Diabetes insipidus following neurosurgery at a university hospital in Western Saudi Arabia

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ABSTRACT

الأهداف: هي دراسة بأثر رجعي لمعرفة نسبة حدوث مرض السكري الكاذب بعد جراحة المخ والأعصاب للغدة النخامية، وكذلك المظاهر السريرية، والعوامل المؤدية للإصابة بالمرض.

الطريقة: تم استعراض الملفات بأثر رجعي ل 24 مريضاً خضعوا لجراحة المخ والأعصاب للآفات سرجي أو ورم قرب الغدة تحت المهاد أو الغدة النخامية، في قسم جراحة المخ والأعصاب من مستشفى الملك عبدالعزيز الجامعي بجدة، المملكة العربية السعودية. وتضمنت البيانات المدخلة وسائل الرسم البياني الإخراج، الشوارد المصل والبلازما والبول الأسمولية، فضلاً عن التقييم الإشعاعي والهرموني للغدة النخامية (الكورتيزول، FT3، FT4، البرولاكتين، LH، FSH) قبل وبعد جراحة المخ والأعصاب من الغدة النخامية.

النتائج: عانى 13 (54.2%) من أصل 24 مريضاً من مرض السكري الكاذب بعد جراحة المخ والأعصاب، التي كانت عابرة في 5 (38.8%) ودائمة في 8 (61.2%). وتضمنت المجموعة الفرعية المصابه ب DI ارتفاع معدل انتشار برولاكتيني، ورم قحفي بلعومي، قصور نخامي شامل قبل الجراحة، كذلك macroadenoma في التصوير بالرنين المغناطيسي وجراحة transphenoidal. سجلت الأسمولية البولية أقل بكثير من المجموعة الغير مصابة ب DI بعد الجراحة مع قيمة إحصائية كبيرة p=0.023. في مجموعة دراستنا كان من المسلم به أن DI دائم بمعنى أن مرضانا بحاجة desmopressin لأكثر من 3 أشهر. التي وثقت عدداً أكثر أهمية من دراسات أخرى.

الخاتمة: في هذه الدراسة كان مرض السكري الكاذب عند المرضى الذين أجريت لهم عمليات في المخ وإحتياجهم لهرمون desmopressin مدة 3 أشهر أكثر مما سجل في الدراسات الأخرى.

Objectives: To review the incidence, spectrum of clinical manifestation, course, risk factors, as well as treatment of diabetes insipidus (DI) following neurosurgery of the pituitary gland.

Methods: The files of 24 patients that underwent neurosurgery for sellar lesions, or tumor near the hypothalamus or pituitary gland at the Department of Neurosurgery, King Abdulaziz University Hospital, Jeddah, Kingdom of Saudi Arabia were retrospectively reviewed between January 2011 to December 2014. A total of 24 patients were studied, and were divided into 2 groups namely; DI and non-DI. Patient characteristics were studied using descriptive statistics. The differences in proportion between the 2 groups were found out using Z-test for proportion in 2 populations. The mean differences in the hormonal abnormalities for the 2 groups were assessed using independent t-test. All statistics are considered statistically significant when p<0.05.

Results: During hospitalization, 13 (54.2%) out of 24 patient that underwent neurosurgery had manifestations of DI, which was transient in 5 (38.8%) and permanent in 8 (61.2%). The DI subgroup contained higher prevalence of prolactinoma, craniopharyngioma, pre-operative panhypopituitarism, and macroadenoma in MRI imaging and transphenoidal surgery. Furthermore, urine osmolality was significantly lower in the DI group post-operatively with a significant p=0.023. It was recognized that the permanent DI documented more significant numbers than other studies.

Conclusion: In our study group, it was recognized that permanent DI meant that our patients needed desmopressin for more than 3 months, which documented a more significant number than other studies.

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Surgery in the sellar region is often associated by disturbances of water/electrolyte metabolism and osmoregulation, probably due to manipulation and/or vascular alterations of the neurohypophysis,[1] therefore, diabetes insipidus (DI) is the result of a lack of antidiuretic hormone (ADH) arginine vasopressin (AVP).[2] Furthermore, it is a common complication following pituitary surgery, and could be either transient or permanent.[3] Central DI is observed in 16-34% of patients recovering from sellar region operations and is generally transient; however, this condition may increase the length of hospitalization, as well as cause morbidity after pituitary surgery. In addition, DI can lead to severe hypernatremia if the fluid is not instantly replenished. Hence, monitoring for DI is essential during the first post-operative days; correspondingly, accurate diagnosis followed by correct treatment is crucial.[4,5] Diabetes insipidus could be identified in several ways, the most important being fluid balance determination. It could also be identified by the measurement of the plasma and urine sodium concentration, as well as osmolality.[5] Risk factors for developing DI include: Rathke's cleft cyst, craniopharyngioma, or extensive intra-operative pituitary gland handling.[6,7] The objective of this retrospective study was to review the incidence, spectrum of clinical manifestation, course, risk factors, as well as treatment of DI following neurosurgery of the pituitary gland.

Methods. The data including age, gender, hormone assay data, neuro-imaging, histopathological confirmation of a pituitary adenoma, and complications surgery were collected from patients that underwent neurosurgery for sellar lesions or tumor near the hypothalamus, or the pituitary gland at the Department of Neurosurgery at King Abdulaziz University Hospital in Jeddah, Kingdom of Saudi Arabia between January 2011 to December 2014. The surgical procedures were performed by experienced neurosurgeons from the department using a model microsurgical technique. The study included all patients who underwent neurosurgery for sellar lesions or tumor near the hypothalamus of pituitary gland.

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Pre-operative data. Initially, secondary hypothyroidism was diagnosed by the presence of low free thyroxine with normal thyroid stimulating hormones (TSH) levels. Moreover, secondary adrenal insufficiency was diagnosed in patients with morning cortisol levels between 50 and 130 ng/ml. In addition, hypogonadotropic hypogonadism was diagnosed in premenopausal, and in adult males and females with high follicle stimulating hormones (FSH) and luteinizing hormone (LH) levels. The hyperprolactinemia was diagnosed by prolactin (PRL) levels 170-300 mIU/L in the absence of dopaminergic therapy. Tumors were classified by MRI into 4 categories ranging from normal to microadenoma, macroadenoma, and craniopharyngioma.

Post-operative evaluation data. After the tumor was resected either by a transsphenoidal or craniotomy approach, unrestricted intravenous (IV) fluids were given as indicated during surgery and post-operatively. Most patients received stress doses of glucocorticoids pre-operatively to avoid a secondary adrenal insufficiency.

Diagnosis and treatment of DI. Patients were monitored daily for their vital signs, polyuria, polydipsia, in addition to their fluid balance. However pre-operatively, serum sodium and serum/urine osmolality were determined, and if the following conditions were fulfilled - polyuria DI of >2.5 L a day with concomitant polydipsia, serum Na >140 mmol/L, serum osmolality 295 mmol/kg H_20, and urine osmolality 200 mmol/L; the patient would be diagnosed by DI. To begin with, the DI was treated with oral or IV fluids and desmopressin 0.1 or 0.2 mg orally or one g IV, or 10 g/puff via nasal inhalation, once or more than once a day. After a period of 3 months, patients would be reassessed in order to determine if the DI was transient or permanent, therefore, deciding whether the patient should continue the treatment of desmopressin.[8]

Statistical analysis. A total of 24 patients were studied and divided into 2 groups namely; DI and non-DI. The patient characteristics were studied using descriptive statistics. Mean and standard deviation were calculated for continuous variables, such as age. Frequency and percentage were calculated for categorical variable. The differences in proportion between the 2 groups were found out using Z-test for proportion in 2 populations. The mean differences in the hormonal abnormalities for the 2 groups were assessed using independent t-test. All statistics are considered to be statistically significant when $p<0.05$. A bar graph was used to represent the pattern of desmopressin in DI patients. All statistical analysis was performed using Statistical Package for

Social Sciences version 20 (IBM Corp., Chicago, IL, USA). Graphs were drawn using Microsoft Excel.

Results. *Incidence of post-operative DI.* During hospitalization, 13 out of 24 (54.2%) patients that underwent neurosurgery of the pituitary gland had DI, 5 (38.8%) were transient, and 8 (61.2%) were permanent.

Characteristics of DI versus non-DI. **Table 1** shows the main characteristics of the DI group, where most of the 13 patients were female (n=8 [61.5%]), and the median age of the 13 patients was 34 years. Compared with its counterpart, the DI subgroup contained a higher prevalence of prolactinoma, as well as craniopharyngioma. However, the non-DI group consisted mainly of hormone-producing adenomas (acromegaly) in 18.2% and Cushing's disease in 18.2%. The incidence of clinically hormone-inactive adenomas (incidentaloma) was similar between the DI and the non-DI group patients, since it was found to be 7.7% in the DI group, and 9.1% in the non-DI group. Furthermore, the DI subgroup contained a higher prevalence of prolactinoma, craniopharyngioma, pre-operative panhypopituitarism, and macroadenoma in MRI imaging and transphenoidal surgery.

Hormonal abnormalities before and after surgery in DI versus non-DI. The DI subgroup contained a significantly higher prevalence of pre-operative and post-operative panhypopituitarism. Urine osmolality was significantly lower in the DI group post-operatively with a significant $p<0.001$ (**Table 2**).

Hormonal abnormalities before and after surgery in DI and non-DI group. The DI subgroup showed a significantly lower prolactin level post-operatively with a $p=0.037$. In addition, urine osmolality was considerably lower in the DI group post-operatively with a significant $p=0.023$. However, non-DI group exhibited no significant changes in urine osmolality post-operatively since $p=0.412$ (**Table 3**).

Table 1 - Characteristtics of diabetes insipidus (DI) versus non-DI.

Variables	DI group N=13	Non-DI group N=11	*P*-value
Characteristics			
Age (years), median (IQR)	34 (12)	34 (9)	
Female	8 (61.5)	8 (72.7)	0.56
Saudi	3 (23.1)	4 (36.4)	0.47
Clinical presentation			
Prolactinoma	5 (38.5)	2 (18.2)	0.28
Cushing	--	2 (18.2)	
Acromegaly	--	2 (18.2)	
Craniopharingioma	2 (15.4)	4 (36.4)	0.23
Iincidental finding	1 (7.7)	1 (9.1)	0.90
Partial pituitary dysfunction	4 (30.8)	7 (63.6)	0.11
Panhypopituitarism	9 (69.2)	4 (36.4)	0.11
Tumor characteristics in MRI			
macroadenoma	12 (92.3)	7 (63.6)	0.085
microadenoma	--	1 (9.1)	
Craniopharingioma	1 (7.7)	--	
Not performed	--	3 (27.3)	
Type of surgery			
Transphenoidal surgery	7 (53.8)	3 (27.3)	0.18
Transcranial surgery	3 (23.1)	1 (9.1)	0.36
Not performed	3 (23.1)	7 (63.6)	0.04*

* Significant $p<0.05$, IQR - interquartile range, MRI - magnetic resonance imaging

Table 2 - Hormonal abnormalities before surgery diabetes insipidus (DI) versus non-DI.

Hormonal abnormalities	DI	Non-DI	*P*-value
Prolactin	2373.52 (3248.92)	780.99 (1413.85)	0.15
FT4	10.93 (2.82)	12.68 (8.34)	0.48
FT3	3.61 (1.56)	3.38 (3.23)	0.82
TSH	1.87 (1.42)	0.92 (1.47)	0.12
Cortisol	261.95 (182.55)	349.06 (284.01)	0.37
FSH	17.33 (54.94)	9.09 (14.33)	0.63
LH	2.53 (4.44)	4.72 (3.27)	0.19
Urine osmolality	661.25 (90.55)	470.50 (44.54)	<0.001*

* Highly significant $p<0.05$, FT4 - free thyroxine, FT3 - free triiodothyronine, TSH - thyroid stimulating hormones, FSH - follicle stimulating hormones, LH - luteinizing hormones

Table 3 - Hormonal abnormalities before and post surgery in DI group.

Hormonal abnormalities	DI (before)	DI (after)	*P*-value
Prolactin (ng/mL)	2373.52 (3248.92)	431.15 (538.64)	0.037*
FT4 (ng/dl)	10.93 (2.82)	11.54 (3.61)	0.65
FT3 (Pq/ml)	3.61 (1.56)		
TSH (IU/ml)	1.87 (1.42)	0.73 (0.99)	0.007*
Cortisol (ug/dl)	261.95 (182.55)	230.01 (176.71)	0.913
FSH (mIU/mL)	17.33 (54.94)	2.34 (2.02)	0.248
LH (IU/L)	2.53 (4.44)	1.05 (0.88)	0.661
Urine osmolality (mOsm/kg)	661.25 (90.55)	217.07 (117.98)	0.023*

* Mean values are significantly different with $p<0.05$, DI - diabetes insipidus, FT4 - free thyroxine, FT3 - free triiodothyronine, TSH - thyroid stimulating hormones, FSH - follicle stimulating hormones, LH - luteinizing hormones

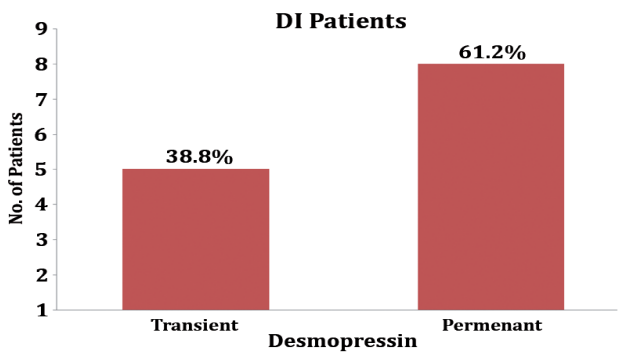

Figure 1 - Desmopressin treatment for diabetes insipidus patients.

Of the 13 patients, 8 (61.2%) suffered from permanent diabetes insipidus meaning that the patients required desmopressin for more than 3 months (**Figure 1**).

Discussion. Our data shows that DI was more common in patients with known clinical risk factors, such as craniopharyngioma, or extensive intra operative pituitary gland handling; this corresponds to reports in other studies.[2,6] Therefore, it is important to keep it as a clinical predisposing factor to allow early identification of DI in affected patients.

It has been found that the percentage of DI in our patients post neurosurgery of the pituitary gland was greater than the one published in the other study[9] with 16-34% range. Diabetes insipidus occur in most patients following neurosurgery of the pituitary gland, especially with the transsphenoidal approach, due to our patients previously having macroadenoma and panhypopitutrism before neurosurgery according to the neurosurgeon's opinion.[10] In most cases, DI was transient and limited, therefore, they did not require treatment and recovered within the first 2 post-operative weeks. The treatment required ADH analogs (desmopressin), and was handled restrictively during the first 2 post-operative weeks, in addition, the patients were provided with free access to fluids.

In our study group, it was found that the permanent DI meant that our patients needed desmopressin for more than 3 months that documented a more significant number than other studies;[10,11] which could be due to our patients having panhypopiturism before surgery, or that during the surgical procedure, there was an increase in manipulation. However, post-operative hyponatremia was due to syndrome of inappropriate antidiuretic hormone secretion, which is usually reversible and minimal in most patients, requiring no treatment. If the hyponatremia is <130 mmol/L, it could be treated by fluid intake restriction.[12] One of the patients included in this study, developed severe hypernatremia due to the administration of hypertonic saline for the correction of hyponatremia, since it was suspected that the patient had a mixed syndrome. The coexistence of DI and cerebral salt-wasting syndrome - the mixed syndrome - resulted in the patient developing severe natriuresis and hyponatremia. Consequently, the rapid correction of hyponitremia resulted in the patient developing central pontinemylenosis, and dying after 2 weeks. Therefore, a close monitor of severe hyponatremia is crucial in patients suffering from DI to avoid severe complications and death.[13] Furthermore, it is a necessity to carefully monitor the DI in patients, who manipulation of neurohypophysis, hormone-producing adenomas, and young age.

The monitoring period for post-operative DI should last up to the tenth day. However, the period of closely monitoring the DI can be extended beyond 10 days in a proficient center. Yet, if patients are cooperative, we would be able to monitor them safely as an outpatient.[14] It is important to decide whether the treatment for DI is necessary and to identify treatment failures, as well as complications. We faced several limitations in our study; one is that it was a retrospective study, and second, is that we had a small number of patients.

In conclusion, it was found that following the neurosurgery of the pituitary gland patients developed DI; which was caused by the macro adenoma, as well as the surgical manipulation of the neurohypophysis. Furthermore, it was recognised in our study group that the higher prevalence of permanent DI meant that our patients needed desmopressin for a minimum of 3 months.

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