Delayed Occurrence of Diabetes Insipidus After Transsphenoidal Surgery with Radiologic Evaluation of the Pituitary Stalk on Magnetic Resonance Imaging

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Original article

**Delayed occurrence of diabetes insipidus following transsphenoidal surgery with
radiological evaluation of the pituitary stalk on magnetic resonance imaging**

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Abstract

Introduction Diabetes insipidus (DI) is a major complication of transsphenoidal surgery (TSS). DI usually occurs within a couple of days after TSS. Delayed occurrence of postoperative DI is rarely observed and its developing mechanisms remain unknown.

Methods Six patients were identified as having postoperative delayed DI, which was defined as DI that first occurred two or more weeks after TSS. They consisted of one male and five females, and their mean age was 38.3 (range: 10-76) years. Five patients were histologically diagnosed with Rathke cleft cyst (RCC), while one was RCC co-existed with prolactin-secreting adenoma. Sequential T1-weighted magnetic resonance imaging (MRI) was evaluated for hyperintensity (HI) in the pituitary stalk and the posterior lobe, indicating the location of antidiuretic hormone (ADH).

Results No patients had any DI before TSS. Delayed DI occurred two weeks to three months after TSS and persisted for two weeks to five months. T1-weighted MRI revealed that the HI in the posterior lobe became faint, but did not disappear after DI occurrence, and their intensities increased with recovery from DI. In contrast, the HI in the pituitary stalk was found faintly preoperatively and turned clear postoperatively, and

decreased with recovery from DI. Their morphological patterns were dependent on DI duration.

Conclusion In the delayed occurrence of DI, it was suggested that preoperative ADH transport was mildly congested, yet not completely blocked when DI manifested postoperatively. Gradual spreading of inflammation to the infundibulum after RCC removal was considered as one possible mechanism of this delayed DI development.

Introduction

Transsphenoidal surgery (TSS) has become the main surgical procedure for sellar and parasellar lesions. Despite remarkable advances in operative techniques and instruments, including endoscope, central-type diabetes insipidus (DI) remains a major complication of TSS. Because superconductive magnetic resonance imaging (MRI) has recently made it possible to visualize normal and pathological anatomy, the pathophysiology of the infundibuloneurohypophyseal (INH) system and the mechanism underlying DI development have been gradually elucidated [1-3]. Generally, postoperative DI occurs immediately after TSS [4-6], however, rarely has it been observed occurring postoperatively after some extent of time.

The complex of antidiuretic hormone (ADH) and neurophysin (carrier protein) is packed within a phospholipid membrane and the existence of these neurosecretory granules is depicted as hyperintensity (HI) in the posterior lobe of the pituitary gland on T1-weighted MRI [7-9]. In order to preserve the function of the INH system normally, the transportation of the granules is maintained along the axon in the pituitary stalk to its terminal in the posterior lobe [7,9,10]. The disappearance of the HI in the posterior lobe

suggests the development of central-type DI [10-13]. In addition, the HI in the pituitary stalk indicates the ADH transport is disturbed from the hypothalamus to the posterior lobe. At the proximal site of obstruction, ADH is congested in the pituitary stalk, leading to a lack of ADH in the posterior lobe [1,14,15,16]. Therefore, MRI can evaluate the function of the INH system, as well as a morphological diagnosis [3,7,9,17].

Most cases of postoperative DI arise within a couple of days after TSS and are transient because the transport of ADH recovers after some period [4-6]. However, few cases manifest permanent DI, requiring ADH replacement. In the current study, six cases of delayed occurrence of postoperative DI were analyzed from clinical and radiological aspects. Assessment of the changes in HI, on T1-weighted images (WIs) in both the pituitary stalk and the posterior lobe, were useful to elucidate both the clinical pictures and the developing mechanisms of this unusual type of DI after TSS, which suggests important clues for proper management.

Methods

Patient characteristics

This study was approved by the Kanazawa University Institutional Review Board. In this retrospective clinical study, 310 patients, who underwent TSS for sellar and parasellar tumors between 2006 and 2016 at Kanazawa University Hospital, were reviewed.

Delayed occurrence of postoperative DI was defined as DI that first manifested more than two weeks after TSS. In our clinical database, we found six suitable patients (1.9%) who suffered from the delayed occurrence of postoperative DI. Pituitary tumors had been detected and diagnosed preoperatively in the patients by 3-tesla MRI. We compiled the following items from their clinical charts: sex, age, tumor histology, initial symptoms, duration from TSS to DI onset, and disease duration of DI. Informed consent for review of their clinical data was obtained from all the patients included in this study.

Diagnosis of Diabetes Insipidus

In this study, if patients' complaints of polydipsia and polyuria were confirmed and the following two conditions were met, central-type DI was diagnosed: total urine volume per day > 2500 mL and a urine specific gravity of < 1.005 [4]. In the determining of a final diagnosis of DI, endocrinologists confirmed low levels of urine osmolality that did

not increase with hypersaline loading. Desmopressin, synthetic forms of ADH, was used for the control of DI in the hospital and after discharge. At the subsequent outpatient interview, the patients gave us their own information about DI. We considered that DI was cured in patients with no complaints of polydipsia and polyuria, and no requirement for DDAVP.

Neuroradiological evaluation

MR images were obtained using a Signa HDx 3 T (GE Medical Systems, Milwaukee, WI). MRI was performed with spin echo T1-weighted sequences and detailed conditions of the sequences were described previously [12]. Pre- and postoperative T1-WIs were used to obtain the radiological features, including their shape, signal intensity, and location in the pituitary stalk and the posterior lobe of the pituitary gland. On both coronal and sagittal sections of T1-WIs, HI in the pituitary stalk and the posterior lobe were evaluated before contrast enhancement. Because both structures revealed remarkable enhancement, the anatomical relationships of the HIs between before and after enhancement were confirmed after contrast enhancement.

Subsequently, the morphological features of HI on the coronal and sagittal sections

of T1-WIs, before contrast enhancement, were assessed on the basis of results from our previous studies [12]. These are described as follows: pattern A, ovoid in the distal end of the pituitary stalk; pattern B, linear in the distal part of the pituitary stalk; and pattern C, linear in the whole pituitary stalk. The grade of intensity was assessed as follows: ++; hyperintensity was strongly detected; +, hyperintensity was clearly detected; ±, hyperintensity was faintly detected; and -, hyperintensity was not detected. The HIs on the MR images were evaluated by at least two neurosurgeons and a neuroradiologist, and the final decision was made by consensus.

In the six patients included in this study, MR imaging was performed before, and 1 week after TSS, immediately after the occurrence of postoperative DI, and a couple of months after recovery from DI. The absence of HI in the posterior lobe, the presence of HI in the pituitary stalk, the appearance of DI, the duration of DI persistence, and the duration until recovery of HI in the posterior lobe were noted in this study.

Surgical procedures

Our surgical strategy for RCC was to evacuate the cyst content completely with endoscope and to remove the cyst wall partially. The thinnest part of the inferior aspect

of the RCCs at the sellar floor was confirmed with the sagittal section of T1WI with contrast enhancement. The minimal and accurate dural incision was put on the inferior thinnest wall described above. After the opening of the cyst wall, the cyst content was aspirated out completely with angled endoscope and the part of the cyst wall was resected for pathological diagnosis. The procedure of peeling off the cyst wall from the normal gland was not performed. Sellar floor was not reconstructed unless the leakage of cerebrospinal fluid occurred. [18]

Results

Patient characteristics

The patients consisted of one male and five females, with a mean age of 38.3 (range: 10-76) years old. Their histological diagnoses were Rathke cleft cyst (RCC) in five, and RCC co-existed with prolactin-secreting adenoma in one. Their symptoms were headache in four patients, visual function disturbance in two, and amenorrhea caused by prolactin-secreting adenoma in one. No patients encountered any intra- or postoperative complications (Table 1).

Radiographic features of the patients in this study are described as follows: the maximum tumor diameter was 20.5 (range; 12-32) mm on average; the RCCs were isointense in four and hyperintense in two on T1-WI, and HI in two and hypointensity in four on T2-WI; and the prolactinoma was isointense on T1-WI and HI on T2-WI (Table 2).

Diabetes insipidus characteristics

The mean period from TSS to onset of DI was 1.3 (range: 0.5-3) months. No patients suffered from DI during the two weeks immediately after TSS, and urine-osmolarity of

these patients was within normal range at that time. Three patients with a longer duration (4-6 months) of DI persistence (patients 1, 2, and 4) used DDAVP for the control of urine volume and relief for their symptoms, meanwhile, only one of the other three patients, who suffered from shorter duration (0.5-2 months) of DI persistence (patients 3,5,6), used DDAVP. The urine-osmolarity decreased significantly after the occurrence of delayed DI (82-177 mEq/L), and did not elevate after hypersaline loading. However, the urine-osmolarity increased after recovery of DI (241-787). No patients encountered recurrence of DI after recovering from the first experience of delayed DI (Table 1).

Neuroradiological findings of hyperintensity in the posterior lobe and the pituitary stalk

1. Preoperative period: All the patients in this study presented with clear HI in the posterior lobe of the pituitary gland and faint HI in the pituitary stalk.
2. Postoperative period one week after TSS: In the posterior lobe, patients with longer DI duration (patients 1, 2, and 4) showed fainter HI, but patients with shorter DI duration (patients 3, 5, and 6) revealed clearer HI than at preoperative. In contrast, the HI in the pituitary stalk became more obvious than at preoperative in all the patients.

3. Delayed DI period: In the posterior lobe, patients with shorter DI duration still revealed faint HI and patients with longer DI duration showed much fainter HI, though still detectable, than what was seen one week after TSS. The HI in the pituitary stalk was stronger than what was seen one week after TSS. The morphological patterns were also different among these patients according to the duration of DI persistence. Patients with shorter DI duration showed HI as linear in the distal part of the pituitary stalk, which corresponded to pattern B. In contrast, patients with longer DI duration revealed HI in the whole pituitary stalk, which corresponded to pattern C.

4. Recovery after delayed DI period: All patients showed faint HI in the posterior lobe which was clearer than in the occurrence of delayed DI. In contrast, the HI in the pituitary stalk still persisted after recovery from DI. However, the patients with longer DI duration revealed clear HI in the whole pituitary stalk, and the patients with shorter DI duration showed faint HI linearly in the distal part of the pituitary stalk.

It is really important to recognize the specificity of this MR findings described above, the hyperintensity of both the posterior lobe and the pituitary stalk in the preoperative and postoperative periods, in the total 310 patients performed TSS. Five patients were

found to have the same MR findings of the patients with delayed DI. The pathologies of these patients were pituitary adenoma in 4 (non-functioning in 3 and prolactin-secreting in one) and Rathke cleft cyst in one. Among the 5 patients, two suffered from DI which was persistent only a couple of days after TSS and the rest of three did not experience DI. Therefore, the strength of the hyperintensity both in the posterior lobe and the pituitary stalk was observed to be faint and has not changed as what was found in the patients with delayed DI.

Representative series of MRIs are shown in Figure 1 (case 3) and Figure 2 (case 4).

Discussion

Postoperative transient DI has been reported in 10-60% of patients who have undergone TSS¹⁷. In most cases, DI occurs immediately after TSS but infrequently can remain permanent [4-6,19]. As the delayed occurrence of postoperative DI is rarely observed, the clinical features and developing mechanisms have not been examined in detail. In the present study, six cases of delayed occurrence of postoperative DI were diagnosed and all of them were transient to recover completely.

First of all, one of the notable points in this study is tumor histology specifically RCC in all of the cases. Therefore, it was suspected that the spreading of chemicals from cyst contents inducing inflammation to the adjacent neurohypophysis, is the most possible development mechanism of this delayed DI occurrence [20-22]. Preoperative hypopituitarism caused by the spread of inflammatory cyst contents to the hypophysis can lead to irreversible changes, due to the long duration of continuous inflammatory spreading [23,24]. In most cases, postoperative DI occurs immediately after the operation, and is rapidly cured due to transient inflammatory spreading. Although the detailed pathogenesis of this delayed occurrence of postoperative DI remains unclear in

this study, the ADH transport in this pathological state was analyzed from the radiological perspective.

Accordingly, the whole process in the delayed occurrence of postoperative DI was divided into four phases described in the sections of Methods and Results, and the HIs in the posterior lobe and the pituitary stalk on T1-WI of MRI were investigated. In the preoperative period, the HIs in the posterior lobe were clearly observed, however, only faint HIs in the pituitary stalk could be seen in all six cases. This result may mean a disturbance in the transport process along axons, resulting in stagnation of ADH in the pituitary stalk proximal to the site of obstruction. However, this disturbance was incomplete and DI did not manifest because ADH was transported to the posterior lobe sufficiently. The etiology of this mild disturbance of ADH transport remains unknown, but the preoperative spreading of inflammation due to RCC was speculated more than mass effect, because the histology of the surgical specimen in all patients of this study demonstrated inflammation evident in the cyst wall of RCC.

In the postoperative period, the HIs in the posterior lobe could be found, but became faint in the patients with longer DI duration, meanwhile, the HIs in the pituitary stalk

became clearer in all cases. This result suggests that despite the incomplete disturbance of ADH transport to the posterior lobe due to mild inflammation spreading from RCCs, DI did not appear because ADH was transported to the posterior lobe sufficiently to control urine volume normally.

In the period of occurrence of delayed DI, the HIs in the posterior lobe could be still detected yet became fainter in all patients in this study, but the grade was more severe in the patients with longer DI duration than in the patients with shorter DI duration. The HIs in the pituitary stalk were stronger than what was seen in previous periods in all cases. This result may indicate that ADH transport was much more disturbed when DI manifested, though still incomplete, and ADH was yet to be transported to the posterior lobe. In addition, the morphological patterns of HIs were linear in the whole pituitary stalk in patients with longer DI duration (pattern C), as well as in the distal part of the pituitary stalk in patients with shorter DI duration (pattern B). The results concerning DI duration shown in our previous study [12] were as follows; the duration of DI in each pattern, with or without HI in the posterior lobe, respectively: pattern A, 1.5 and 5.9 days; pattern B, 10.8 and 62.2 days; pattern C, 12.0 and 11.0 months. Therefore,

because the HI remained in the posterior lobe in all of the patients in the present study, the results of the patients with longer DI duration (4-6 months) applied to pattern C, whose HI morphology was linear in the whole pituitary stalk, and those of patients with shorter DI duration (0.5-2 months) were applied to pattern B, whose HI morphology was linear in the distal part of the pituitary stalk. These results indicate that DI duration can be predicted with the morphological pattern of the HIs in the pituitary stalk with the grades of HIs in the posterior lobe. Fujisawa et al. described that the underlying mechanism of this HI development can be interpreted by a '*damming-up phenomenon*' [19]. Once axonal flow became obstructed, the neurosecretory granules would accumulate proximal to the site of obstruction [19,25]. It is also known that as long as the HI in the pituitary stalk exists, postoperative DI is transient [26,27].

In the period of recovery from DI, the HIs in the posterior lobe remained faint, but became clearer than the intensity in the DI period. The HIs in the pituitary stalk became fainter than those in the DI period. Moreover, the grades of HI became stronger in the longer DI duration than in shorter DI duration. This result suggests that the obstruction

in the pituitary stalk was partially relieved and the disturbed ADH transport to the posterior lobe recovered sufficiently to control the urine volume normally.

The small number of cases is a major limitation of this study; however, because delayed occurrence of DI after TSS is a very uncommon and/or underreported concept, there have been no previous studies found in the literature. Therefore, in our study, this delayed occurrence of DI was transient and resolved completely, but follow-up results have not yet been uncovered. The results of this study may be helpful in making treatment decisions in this unusual or unrecognized clinical setting after TSS for RCCs.

Conclusion

Preoperative ADH transport was mildly congested in the patients with postoperative delayed DI, and was not completely blocked even during the DI manifestation. Moreover, as long as HI can be observed in the pituitary stalk, the postoperative DI is self-limiting and the functional integrity of the INH system is maintained. The HI in the posterior lobe was preserved, though it became faint during the DI. In addition, their pathologies were RCC in five of 6 patients and RCC co-existed with pituitary adenoma in the rest one, therefore, the common pathology in this study was RCC. Gradual and reversible spreading of inflammation to the infundibulum after RCC removal was suggested as one possible mechanism of this delayed DI development.

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Figure Legends

Figure 1. Case 3: A series of sagittal sections of magnetic resonance imaging (MRI) are shown; (A) preoperative period: a remarkable hyper-intensity (HI) in the posterior lobe (arrow head) and a faint HI in the pituitary stalk (arrow), (B) postoperative period one week after TSS: the HI in the posterior lobe (arrow head) was unchanged and the HI in the pituitary stalk (arrow) became clearer, (C) delayed DI period: the HI in the posterior lobe (arrow head) became faint and the HI in the pituitary stalk (arrow) became stronger, and (D) recovery after DI period: the HI in the posterior lobe (arrow head) became clearer and the HI in the pituitary stalk (arrow) persisted. The morphological pattern of HI in the pituitary stalk was linear in the distal part of the pituitary stalk.

Figure 2. Case 4: A series of sagittal sections of MRI are shown; (A) preoperative period: the remarkable HI in the posterior lobe (arrow head) of the pituitary gland and faint HI in the pituitary stalk (arrow) could be found, (B) postoperative period one week after TSS: the HI in the posterior lobe (arrow head) became fainter, and the HI in the

pituitary stalk (arrow) became stronger, (C) delayed DI period: the faint HI in the posterior lobe (arrow head) persisted, but the HI in the pituitary stalk (arrow) became clearer, and (D) recovery after DI period: the HI in the posterior lobe (arrow head) could be found and the HI in the pituitary stalk (arrow) persisted. The morphological pattern of the HI in the pituitary stalk was linear in the whole of the pituitary stalk.

Table Legends

Table 1.

Clinical features of the patients with delayed occurrence of diabetes insipidus following transsphenoidal surgery

Table 2.

Radiological features of the patients with delayed occurrence of diabetes insipidus following transsphenoidal surgery

Table 1 **Clinical features of the patients with delayed diabetes insipidus following transsphenoidal surgery**

Patients	Age (yrs)	Sex	* Tumor	** Symptoms	Onset from TSS	Duration of DI	Use of DDAVP	urine osmolarity			Hypopituitarism	*** Operation	Pathology		Complication
								postoperative	delayed DI	recovery from DI			lymphocytes	hemorrhage	
1	10	F	RCC	VD	2M	4M	+	345	123	491	-	TSS	+	+	-
2	42	F	RCC	VD	3M	5M	+	484	84	241	-	TSS	+	+	-
3	28	F	RCC	HA	0.5M	1M	-	637	159	319	-	TSS	+	-	-
4	36	F	RCC + PRL	HA + AM	1.5M	6M	+	341	82	720	-	TSS	+	-	-
5	39	F	RCC	HA	0.5M	0.5M	-	384	177	787	-	TSS	+	+	-
6	76	M	RCC	HA	0.5M	2M	+	351	169	550	-	TSS	+	+	-

* RCC; Rathke cleft cyst, PRL; prolactin-secreting adenoma

** VD; visual function disturbance, HA; headache, AM; amenorrhea

*** TSS; transsphenoidal surgery

Table 2 **Radiological features of the patients with delayed diabetes insipidus following transsphenoidal surgery**

Patients	* Tumor	Diameter (mm)	MRI (T1/T2)	Existence of Hyperintensity on T1WI								
				Preoperative		Postoperative		Delayed DI			Recovery from DI	
				*** PL	Stalk	PL	Stalk	PL	Stalk	Morphology	PL	Stalk
1	RCC	22	iso / hypo	+	±	±	+	±	+	whole	+	+
2	RCC	32	iso / hyper	+	±	±	+	±	+	whole	+	+
3	RCC	24	iso / hypo	+	±	±	+	±	+	distal	+	±
4	RCC + PRL	12	**hyper / hypo + iso / hyper	+	±	±	+	±	+	whole	+	+
5	RCC	15	iso / hypo	+	±	±	+	±	+	distal	+	±
6	RCC	18	hyper / hyper	+	±	±	+	±	+	distal	+	±

* RCC; Rathke cleft cyst, PRL; prolactin-secreting adenoma
** MRI signals of RCC + PRL
*** PL; posterior lobe

Figure 1

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Figure 2

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