

Original Article

Risk Factors and the Incidence of Diabetes Insipidus after Pituitary Surgery

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ABSTRACT

Background: To improve patient care, determining the post-surgery risk factors for diabetes insipidus are extremely significant. We demonstrated the pre-operative factors and postoperative incidence of diabetes insipidus in pituitary surgery.

Materials and Methods: Patients of both genders with ages between 18-65 years having pituitary adenoma amenable to surgery were included. The sample size mainly constitutes macroadenomas and giant adenomas i.e., greater than 1 cm and equal to or greater than 4 cm, respectively. The Hosmer-Lemeshow test was used to measure model fit. The receiver operator characteristic curve was used to evaluate the model and variables such as preoperative serum sodium and urine specific gravity.

Results: Only 210 of 279 patients met the selection criteria. Most of the patients have lesions greater than 1cm, as a result of which a greater number of patients had undergone transcranial approach. Out of these patients, 27% have developed diabetes insipidus. The mean age was 53 years in the non-DI group, whereas, 47 years was the mean age in the patients with DI. 25% of females and 31% of males developed diabetes insipidus. 75% of females and 64% of males did not develop DI. The highest percentage (61%) of patients who developed DI came from giant adenomas. Higher incidence of DI was related to greater surgical intervention (primary resection-35%, total-38% or subtotal resection-19%, and resection of regrowth of pituitary adenoma-20%). Patients who underwent a transcranial approach had large adenomas and a higher likelihood of developing diabetes insipidus, according to the study (61 percent).

Conclusion: Giant adenomas, aggressively primarily treated adenomas, and those lesions that were approached transcranially, showed an increased risk of diabetes insipidus and those who have undergone redo surgery have reduced incidence of diabetes insipidus.

Keywords: Diabetes Insipidus, Pituitary Adenoma, Macroadenoma, Giant Adenoma, Transsphenoidal Approach, Cranial Approach.

Abbreviations: DI: Diabetese Insipidus. USG: Urine Specific Gravity.

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INTRODUCTION

Magnocellular neurons produce a non-peptide antidiuretic hormone (ADH) in the hypothalamic supraoptic and paraventricular nuclei. The hypothalamic-hypophyseal tract transports and matures it before storing it for later release.¹ In patients undergoing sellar/suprasellar surgery, one of the most common postoperative complications is an imbalance in ADH secretion, leading to fluid retention.² If diabetes insipidus (DI) is not treated, there would be excessive loss of water which can lead to increased serum sodium concentration that can also affect mental activity. Postoperative DI symptoms are often transitory and mild after pituitary surgery. A persistent DI may also occur as a result of injury to the hypothalamus or proximal infundibulum.³⁻⁴ From the data, between 1.6 and 31% of individuals suffer postoperative DI (whether temporary or permanent).²⁻⁶

International research has made some progress in identifying risk factors for postoperative DI. Cushing's disease and intraoperative CSF leak, a microadenoma, tumor volume, a shift in preoperative to postoperative serum sodium, tumor location, and functionality all have the potential to alter the surgical results. Varying results have been reported.⁷⁻¹¹ It is vital to have a better knowledge of how postoperative DI develops following sellar lesion surgery to avoid this potentially fatal complication. Physicians can readily identify patients who are at high risk of developing early DI, which will assist them plan treatment options for such patients. It is envisaged that this study will assist physicians in identifying and monitoring patients who have had pituitary surgery at an earlier stage by building a predictive model that will assist them in identifying and monitoring patients who have had pituitary surgery at an earlier stage. Identifying post-surgery risk factors for diabetes insipidus (DI) is critical for improving patient management. The primary goal of this study was to identify preoperative risk factors and postoperative

incidence of diabetes insipidus in connection to pituitary surgery.

MATERIALS AND METHODS

Study Settings

The Ethical Research Committee of the Ayub Medical College, Abbottabad, has approved this retrospective study. This study was conducted at Ayub Teaching Hospital, Abbottabad from September 2016 to January 2021.

Inclusion Criteria

Patients of both genders with ages between 18 – 65 years having pituitary adenoma amenable to surgery were included. The sample size mainly constitutes macroadenomas and giant adenomas i.e., greater than 1 cm and equal to or greater than 4 cm, respectively.

Exclusion Criteria

Urine-specific gravity (USG > 1.005) was used to distinguish DI from other causes of polyuria such as post-surgical, or glycosuria from diabetes mellitus or steroid use in these instances. Patients having preoperative urinary output (UO) > 2.5 mL/kg body weight/hour or at least 4 L/day, urine specific gravity (USG) > 1.005, or urinary osmolality (UA) > 200 mm per kg, with or without hyponatremia and hyperosmolality, were excluded. Those patients who have already diabetes insipidus before surgery were not included in the study. Those who did not have any medical records were also deleted from the database.

Data Collection

Only 210 of 279 patients met the selection criteria. Patients for this study were identified through the use of endocrinology and pathology sections in computerized database records. To obtain the information, standard data gathering

procedures were employed. To protect participants' identities, code numbers were issued to them. This data was compiled by taking into account the tumor's size and kind (macroadenoma vs. microadenoma), as well as histology and function. Serum Na and USG levels were measured before, during, and after the operation. Within six hours of operation, our institution collected the data on serum Na and USG. By subtracting preoperative serum sodium from postoperative serum sodium, the percent change in serum sodium was estimated. Similar methods were used to estimate changes in the USG. In all statistical investigations, the SPSS 26 version was employed.

Sample/Statistical Calculations

Demographic data were presented using descriptive statistics. All variables with P-values less than 0.05 were eliminated from the final predictive model (preoperative serum sodium and preoperative urine specific gravity (USG), type of surgery, and histology). The Hosmer-Lemeshow test was used to measure model fit. The receiver operator characteristic curve was used to evaluate the prediction model and individual variables such as preoperative serum sodium (Na) and urine specific gravity (USG). The statistical values through the Hosmer-Lemeshow test were gathered showing insignificant effect ($p > 0.5$) despite the higher sample size of females with the mean difference of greater than 4. Furthermore, the significance level is 78.45% depicts that there is a higher probability of success rate and minimum error (**Table 1**). T-test for mean values and chi-square as cross-tabulation were used to find significant/insignificant differences from the respective distribution.

RESULTS

Out of 279 patients, about 210 patients were included in the study that fulfilled the inclusion criteria. Most of the patients have lesions greater

than 1 cm, as a result of which a greater number of patients had undergone transcranial approach. Overall, 27% of patients have developed diabetes insipidus.

Table 1: Statistical Values of The Sample Size.

P-value	0.2155
T-score	0.8028
Degrees of Freedom	27.231
Significance Level	78.45%
SEM	5.5533
Sample Male	80
Sample Female	130
Mean Male	6.875
Mean Female	11.333
Difference (B – A)	4.4583

Age Distribution

The overall mean age was 50 years. The mean age was 53 years in the non-DI group, whereas, 47 years was the mean age in the patients with DI (**Table 2**). There existed a significant difference in the mean values between non-DI and DI groups (p-value: 0.0091).

Gender Distribution

There were 130 (62%) females and 80 (38.1%) males. 25% of females and 31% of males developed diabetes insipidus. 74% of females and 70% of males did not develop DI (**Table 2**). There existed an insignificant difference in male/female for non-DI and DI groups (p-value: 0.8523).

Postoperative Diabetes insipidus (DI) Prevalence in Various Situations:

The highest percentage (61%) of patients who developed DI came from giant adenomas. The lowest incidence of DI came from Transsphenoidal surgery. Higher incidence of DI was related to greater surgical intervention (primary resection-35%, total-38% or subtotal resection-19%, and resection of regrowth of pituitary adenoma-20%. According to our data,

Table 2: Clinical Characteristics and Demographic Data of Patients.

Characteristic	Non-DI	DI	Overall	Statistical calculations
Mean Age (years)	53 ± 14.1	47 ± 16.4	50 ± 15.1	P value 0.0091 (Significant result) T test: 2.63 Df: 208
Sex				P value: 0.355 (Insignificant result)
Female	97 (74.61%)	33 (25.38%)	130 (87.03%)	Chi-square: 0.8523
Male	55 (70.12%)	25 (31.25%)	80 (50.68%)	

the incidence of DI is higher in patients who undergo aggressive total resection via transcranial approach, as well as those who were operated on for the first time. 20% of new-onset DI was seen in recurrent cases. Patients who underwent a transcranial approach had large adenomas and a higher likelihood of developing

diabetes insipidus, according to the study (61 percent). Furthermore, DI was more common in patients with non-functional adenomas than in those with functional adenomas. See **Table 3** for more details. Imaging of pituitary adenoma on CT and MRI showing size and location, see **Figures 2-4**.

Table 3: Postoperative incidence of diabetes insipidus (DI) in Different Situations.

Situations	Situations	Classes	Situations
Macroadenomas > 1cm	37%	Giant Adenoma > 4 cm	61%
Transsphenoidal Approach	15%	Cranial Approach	27%
Recurrent Cases	20%	Primarily treatment	35%
Sub-Total Resection	19%	Total Resection	38%
Functional	18%	Non-Functional	29%

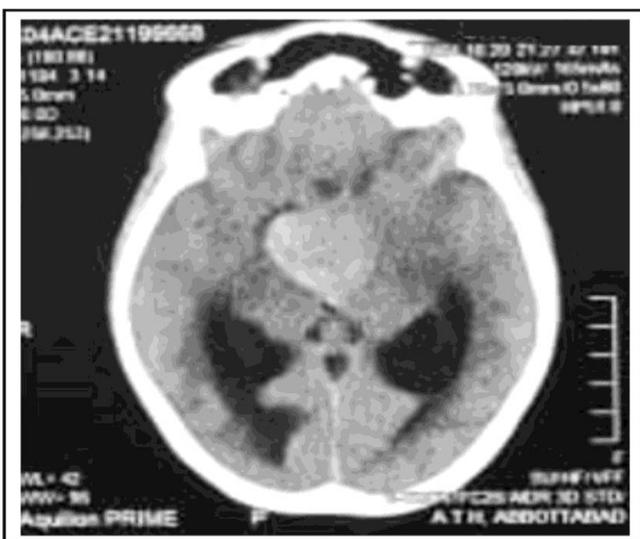


Figure 1: Large pituitary adenoma on CT scan (images used with patient's permission).

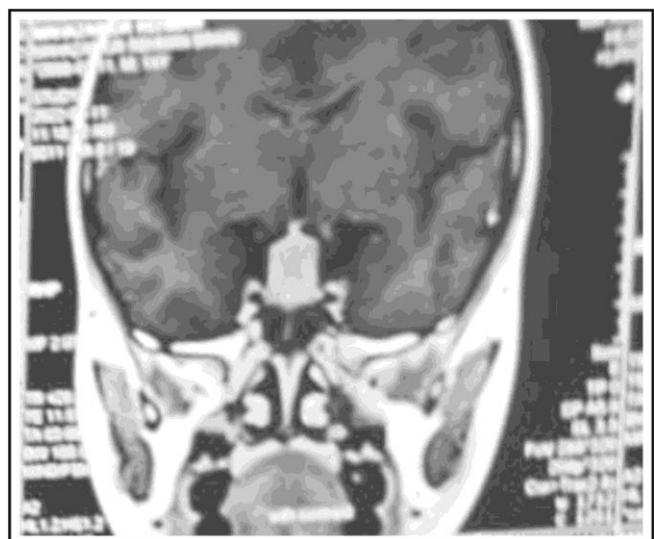


Figure 2: A suprasellar mass on coronal MRI.

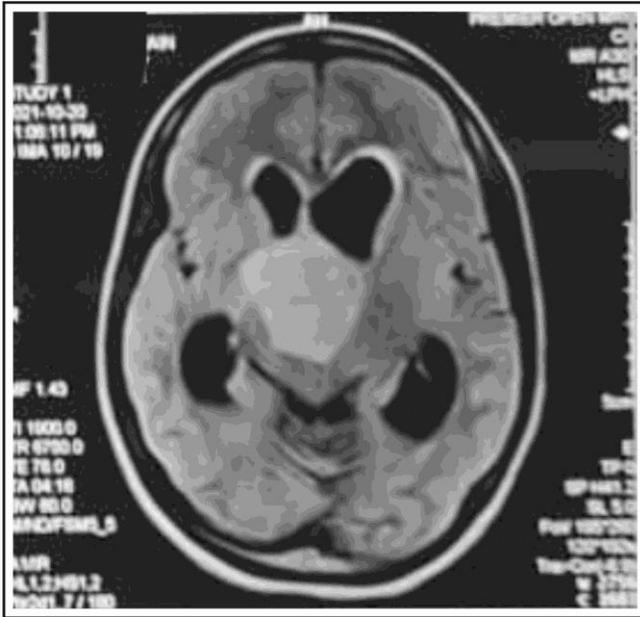


Figure 3: Axial MRI view showing large midline tumor (pituitary adenoma).

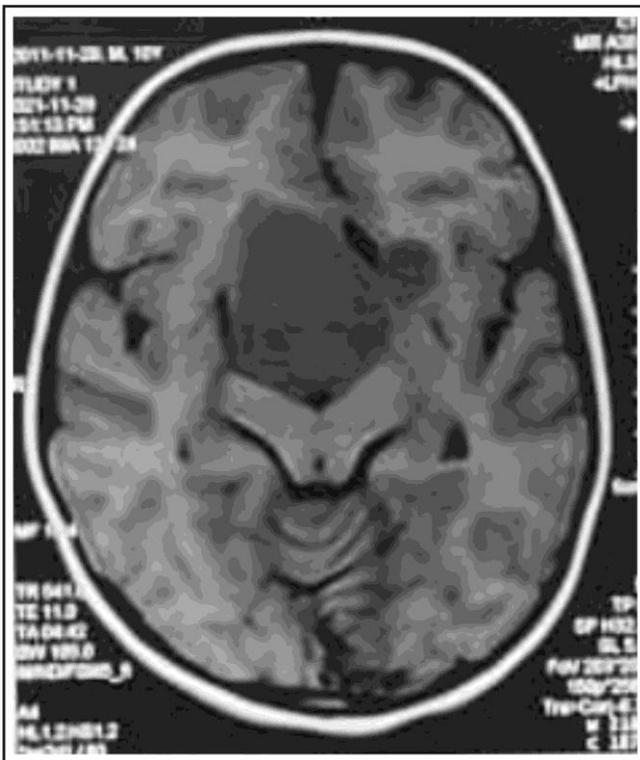


Figure 4: Axial MRI showing a large pituitary adenoma.

DISCUSSION

Diabetes insipidus is still a common consequence of transsphenoidal surgery, but it is usually

temporary. Patients who have an intraoperative CSF leak, a microadenoma, a craniopharyngioma, or an RCC (Rathke cleft cyst) appear to be at a higher risk of transitory DI. An intraoperative CSF leak, a craniopharyngioma, or an RCC are all risk factors for chronic DI.⁸ The present study is the First-of-its-kind research on the incidence of DI following pituitary surgery in Pakistan. We found that giant adenomas, aggressively treated adenomas, and lesions approached transcranially were associated with a greater risk of diabetes insipidus, but individuals who underwent redo surgery had a lower incidence of diabetes insipidus. Overall, 27% of our patients have developed diabetes insipidus. Because the majority of the patients had lesions larger than 1cm in size, a greater percentage of patients underwent a transcranial approach. The majority of individuals who had DI had large adenomas. Transsphenoidal surgery resulted in the lowest incidence of DI. A higher incidence of DI was associated with more surgical intervention (primary resection, total or subtotal resection, and resection of regrowth of pituitary adenoma). According to our statistics, the incidence of DI is greater in patients who have aggressive entire resection through transcranial technique, as well as in those who have had their first operation. According to the study, patients who received a transcranial approach had bigger adenomas and a greater risk of developing diabetes insipidus (61%). DI was also more prevalent in patients with non-functional adenomas than in those with functional adenomas.

Patients receiving minimally invasive pituitary surgery had a low risk of postoperative diabetes insipidus. Rathke's cleft cyst histology, intraoperative cerebrospinal fluid leak, and prior non-endoscopic lesion removal have all been linked to the development of DI after minimally invasive pituitary surgery. Elevated blood sodium within the first 5 days postoperatively had a high sensitivity, specificity, and negative predictive value for the development of persistent

postoperative DI. Using regular monitoring, a higher blood sodium level in the first 5 postoperative days can predict the likelihood of developing persistent DI. Patients with no increased blood sodium readings, defined as > 145 mmol/L, in the first 5 days postoperatively are unlikely to develop persistent DI, justifying short postoperative hospital stays with a low risk of readmission for DI therapy. Those who have a single blood sodium reading of more than 145 mmol/L have a 15% chance of getting persistent DI.⁹

When compared to the standard sublabial transseptal method, Shah et al.¹⁰ identified a lower incidence of acute DI after transnasal endoscopic pituitary surgery. The incidence of long-term DI, on the other hand, did not differ substantially between the two groups. Similar to earlier studies, gender, size of tumor, age, and approach was related to the enhanced incidence of postoperative DI. As compared to earlier reports,^{9,12} our study included more females than males. In this study, the majority of our patients presented for medical attention late from the time of their initial symptom or received symptomatic treatment by themselves or by local clinics, and by the time they receive neurological consultation, the lesion has enlarged and is more likely to be associated with postoperative diabetes insipidus.

Previous studies found inconsistent results in terms of lesion size and postoperative DI. According to certain studies, individuals with macroadenoma were more likely to develop postoperative diabetes insipidus,^{5,13} although other studies found that microadenoma was more associated with Diabetes insipidus.^{6,9} In this study, the size of the tumor is well correlated with the incidence of postoperative DI; the larger the lesion, the more dissection will be required, and the dissection will be more difficult if the surrounding structures are involved, even if the size is smaller, as more traction and extensive dissection will be required during surgery.

Similarly, for these types of injuries, a transcranial approach was used; all of them are unambiguous indicators of an elevated risk of DI. The recurrent cases in our study simply get intrasellar decompression to minimize the bulk effect with minimum traction on the surrounding structures. These recurring lesions are more likely to invade or adhere to the surrounding structures. In keeping with the results of Nemergut et al.,⁹ redotranscranial surgeries, the incidence of postoperative DI was not altered.

Cases undergoing surgery for the first time, on the other hand, had a greater frequency because the lesion was handled more aggressively in an attempt to remove it entirely, which is reliant on the surgeon's expertise and varies per operational finding as suspected on pre-surgical examination. Finally, patients with nonfunctioning adenomas had larger lesions, delayed consultation due to extended mild symptoms or asymptomatic period, and the majority of them underwent transcranial approach, all of which demonstrated a collective rise in the incidence of DI in our study. Preoperative magnetic resonance imaging may assist predict postoperative DI by assessing the degree of distortion of the third ventricle and hypothalamus. Postoperative bleeding may increase the likelihood of postoperative DI, whether it is immediate or long-term.¹³

Pituitary adenoma (PA), is one of the most frequent sellar diseases, accounting for 10% of primary intracranial tumors. The reported prevalence of postoperative diabetic insipidus (DI) varies greatly. Previous research comprised 178 individuals who had PAs endoscopically resected. The term "early DI" refers to DI that occurs within the first postoperative week. In research by Ajlan et al., the average duration of follow-up was 36 months. Long-term DI was defined as DI visible at the most recent follow-up visit. The tumors in 77 percent of the 178 participants in the research were macroadenomas. Early DI occurred in 47 individuals (26 percent). Long-term DI was found

in 18 (10.1%) of the whole cohort. A greater incidence of long-term DI was shown to be substantially linked with age less than 50 years. Macroadenoma and extensive complete resection were shown to be strongly related to an increased risk of DI in the early stages. The average length of stay for patients with early postoperative DI was 4 days, compared to 3 days for those who did not have it.¹⁴

Macroadenoma and extensive complete resection were shown to be strongly related to an increased risk of DI in the early stages. The average LOS for patients with early postoperative DI was 4 days, compared to 3 days for those who did not have it. The reported incidence of postoperative DI varies greatly. We discovered that being younger than 50 years old is a risk factor for having long-term postoperative DI. The development of early DI was linked to gross total surgical resection and tumor size (> 1 cm).¹⁴

CONCLUSION AND RECOMMENDATION

With a prediction model based on our work, we can create a scoring system that will assist clinicians in assessing point-of-care risk for postoperative Diabetes insipidus, thus improving postoperative therapy and surveillance. Our study discovered that patients with Giant Adenomas who are approached transcranially are more prone to DI post-surgery. Patients with functioning adenomas and those who have total resection are also more likely to develop DI. While recurring cases who had previously been operated on acquired DI, the effects were insignificant. Monitoring fluid balance and repeating USG every 3 to 6 hours, helps in managing DI in the perioperative period. The therapeutic dosage of Desmopressin is the mainstay of surgical DI.

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Additional Information

Disclosures: Authors report no conflict of interest.

Ethical Review Board Approval: The study was conformed to the ethical review board requirements.

Human Subjects: Consent was obtained by the patient in this study.

Conflicts of Interest:

In compliance with the ICMJE uniform disclosure form, all authors declare the following:

Financial Relationships: All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work.

Other Relationships: All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

AUTHORS CONTRIBUTIONS

Sr.#	Author's Full Name	Intellectual Contribution to Paper in Terms of:
1.	Abdul Aziz Khan	1. Study design and methodology.
2.	Ehtisham Ahmed Khan Afridi	2. Paper writing and data calculations.
3.	Sohail Ahmad, Rafia Khurshid	3. Data collection and calculations.
4.	Idrees Ahmed	4. Analysis of data and interpretation of results etc.
5.	Muhammad Wasim	5. Literature review and referencing.
6.	Meena Hayat	6. Analysis of data and quality insurer.