

Identification of Factors Predicting Diabetes Insipidus Occurrence Following Endoscopic Trans-Sphenoidal Surgery for Pituitary Adenoma in Developing Country

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Abstract

Introduction

Transient diabetes insipidus (DI) is a common problem following endoscopic transphenoidal surgery of pituitary adenoma. Delayed intervention may lead to increased morbidity, and prolonged hospitalization. Predicting which patients are at higher risk for developing transient DI can improve medical services to ensure adequate care.

Methods

We retrospectively performed a cross sectional study to identify which variables are associated with transient DI at our department during March 1, 2018 - May 31, 2020.

Results

From 51 patients, transient DI was observed in 26 of 51 patients (50.98%). Upon bivariate analysis, we found 4 variables that potentially become predictors for transient DI occurrence: visual field disturbance ($p=0.0238$), hormonal disturbance ($p=0.0109$), larger tumor ($>2.8\text{cm}$) ($p=<0.0001$) and total resection ($p=0.0008$). Multivariate analysis confirmed that larger tumor and total resection as predicting factors for transient DI occurrence after surgery of pituitary tumors.

Conclusion

Tumor size and type of resection potentially become predicting factors for transient DI occurrence following endoscopic surgery of pituitary tumors. These finding might foster adequate care for those patients.

Introduction

Diabetes insipidus (DI) is a group of signs and symptoms caused by insufficiency of antidiuretic hormone in the kidneys, which causes excess fluid and electrolyte excretion from the kidneys and increased serum osmolality, resulting in the patient's symptoms of polyuria with low urine osmolality, and polydipsia. DI can be divided into 2 major groups, which are neurogenic or central DI, which is caused by disorders of the hypothalamic-pituitary axis, and nephrogenic DI, which is caused by the kidney's resistance to antidiuretic hormones. Transient DI is a type of neurogenic DI that often occurs after transsphenoidal endoscopic surgery for pituitary adenomas, a result of injury to the posterior pituitary or pituitary stalk which generally returns to normal within 3-5 days postoperatively [1,2] although some studies suggest the duration of transient DI may vary up to 2 weeks, 6 months or even 1 year before being categorized as permanent DI [2-4]. Transient DI is the result of temporary dysfunction of the hypothalamus-pituitary axis due to surgical trauma, and strain of the pituitary stalk due to a fallen diaphragm after removal of the adenoma.

The incidence of transient DI after endoscopic trans-sphenoidal surgery for pituitary adenoma is approximately 63-86%. It is more common compared to permanent DI and triphasic response, in which the incidence rate ranges from 0.5-5% [5-19].

Factors that influence the occurrence of transient DI after endoscopic trans-sphenoidal surgery can be divided into 2 major groups. First, the preoperative factor is the tumor diameter. Larger tumor size is associated with more involvement of the surrounding tissue, particularly the pituitary stalk. Second, the intraoperative factor is the tumor resection rate. The more tumors that are resected, the greater the chance that the breakdown of the diaphragm will occur, which can irritate the pituitary stalk [6,17].

Inaccurate identification and management given during the patient’s postoperative transient DI can cause various complications, thus prolonging the length of stay in the hospital, and can also interfere with the patient’s quality of life in the future. Therefore, we sought to investigate about on the predicting factors for transient DI occurrence in patients with pituitary adenoma after endoscopic trans-sphenoidal surgery.

Methods

Patients Selection

The study was approved and conducted according to the Ethical Committee of Hasan Sadikin Hospital. All adult patients with pituitary adenoma after endoscopic trans-sphenoidal surgery in the Department of Neurosurgery, Faculty of Medicine, Universitas Padjadjaran during March 1, 2018 - May 31, 2020 was included in the study. Patients with previous electrolyte disturbances or previous kidney disease were excluded from the study. A total 51 of patients with pituitary adenoma were included in the study.

Data Collection

The relevant information regarding patients’ clinical condition: age, sex, symptoms, urine output, serum sodium levels, and type of resection were retrieved from archived medical records. Meanwhile, the largest diameter of the pituitary adenoma was measured based on the latest patients’ neuroimaging data either CT-Scan or MRI. The value was stated in cm. The raw clinical data was presented as Supplementary Table 1.

Table 1: Interpretation of Post-Operative Polyuria

Parameters	Normal	Fluid Overload	Transient DI
Urine Output	0.5-1mL/kg/hour	> 1mL/kg/hour	> 2mL/kg/hour
Δ Serum Na	NA	< 5mEq/L	> 5mEq/L
Urine Osmolality	300 - 900mOsm/kg	> 300mOsm/kg	< 300mOsm/kg

The definition of post-operative DI is varied across literatures, lead to high variation of incidence rates. Polyuria is the most overt symptoms of DI, but can also reflect several physiological adaptive mechanisms in the postoperative phase. These may be difficult to distinguish from and might coincide with DI. Therefore, we modified available criteria¹⁸ for post-operative DI to diagnose the occurrence of post-operative DI in this study, as follow: polyuria (urine output $\geq 2\text{mL/kg/hour}$), post-operative increased of serum natrium level ($\Delta\text{Na level} > 5\text{mEq/L}$), and low urine osmolality ($< 300\text{mOsm/kg}$), detailed description of post-operative DI was presented as Table 1.

Statistical Analysis

For descriptive statistics, numerical variables are presented as mean with standard deviation (SD) and categorical variables are presented as counts and percentages. Categorical variables were compared with chi-squared test or Fisher’s exact test. Multivariate analysis was performed with multiple linear regression.

P<0.05 was considered as statistically significant. All statistical analyses were performed with Graph Pad Prism 8.0.

Results

Patients Characteristics

Characteristics of the patients taken in this study were age, sex, clinical symptoms (visual field disturbance, blurred vision, headache, and hormonal disturbance), tumor size, type of adenoma, sodium levels before and after surgery, mean urine output 2 hours after surgery, and urine osmolality. The summary of patients characteristics were presented as table 2.

Table 2: *Clinical Characteristics of the Patients*

Variables	Values
Age (year)	41.43±9.515
Sex	
Male	26 (51.0%)
Female	25 (49.0%)
Visual Field Disturbance	
Yes	43 (84.3%)
No	8 (15.7%)
Blurred Vision	
Yes	33 (64.7%)
No	18 (35.3%)
Headache	
Yes	29 (56.9%)
No	22 (43.1%)
Hormonal Disturbances	
Yes	10 (19.61%)
No	41 (80.39%)
Types of Adenoma	
Macroadenoma	50 (98.0%)
Microadenoma	1 (2.0%)
Tumor Diameter (cm)	2.92±0.81
Sodium Level Pre-Operative (mEq/L)	138.16±4.571
Sodium Level Post-Operative (mEq/L)	144.76±6.153
Urine output at the first 2 hours post-surgery (cc/kg hr)	3.00±1.49

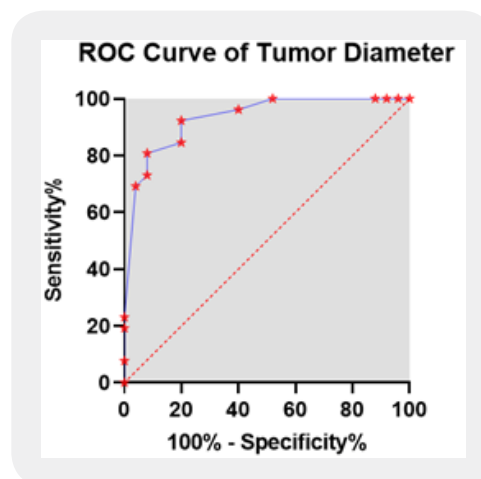
The average age of the patients was 41.43 ± 9.515 years consisting of 26 (51.0%) male patients and 25 (49.0%) female patients. Forty-three (84.3%) patients had clinical symptoms of visual field disorders (84.3%), 33 patients had blurred vision (64.7%), 29 patients had headache (56.9%), and 10 patients had hormonal disturbance (19.61%). A total of 50 patients (98.0%) presented with pituitary macroadenoma. Only 1 patient presented with a pituitary microadenoma with a tumor size of 0.9cm. Average preoperative sodium levels was 138.16 ± 4.571 mEq/L and post-operative was 144.76 ± 6.153 mEq/L. The average urine output (the first 2 hours post-operative) was 3.00 ± 1.49 mL/kg hr.

Identification of Predicting Factors

In this study, the majority of the patients (n=50 or 98.03%) were having polyuria (> 1mL/kg hr) post operatively, suggesting the importance of distinguishing DI from physiological adaptation following surgery. Transient DI was identified in 26 (50.91%) patients in our series. DI requires a delicate medical intervention to maintain fluid balance particularly for post-operative patients to ensure optimal recovery from surgery. Identification of predicting factors might improve awareness of the surgical team to avoid this complication.

In the initial analysis, transient DI was more commonly observed in patients with visual field disturbance than patients without visual field disturbance (OR=9.72 (1.41-113.1), p=0.0238). Transient DI was also more commonly observed in patients with hormonal disturbance than patients without hormonal disturbance (OR=12.71 (1.59-144.2), p=0.0109).

In our series, the tumor diameters tend to be larger in patient with transient DI (3.41 ± 0.56 cm) than without transient DI (2.21 ± 0.53 cm, p<0.0001). To determine the cut off for the occurrence of post-operative DI, ROC analysis was conducted. As a result, a value of 2.8cm (sensitivity = 92.31%, specificity = 80.00%, Supplementary Figure 1) was chosen as the cut off value. Patients with large tumor diameter (≥ 2.8 cm) had a higher risk of having transient DI (OR=48.00 (8.60-229.30), p<0.0001).



Supplementary Figure 1: The ROC curve of the largest tumor diameter with transient DI occurrence. The ROC curve indicated that tumor diameter is a good diagnostic value because it moved away from the 50% line toward 100%. The AUC (area under the curve) value obtained from the ROC method was 0.9323 (95% CI: 0.8664 – 0.9982, p<0.0001).

Patients that underwent total resection had a higher risk of having transient DI than patients with subtotal removal (OR=19.64 (2.59-218.70), p=0.0008). The summary of analysis was presented as table 3.

Table 3: Comparison of clinical characteristics

Variable	DI Transient		P	OR (95% CI)
	(+)	(-)		
	N=26	N=25		
Age (year)				
≥ 40	14 (53.85%)	14 (56.00%)	0,8772	0.92 (0.29-2.80)
< 40	12 (46.15%)	11 (44.00%)		
Gender				
Male	14 (53.85%)	12 (48.00%)	0.6763	1.26 (0.42-3.93)
Female	12 (46.15%)	13 (52.00%)		
Vision Field Disturbance				
Yes	25 (96.15%)	18 (72.00%)	0.0238*	9.72 (1.41-113.1)
No	1 (3.85%)	7 (28.00%)		
Blurred Vision				
Yes	19 (73.08%)	14 (56.00%)	0.2021	2.13 (0.64-6.86)
No	7 (26.92%)	11 (44.00%)		
Headache				
Yes	16 (61.54%)	13 (52.00%)	0.4917	1.48 (0.48-4.82)
No	10 (38.46%)	12 (48.00%)		
Hormonal Disturbance				
Yes	9 (34.62%)	1(4.00%)	0.0109^	12.71 (1.59-144.2)
No	17 (65.38%)	24 (96.00%)		
Tumor Diameter (cm)				
≥ 2.80	24 (93.64%)	5 (20.00%)	<0.0001^^	48.00 (8.60-229.30)
< 2.80	2 (20.83%)	20 (80.00%)		
Tumor Resection				
Total	25 (96.15%)	14 (56.00%)	0.0008**	19.64 (2.59-218.70)
Subtotal	1 (3.85%)	11 (44.00%)		

*p<0.05, analyzed with Chi-squared test;

**p<0.001, analyzed with Chi-squared test;

^p<0.05, analyzed with Fisher’s exact test;

^^p<0.0001, analyzed with Fisher’s exact test.

To identify the independency of those predicting factors, those candidates (visual field disturbance, hormonal disturbance, tumor diameter and type of tumor resection) were analyzed with multiple logistic regression for multivariate analysis. We found that among pre-operative factors, large tumor diameter (≥ 2.8 cm) was associated with a higher risk of having transient DI post-operatively (OR=31.65 (5.62 -290.20), $p < 0.0001$). Subtotal of resection was also associated with a lower risk of having transient DI post-operatively (OR=0.07 (0.003 - 0.62), $p = 0.0217$). The analysis was presented as Table 4.

Table 4: Multivariate Analysis of Predicting Factors

Variable	OR	95% CI	P
Visual field disturbance	0.65	0.05 - 9.41	0.8788
Hormonal disturbance	0.07	0.00 - 2.09	0.1294
Tumor diameter	31.65	5.62 -290.20	<0.0001**
Tumor resection	0.07	0.003 - 0.62	0.0217*

Analyzed with multiple logistic regression

Discussion

This study included 51 subjects, who were divided into two groups, with transient DI and without transient DI. In both groups, the most common clinical symptoms were visual field disturbance, blurry vision, and headache. This was in line with the literature, where most large adenomas were non-functional adenoma that gave symptoms due to pressure to the surrounding structures, i.e. the optic nerve and the optic chiasm. Meanwhile, the headache was caused by increased intrasellar pressure [20,21]. Upon the analysis, we obtained that visual field disturbance were more commonly observed in patients with transient DI, which in line with subsequent findings that patients with transient DI tend to have larger tumor. This association had been previously that patients with DI tend to have a larger tumor (10.7mL) compared to those without (5.5 ± 6.6mL) [22,23]. Gondim *et al.* also found that the incidence of post-operative DI was correlated with a large tumor size (width > 4cm) which caused the compression of the pituitary stalk and caused hypothalamus injury due to suprasellar dissection [24]. Similar result was published by Nayak *et al.*, which showed that the larger the tumor, the higher the risk of post-operative DI, with a mean tumor size of 28.8mm for patients with DI [25].

Our study confirmed that a larger tumor is a risk for having transient DI post-operatively, with a cut-off size of 2.8cm. Compression of the pituitary stalk was affected by tumor size, extension, and size of sella tursica, which may be different between individuals. Other than tumor size, the size of sella can also be a factor to be considered in predicting the degree of pituitary stalk compression that may occur. A tumor with the same size occurring in a smaller sella will cause more compression to the pituitary stalk. Tumor extension might also contribute to the disturbance to the pituitary stalk, which will cause post-operative transient DI. Previously reported that adenoma with extension to the suprasellar is associated with a higher incidence of post-operative DI [26].

Polyuria is the most obvious symptoms of DI, but can also reflect several physiological adaptive mechanisms in the postoperative phase, particularly due to peri-operative fluid balance [20-27]. Defining and distinguishing

DI from other conditions is necessary to ensure proper treatment for post-operative patients [4,18,23]. Peri-operative fluid overload often difficult to distinguish from DI, additional examinations of serum sodium level or osmolality and urine osmolality are needed.

In a triphasic response, post-operative polyuria occurred because of a failure from the action potential from the hypothalamus to the posterior hypophysis, which resulted in decreased ADH production. The second phase consisted of reduced urine output followed by hyponatremia because the terminal axon in the posterior hypophysis released stored ADH. In this state, if too much fluid was given, then a condition similar to SIADH will occur. During the third phase, ADH was no longer released and produced a classic DI characteristic of polyuria [20-29]. The incidence permanent DI is relatively rare following either microsurgical or endoscopic surgery and it takes > 6 months to consider a patient having a permanent DI [18]. The progression of transient DI to permanent is approximately 25% [4].

In our study, the type of resection was also risk factor for having post-operative DI. Similar results were also stated by Ajlan *et al.*, who found that tumor diameter of more than 1cm (macroadenoma) and total gross resection was correlated to a higher early DI incidence, but not in long-term DI [27]. Theoretically, the effort of total resection from large tumors can cause more manipulation of the hypophysis gland, pituitary stalk, and its vascular supply [6,17]. Variation in anatomical factors may cause disturbance to the hypothalamus - hypophysis axis due to a strain on the pituitary stalk. Along with tumor size and extension, the anatomy and size of the sellar space can vary between individuals. Anatomical factor and operator effort in identifying and preserving the pituitary stalk might contribute to possibility of transient DI occurrence [25-27].

Limitation of the Study

This study has several limitations such as incomplete examination for diagnosis of DI and limited follow-up duration. Further study with measurement of serum ADH level and longer follow-up (> 6 months) might provide more comprehensive insight regarding post-operative DI.

During surgery, the manipulation degree of the pituitary stalk can also be affected by operator maneuvers, thus may be different between one patient with the others [30].

Conclusion

Tumor diameter and type of tumor resection potentially become predicting factors for transient DI occurrence following endoscopic surgery of pituitary tumors. These finding might increase awareness of the potential complication during pre-operative and intra-operative management of patients with pituitary tumors.

Disclosure

Authors declare there is no conflict of interest.

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