromegaly, quality of life, in terms of anxiety and anger, remained lower than that in patients with sufficient GH levels.[26] GH-releasing hormone administration was shown to enhance the quality of sleep in patients with GH deficiency of pituitary origin,[27] and GH replacement and correction of GH levels resulted in a trend of increasing slow-wave sleep duration.[22] In a previous study that examined the quality of life of patients with previous acromegaly long in remission (mean duration of remission, 12 years), sleep quality was impaired compared with that of a normal control population.[12] In the aforementioned study, 48% of the patients underwent radiotherapy or somatostatin-analogue therapy together with surgical treatment and 8% of patients did not undergo surgery. Our study differs from the previous one in that we excluded the effects of other medical treatments and only assessed the effects of general anesthesia and transsphenoidal surgery on postoperative sleep disturbances.

A few studies have reported on the relationship between low IGF-1 level and delirium,[13,14] but in other studies with patients undergoing surgery, there was no relationship between preoperative IGF-1 level and postoperative delirium.[15,16] Generally, IGF-1 decreases during surgery and anesthesia.[28] However, in rare cases of IGF-1 increase during surgery, the increase was associated with postoperative delirium.[16] Delirium is classified into 3 types: hyperactive, hypoactive, and mixed type; hyperactive delirium, characterized by restlessness and agitation, is known to concern less than 2% of total delirium cases.[29] In this study, 6 of 969 patients with nonfunctioning tumors developed hyperactive delirium, and given that the incidence of postoperative delirium in patients undergoing neurosurgery is approximately 10%, the incidence of delirium in these patients is consistent with the previously reported incidence.[30] Although not statistically significant, it is noteworthy that delirium occurred only in patients with nonfunctioning pituitary tumors. In a previous study, improvement in sleep quality through environmental noise and light reduction interventions during the night was associated with low incidence of delirium.[31] Changes in the somatotropic axis of patients with acromegaly might affect the occurrence of postoperative delirium. In a previous study on the personality of patients with pituitary tumors, patients with acromegaly showed less impulsivity than those with nonfunctioning tumors,[32] and

Table 4

Univariable and multivariable logistic regression models of factors associated with postoperative sleep disturbance.

Variables	Univariable			Multivariable		
	OR	95% CI	*P*	OR	95% CI	*P*
Diagnosis (GH-secreting tumor or not)	9.328	1.87–46.45	.006	17.731	2.05–153.25	.009
Sex	4.618	0.57–37.65	.153	4.305	0.49–37.84	.188
Age	1.024	0.99–1.07	.231	1.024	0.96–1.09	.459
ASA	1.701	0.56–5.20	.351	0.809	0.03–21.78	.900
Duration of surgery	1.000	0.99–1.01	.948			
Duration of anesthesia	1.000	0.99–1.01	.905	0.999	0.99–1.01	.756
Type of anesthesia	0.571	0.12–2.77	.486			
Bleeding	1.000	1.00–1.00	.843			
Tumor size (> 1 cm)	0.421	0.09–2.05	.284			
Sinus invasion	0.625	0.12–3.24	.575			
BMI	0.856	0.68–1.07	.171	0.807	0.60–1.08	.147

ASA = American Society of Anesthesiologists physical status classification, BMI = body mass index, CI = confidence interval, GH = growth hormone, OR = odds ratio.

these characteristics could possibly be one of the reasons that we observed no postoperative delirium among patients with acromegaly in this study. Further studies on the relationship between GH and postoperative delirium are required to determine the incidence of postoperative delirium among patients with acromegaly.

This study has some limitations. First, because this study was based on electronic medical records, we could not use standardized polysomnographic recordings or questionnaires to diagnose sleep disturbances. However, we consider that the use of antipsychotic/sedative medication or the need for psychological consultation in postoperative patients without prior history of sleep disturbances signifies the onset of relatively severe sleep disturbance due to surgery. Second, because we could not apply delirium screening methods to all patients in the study population, a considerable number of cases of delirium might have gone unnoticed. However, we believe that significant results regarding hyperactive delirium could be obtained from the medical records.

5. Conclusion

Patients with acromegaly showed increased incidence of sleep disturbance than those with nonfunctioning tumors in the early postoperative period after transsphenoidal tumor surgery. This is the first study to evaluate the effect of surgery and general anesthesia alone on sleep disturbance in patients with acromegaly and could serve as a basis for a prospective study that will evaluate sleep quality and delirium incidence in the early postoperative period among patients with GH-secreting tumors.

Author contribution

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Writing – review & editing: Seung Hyun Kim, Namo Kim, Kyeong Tae Min, Eui Hyun Kim, Hanseul Oh, Seung Ho Choi

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