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Suprasellar pituitary adenomas: a 10-year experience in a single tertiary medical center and a literature review

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Abstract

Background Suprasellar pituitary adenomas (SPAs) are a special type of pituitary adenoma. Although dozens of SPA cases have been reported, the exact definition and the characteristics of SPA have not been exhaustively discussed before.

Methods In a retrospective electronic medical records review, 13 patients with SPA were identified in our hospital between January 2010 and December 2019. A literature review was performed by searching the online database PubMed, and 39 cases conformed to the criteria based on the previous literature. Data regarding clinical symptoms, imaging manifestations, surgical information and follow-ups were analyzed.

Results The mean age at diagnosis of 52 patients with SPA was 36.73 years, and most of the patients were female (61.5%). The most common hormone-secreting subtypes of SPA were nonfunctioning (36.5%) and ACTH-secreting (34.6%) SPA. Macroadenomas (68.9%) were more common than microadenomas (31.1%). The origins of the SPAs included the intrasellar pituitary gland (type I), the subdiaphragmatic (type IIa) and supradiaphragmatic (type IIb) part of the pituitary stalk, and the suprasellar peri-infundibular region (type III). The most common anatomic subtype of SPA was type III, and type IIb was also common. The most common presentations of SPA were visual symptoms, especially for type III SPA. In addition, 64.7% and 73.1% of type IIb and III SPAs, respectively, were suspected to be of suprasellar origin based on presurgical imaging examination. Patients with tumors of suspected suprasellar origin were more likely to receive transcranial surgery (TCS) initially than those with tumors of suspected intrasellar origin (70.6% vs. 22.2%, $p=0.0013$). The intact rate for the pituitary stalk after surgery for type II SPA was lower than that for type I and III SPA (52.6% vs. 92.6%, $p=0.0036$). More patients with type II SPA experienced postoperative central diabetes insipidus (CDI) than those with type I and III SPA (57.9% vs. 11.1%, $p=0.0011$). There was no significant difference in the incidence of postoperative CDI between transsphenoidal surgery (TSS) and TCS ($p=0.1304$). Nine patients in our hospital received extended endoscopic TSS; only one experienced tumor recurrence, and no severe complications occurred after surgery.

Conclusions SPAs could be defined as pituitary adenomas completely or partially located in the suprasellar region. There were both similarities and differences among the different anatomic subtypes of SPA. For patients who were suspected of having SPAs, visual field tests, pituitary hormone evaluation and MRI were necessary. Because imaging examination is not a reliable method, surgery is the only way to confirm the tumor origin. Extended endoscopic TSS might be a safe and efficient approach to remove these tumors, but more studies are needed to verify this conclusion. For type II SPA, the pituitary stalk should be carefully protected during surgery, and postoperative CDI should be monitored.

Keywords Suprasellar pituitary adenoma · Suprasellar · Ectopic · Anatomic origin

Abbreviations

SPA	Suprasellar pituitary adenoma
EPA	Ectopic pituitary adenoma
ACTH	Adrenocorticotrophic hormone
GH	Growth hormone
TSH	Thyroid stimulating hormone
PRL	Prolactin
DS	Diaphragma sellae
MRI	Magnetic resonance imaging

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CT	Computed tomography
TCS	Transcranial surgery
TSS	Transsphenoidal surgery
UFC	Urine free cortisol
DST	Dexamethasone suppression test
IPSS	Inferior petrosal sinus sampling

Introduction

Pituitary adenomas are the most common lesions in the sellar region [1]. Generally, pituitary adenomas present as sellar masses derived from adenohypophysis and can sometimes expand to surrounding areas. When adenomas grow to adjacent structures, such as the cavernous and sphenoid sinuses and the bone, they are considered invasive adenomas [2]. In addition, there are some adenomas located outside the sella turcica and without any connection with the normal pituitary gland, which are called ectopic pituitary adenomas (EPAs) [3]. Previous studies have also reported dozens of cases of suprasellar pituitary adenoma (SPA) [4–35]. While some of the reported SPAs could belong to invasive pituitary adenomas, others belong to EPAs. Although SPAs are considered to be a special type of pituitary adenoma, they have yet to be exactly defined. In this study, we reported 13 cases of SPA in our hospital and reviewed all reported SPAs in the literature to provide a definition of this type of adenoma, analyze their characteristics and raise some opinions about the management of SPAs.

Subjects and methods

Patient collection

The patients in our study were collected retrospectively by using the electronic medical records from Peking Union Medical College Hospital. The keywords "suprasellar lesion OR suprasellar mass" were searched in the database of the medical information system in our hospital between January 2010 and December 2019, and the detected cases were subjected to further inclusion and exclusion criteria.

The inclusion criteria were as follows: (1) lesions that were diagnosed as pituitary adenomas by histopathology; and (2) adenomas that were totally or partially located in the suprasellar space based on intraoperative exploration. The exclusion criteria included the following: (1) lesions that were not diagnosed as pituitary adenomas or the diagnosis was not clear; (2) adenomas that were located completely in the subdiaphragmatic space (such as intrasellar pituitary adenomas extending but not invading the suprasellar space); and (3) patients who were discovered with other ectopic pituitary adenomas located in areas other than the suprasellar region.

After searching, selecting and excluding, 13 patients were finally included. Information was collected from these 13 patients, including their clinical manifestations, endocrine tests, radiological examinations, surgical records, progress notes and follow-up data.

Classification of SPAs

The SPAs were classified in three ways. Based on the secreting hormone and histological cell origin, the SPAs were divided into nonfunctioning adenomas and functioning adenomas (hormone-secreting adenomas). Functioning adenomas included prolactin (PRL), growth hormone (GH), adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), follicle stimulating and luteinizing hormone-secreting subtypes [1, 36, 37]. The SPAs in our series were also categorized based on tumor size. Tumors of diameter 10 mm or larger were classified as macroadenomas, while tumors of diameter less than 10 mm were classified as microadenomas [36]. In addition, the SPAs were also classified into subtypes according to their anatomic origin: the anterior pituitary gland (type I), the pituitary stalk (type IIa and IIb) and the suprasellar peri-infundibular region (type III). Type IIa SPAs were adenomas originating from the intrasellar part of the pituitary stalk, and type IIb SPAs were from the suprasellar part of the pituitary stalk [34] (Fig. 1).

All SPA cases in our study were classified and analyzed according to these three categories. The hormone-secreting subtype was confirmed by endocrine tests and postoperative histopathological examination. The tumor sizes and anatomic origins were evaluated based on imaging examination and intraoperative inspection.

Literature review

A literature review was performed to find all published cases of SPAs. The online database PubMed was searched on February 8, 2020 with the search string "'suprasellar' AND 'pituitary adenomas'"; a total of 1971 results were returned. An article was excluded if (1) the pituitary adenoma extended into but did not invade the suprasellar space, with an intact DS, (2) the diagnosis of pituitary adenoma was not histologically confirmed, (3) the suprasellar location was not confirmed by surgery, (4) it was a review without new cases, or (5) it was written in a language other than English, Chinese or Japanese languages. The related cases mentioned in these articles were considered, and their original literature was also reviewed. Finally, a total of 39 cases in the previous literature were included.

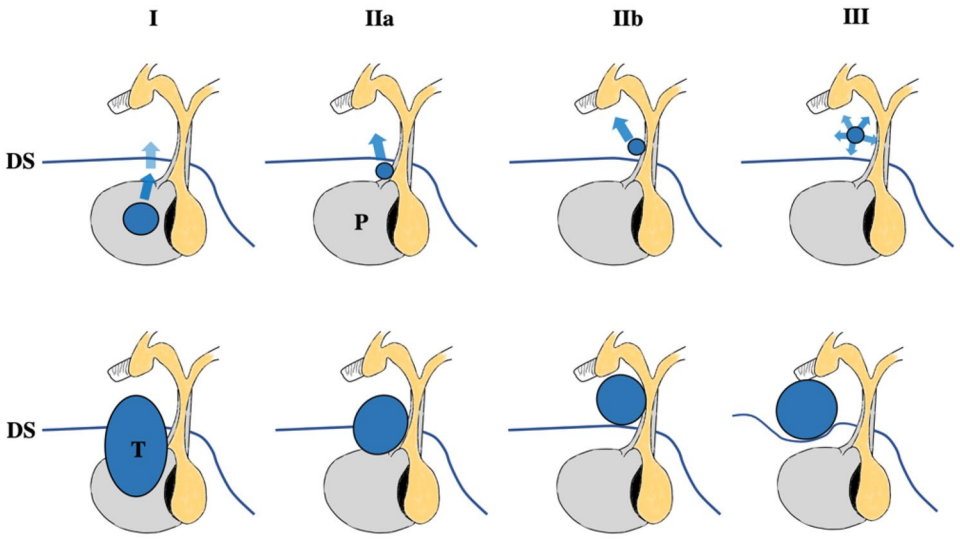

Fig. 1 The anatomic origin subtyping of suprasellar pituitary adenomas (SPAs)

P pituitary gland, DS diaphragma sella, T tumor

Data analysis and graphics

Continuous variables are expressed as the means ± standard deviations, and categorical variables are expressed as numbers or percentages. Statistical differences in a 2 × 2 table were assessed by Pearson's χ^2 test, a continuity correction χ^2 test or Fisher's exact test. The data from the cases were collected in Microsoft Excel 2019 (Microsoft, Seattle, Washington, USA) and analyzed using GraphPad Prism, version 8 (GraphPad Software, San Diego, California, USA). The figures were made in Microsoft PowerPoint (Microsoft, Seattle, Washington, USA) and Photoshop CS6 (Adobe Systems Software, Ireland).

Results

Presentation of 13 cases of SPA

Thirteen patients were diagnosed with SPA in our hospital (Tables 1, 2). Two (15.4%) patients were men, 11 (84.6%) patients were women, and the mean age was 35.6 years (range 10–61 years). Three (23.1%) of the cases were clinical nonfunctioning adenomas, 4 (30.8%) were ACTH-secreting adenomas, 2 (15.4%) were GH-secreting adenomas and 4 (30.8%) were TSH-secreting adenomas.

Cases of nonfunctioning SPAs

Two female patients (Patients 1 and 2) received brain magnetic resonance imaging (MRI) because of chronic headaches and worsening visual disturbance, and similar large sellar masses were found between the two (Fig. 2a–d). No endocrine hypersecretion was identified for these two patients. They both underwent extended endoscopic transsphenoidal surgery (TSS).

For patient 1, a large lesion was found from the intrasellar area invading the suprasellar area through the DS but was not removed completely because the tumor was adhered to the anterior cerebral artery. After surgery, the patient experienced transient diabetes insipidus and meningitis, and her vision worsened but gradually recovered. However, no intrasellar lesions were found for patient 2, but a large suprasellar mass was seen after opening of the dura mater of the DS, and the tumor was removed without residue. In addition, the unaffected pituitary gland and stalk remained intact after surgery.

Patient 3 was an 18-year-old woman who came to our hospital because of amenorrhea for one year. Hormonal tests revealed an elevated serum prolactin level of 89.48 ng/ml (normal range < 30 ng/ml), and pituitary MRI showed a suprasellar lesion (Fig. 2e, f); the boundary between the pituitary gland and the tumor was clear. The lesion was removed through extended endoscopic TSS and finally proved to be a pituitary adenoma by histopathology. The pituitary gland and stalk were well preserved.

Immunohistochemical staining for hormones showed that FSH was positive in patient 2, but none of the hormone stains were positive for patients 1 and 3. No recurrence was found for these patients.

Cases of ACTH-secreting SPAs

There were four patients (Patients 4–7) who came to our hospital because of Cushing's syndrome and were diagnosed with SPA. All of them presented typical manifestations of Cushing's syndrome, such as moon facies, central obesity, facial plethora, etc. All four patients showed impaired

Table 1 The presentations of 13 patients with SPAs in our center

Patient	Age/sex	Symptoms	Elevated hormone	Tumor size (mm)	Surgery	Subtype	IHC	Complications	Follow-up
1	61/F	Headache, visual disturbance	NF	40	Endoscopic TSS	I	None	Transient DI, visual worsening, meningitis	No recurrence at 6-month follow-up
2	58/F	Headache, visual disturbance	NF	21	Endoscopic TSS	III	FSH	Transient visual worsening	No recurrence at 1-year follow-up
3	18/F	Amenorrhea	NF	10	Endoscopic TSS	III	None	None	No recurrence at 7-month follow-up
4	21/F	Cushing's syndrome, amenorrhea	ACTH	10	TCS	III	ACTH	None	Received γ-knife therapy after surgery, and remained in partial remission over 15 years
5	19/M	Cushing's syndrome	ACTH	15	Endoscopic TSS + Endoscopic TSS	III	ACTH	None	Recurrence 2 years after the first TSS, remission again after repeated TSS, and no recurrence at 11-year follow-up
6	50/M	Cushing's syndrome, visual disturbance	ACTH	5	TSS + TCS	IIb	ACTH	None	Received TCS after failing TSS, and remained in remission at 2-year follow-up
7	46/F	Cushing's syndrome	ACTH	5	TCS	III	ACTH	None	Partial remission at 6-month follow-up
8	19/F	Acromegaly, headache, menstrual disorder	GH	18	TCS	III	GH	None	In remission at 4-year follow-up
9	46/F	Acromegaly, amenorrhea	GH	15	Endoscopic TSS	III	GH, FSH	None	In remission at 2-year follow-up
10	45/F	Heart palpitation, polyphagia, headache	Thyroxine	6	Microscopic TSS + Endoscopic TSS	III	TSH	Meningitis	Repeat TSS was performed 1 year after the first failed pituitary exploration and the patient remained in remission at 2-year follow-up
11	10/F	Polyphagia, goiter	Thyroxine	3	Endoscopic TSS	III	TSH, GH, LH	CSF leak, meningitis	In remission at 4-year follow-up
12	37/F	Tachycardia, tremor, menstrual disorder	Thyroxine, TSH	13	Endoscopic TSS	IIb	TSH	Transient DI	In remission at 3-month follow-up
13	33/F	Headache, excessive sweating, tremor, menstrual disorder	Thyroxine	8	Endoscopic TSS	III	TSH, LH, GH, PRL	None	In remission at 3-year follow-up

IHC immunohistochemistry, *M* male, *F* female, *NF* nonfunctioning, *ACTH* adrenocorticotrophic, *GH* growth hormone, *TSH* thyroid stimulating hormone, *PRL* prolactin, *TCS* transcranial surgery, *TSS* transsphenoidal surgery, *DI* diabetes insipidus, *CSF* cerebrospinal fluid

Table 2 Endocrine test results for patients with hormone-secreting SPAs in our center

Patient	Preoperative hormone levels		Postoperative hormone levels	
	Morning ACTH (NR: 0–46 pg/ml)	Morning cortisol (μg/dl)	Morning ACTH (NR: 0–46 pg/ml)	Morning cortisol (μg/dl)
4	126	18.1	51.5	23.2
5	156.5	47.4	32.5*	8.7*
6	135	31.7	95.17*	23.4*
7	54.2	34.3	11.1	8.3
	Age-adjusted IGF-1 (ng/ml)	OGTT-suppressed GH (NR < 1 μg/L)	Age-adjusted IGF-1 (ng/ml)	OGTT-suppressed GH (NR < 1 μg/L)
8	983 (NR: 141–483)	9.75	308 (NR: 141–483)	0.04
9	868 (NR: 94–252)	6.85	102 (NR: 94–252)	0.04
	Thyroxine (NR: FT3 1.80–4.10 pg/ml, FT4 0.81–1.89 ng/dl)	TSH (NR: 0.38–4.34 μIU/ml)	Thyroxine (NR: FT3 1.80–4.10 pg/ml,FT4 0.81–1.89 ng/dl)	TSH (NR: 0.38–4.34 μIU/ml)
10	FT3 5.28, FT4 2.206	1.922	FT3 0.97, FT4 0.974#	0.008#
11	FT3 6.00, FT4 2.074	2.945	FT3 2.27, FT4 1.570	0.032
12	FT3 5.69, FT4 2.26	5.432	FT3 1.35, FT4 1.01	0.009
13	FT3 5.98, FT4 2.063	1.741	FT3 1.72, FT4 0.806	0.125

NR normal range, *ACTH* adrenocorticotrophic hormone, *IGF-1* insulin-like growth factor 1, *OGTT* oral glucose tolerance test, *GH* growth hormone, *FT3* free triiodothyronine, *FT4* free thyroxine, *TSH* thyroid stimulating hormone

*Results after the first surgery

#Results after the second surgery

rhythms of cortisol secretion, elevated plasma ACTH levels and increased 24 h urine free cortisol (UFC) levels. In addition, low-dose dexamethasone suppression test (DST) demonstrated no suppression in any of the four patients. Three patients (4, 6, and 7) showed suppressed results during high-dose DST. Inferior petrosal sinus sampling (IPSS) was performed for three patients (5, 6, 7), all of whom showed positive central to peripheral results. The serum cortisol and plasma ACTH levels before and after the first surgery are shown in Table 2.

Negative findings for the tumors on adrenal CT scans and octreotide imaging helped to exclude adrenal adenomas and ectopic neuroendocrine tumors that could secrete ACTH. All patients received pituitary MRI, and three (4, 5, 7) of these patients with presented lesions in the suprasellar region (Fig. 3a, b, d). Patients 4 and 7 both received transcranial surgeries (TCSs), and the tumors were removed. For these two patients, the diaphragm sellae and the stalk were intact based on intraoperative inspection. Patient 5 underwent an extended TSS, but the suprasellar tumor recurred 2 years later. A second TSS was performed, the suprasellar mass located on the right side of the pituitary stalk was finally removed, and to date the patient has remained in remission.

Notably, patient 6 firstly went to a local hospital and the initial MRI showed 'abnormal signal in pituitary gland' which indicated a suspicious intrasellar lesion. Then the patient received a failed TSS with a negative exploration of pituitary. After that, the patient was transferred to our hospital, and a repeated MRI showed pituitary stalk thickening (Fig. 3c) indicating a lesion within the supradiaphragmatic pituitary stalk. Finally, TCS succeeded in removing the tumor, and confirmed the tumor origin of the pituitary stalk in the suprasellar space.

The diagnosis of corticotroph adenoma was confirmed by histopathology and immunohistochemistry. One patient (4) received γ-knife therapy after surgery and remains in partial remission, and the other three (5, 6, 7) remained in remission during the follow-up years.

Cases of GH-secreting SPAs

Two female patients (Patients 8 and 9) both suffered systemic complications of acromegaly, such as changes in facial features, enlargement of the hands and feet, and sleep apnea; they both also experienced menstrual disorders, but patient 8 also presented with chronic headache. Endocrine evaluation showed elevated GH and IGF-1 levels for these two patients, and GH levels could not be suppressed to less than 1 μg/l by hyperglycemia (Table 2).

For Patient 8, the pituitary MRI showed a large suprasellar tumor (Fig. 4a, b), and a craniotomy was performed to remove the tumor. After entry was made into the suprasellar

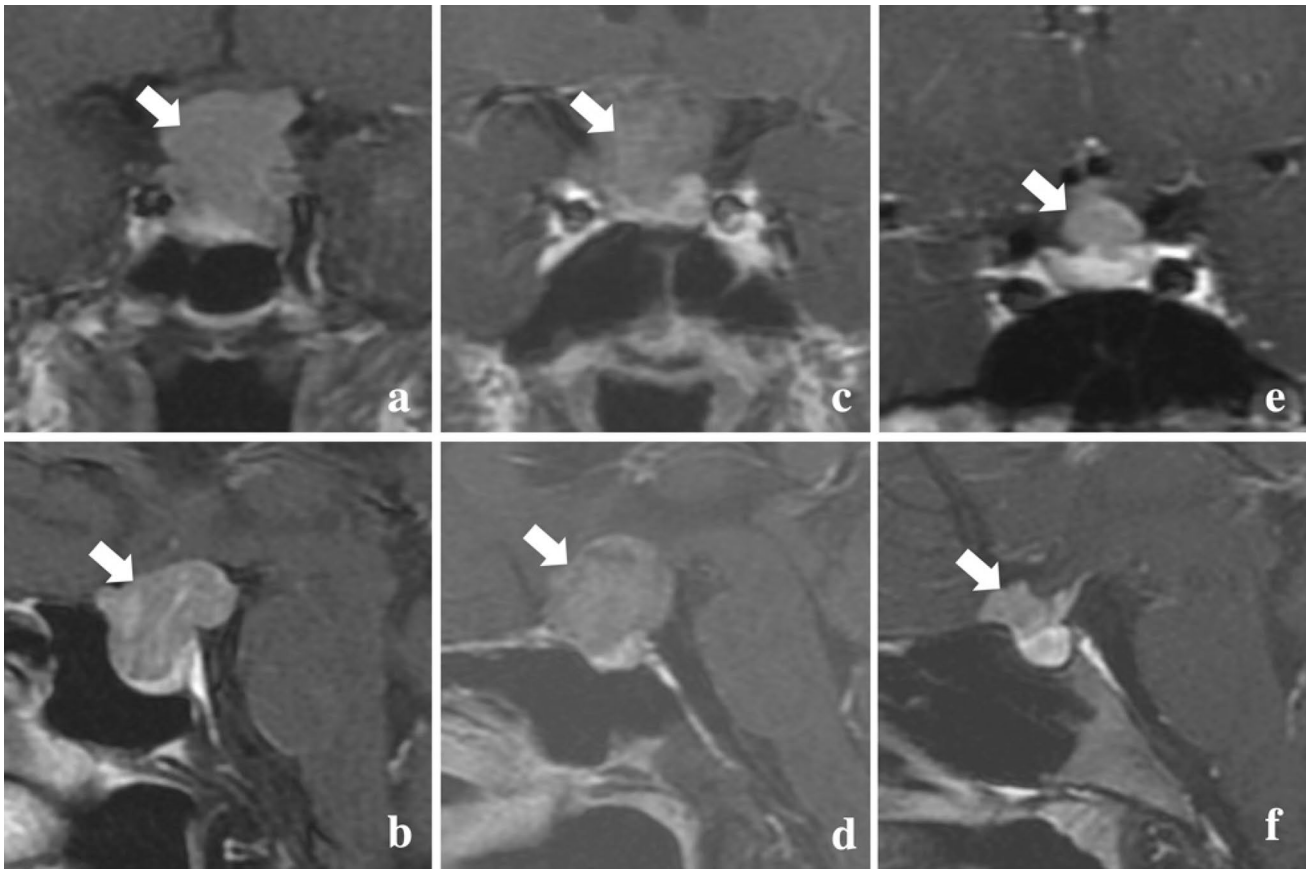

Fig. 2 MRI presentations of Patients 1 (**a**, **b**), 2 (**c**, **d**) and 3 (**e**, **f**). White arrows show suspicious tumors

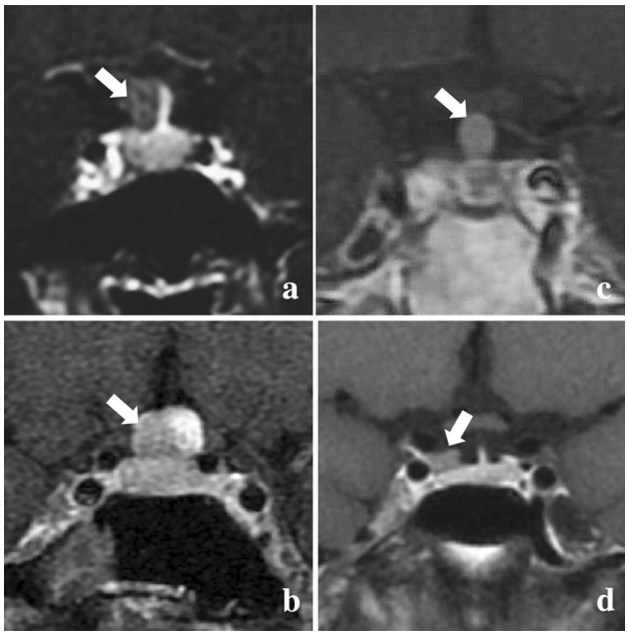

Fig. 3 MRI presentations of Patients 4 (**a**), 5 (**b**), 6 (**c**) and 7 (**d**). White arrows show suspicious tumors

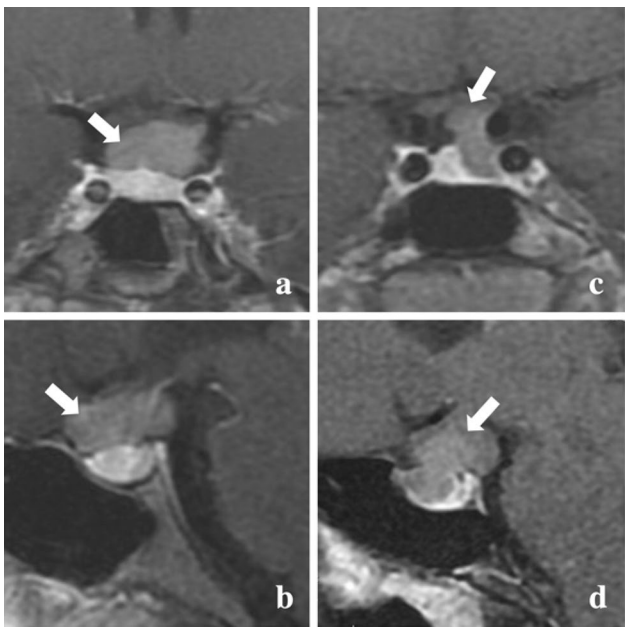

Fig. 4 MRI presentations of Patients 8 (**a**, **b**) and 9 (**c**, **d**). White arrows show suspicious tumors

region, the tumor was completely removed, revealing an intact pituitary stalk and diaphragm sellae. However, the MRI of Patient 9 demonstrated a large tumor potentially originating from the pituitary gland and invading superiorly into the suprasellar cistern (Fig. 4c, d). Because the lesion was mostly located in the suprasellar region on preoperative MRI, an endoscopic trans-tuberculum sellae procedure was performed. After opening the dura mater behind the diaphragm sellae, the gray tumor was found to be completely located in the supra-diaphragmatic region and removed while leaving the pituitary stalk intact. Therefore, the tumor did not originate from the intrasellar region. The postoperative course was uneventful for these two patients, and the GH levels were both suppressed to less than 1 μg/l after surgery (Table 2). They both remained in remission over the follow-up years.

Cases of TSH-secreting SPAs

A 45-year-old female (Patient 10) presented with heart palpitation, polyphagia, and headache for 1.5 years and was seen in another hospital. The endocrine tests showed elevated thyroxine with normal TSH levels (Table 2), and MRI demonstrated a pituitary mass with a diameter of 6 mm. The patient underwent microscopic transsphenoidal surgery, but no intrasellar lesion was found. A repeat MRI showed an enhanced lesion (Fig. 5a) in the left area of the pituitary gland and a mass (Fig. 5b) above the pituitary gland. Endoscopic TSS was performed one year later, and a suprasellar mass was removed from near the pituitary stalk with no connection to the normal pituitary gland.

Three female patients were admitted to our hospital presenting with thyrotoxicosis, and two of them (Patients 12 and 13) also presented with menstrual disorders. Endocrine tests showed that all of them had elevated thyroxine, and two patients (11 and 12) had elevated TSH levels, but one (Patient 13) presented with normal TSH levels (Table 2). All three patients underwent somatostatin tests to exclude resistance to thyroid hormones. The MRI scan of Patient 11 showed a lesion located on the left front of the pituitary stalk, which was suspected as a suprasellar pituitary adenoma (Fig. 5c, d). However, for Patients 12 (Fig. 5e, f) and 13 (Fig. 5g, h), large lesions were observed on MRI, and the relationship between the lesions and the pituitary glands was not clear. All three patients received expanded endoscopic TSS because no lesions were found in the intrasellar areas, and they were all confirmed to have TSH-secreting ESPA based on histological and immunocytochemical examination. Intraoperative exploration showed that the tumors were easily removed without any adhesion to the pituitary stalk for Patients 11 and 13. However, for Patient 12, the boundary between tumor and stalk was unclear, which indicated a pituitary stalk origin, and part of the stalk tissue was removed with the tumor.

Two patients (10 and 11) suffered meningitis after surgery; one (11) further presented with postoperative cerebrospinal fluid (CSF) leak and received CSF leak repair surgery. They both recovered after anti-infectious therapy. One

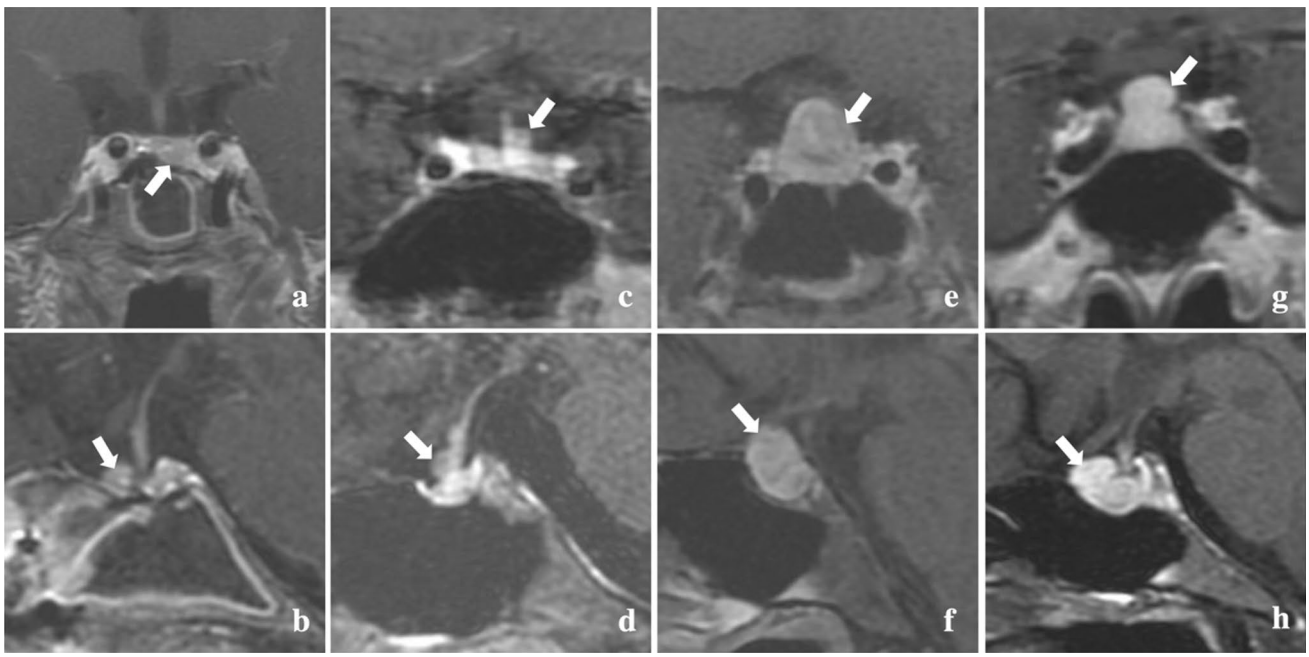

Fig. 5 MRI presentations of Patients 10 (**a**, **b**), 11 (**c**, **d**), 12 (**e**, **f**) and 13 (**g**, **h**). White arrows show suspicious tumors

patient (Patient 12) experienced transient diabetes insipidus after surgery.

All four patients achieved complete remission after surgery, and none of them experienced tumor recurrence in the follow-up years.

Literature review

Demographics and tumor classification

A total of 52 cases of SPAs were reported in previous studies, including the 13 patients from our center. In all, 32 (61.5%) of them were female, and 20 (38.5%) were male. The mean age of the 52 patients at the time of diagnosis was 36.73 ± 16.17 years (range from 10 to 71 years).

Based on the results of hormone tests and histopathology, among the 52 reported patients, 19 (36.5%) were diagnosed with nonfunctioning SPAs [5–9, 12, 13, 16–18, 26, 29–32, 35] and 18 (34.6%) with ACTH-secreting SPAs [10, 14, 15, 19, 20, 22, 23, 27]. In addition, 6 (11.5%) patients were diagnosed with PRL-secreting SPAs [11, 15, 21, 24, 25, 34], 5 (9.6%) with TSH-secreting SPAs [33] and 4 (7.7%) with GH-secreting SPAs [4, 28] (Table 3).

There were 46 cases in which the anatomic origin subtype could be confirmed based on intraoperative inspection. The most common anatomic subtype of SPA was type III (25/46, 54.3%); type IIb (18/46, 39.1%) was also common, but type I (2/46, 4.3%) and IIa (1/46, 2.2%) were rare (Tables 3, 4).

There were 7 cases whose tumor sizes were not available. Among the remaining 45 cases, 31 (68.9%) were macroadenomas, and 14 (31.1%) were microadenomas. In addition, among patients with ACTH- and TSH-secreting SPAs, microadenomas were more common than macroadenomas. However, among patients with nonfunctioning, PRL- and GH-secreting SPAs, macroadenomas predominated (Table 3). All patients with type I or type IIa SPAs had macroadenomas, and most patients with type III SPAs also had macroadenomas. However, among patients with type IIb SPAs, microadenomas were more common (Table 4).

Clinical manifestation

Based on the descriptions in the case reports, the most frequent symptoms were visual symptoms (44.2%), including decreased visual acuity, visual field deficits and bitemporal hemianopia. Fifteen (28.8%) patients experienced headaches. In addition, 15 patients suffered menstrual changes, including menstrual dysregulation and amenorrhea, which accounted for 46.9% of all female patients. Twenty-nine patients presented with symptoms of hormone excess, such as Cushing's syndrome and acromegaly, which accounted for 87.9% (29/33) of all patients with hormone-secreting SPAs.

Headaches were more common in patients with nonfunctioning, TSH- and GH-secreting SPA, while visual

Table 3 Comparison among patients with different hormone-secreting SPA subtypes

Hormone-secreting subtypes n/N (%)	Nonfunctioning (N = 19)	ACTH-secreting (N = 18)	PRL-secreting (N = 06)	TSH-secreting (N = 05)	GH-secreting (N = 04)	Total
Sex						
Female	11/19 (57.9%)	11/18 (61.1%)	3/6 (50.0%)	4/5 (80.0%)	3/4 (75.0%)	32/52 (61.5%)
Male	8/19 (42.1%)	7/18 (38.9%)	3/6 (50.0%)	1/5 (20.0%)	1/4 (25.0%)	20/52 (38.5%)
Clinical manifestations						
Headache	9/19 (47.4%)	2/18 (11.1%)	0	2/5 (40.0%)	2/4 (50.0%)	15/52 (28.8%)
Visual symptoms	12/19 (63.2%)	4/18 (22.2%)	5/6 (83.3%)	1/5 (20.0%)	1/4 (25.0%)	23/52 (44.2%)
Symptoms of hormone excess	–	17/18 (94.4%)	3/6 (50.0%)	5/5 (100.0%)	4/4 (100.0%)	–
Menstrual changes (% in females)	5/11 (45.5%)	4/11 (36.4%)	2/3 (66.7%)	2/4 (66.7%)	2/3 (66.7%)	15/32 (46.9%)
Tumor size (max diameter)						
< 10 mm	1/18 (5.6%)	9/14 (64.3%)	1/4 (25.0%)	3/5 (60.0%)	0/4 (0.0%)	14/45 (31.1%)
≥ 10 mm	17/18 (94.4%)	5/14 (35.7%)	3/4 (75.0%)	2/5 (40.0%)	4/4 (100.0%)	31/45 (68.9%)
NA	1	4	2	0	0	7
Subtype						
I	2/14 (14.3%)	0/17 (0.0%)	0/6 (0.0%)	0/5 (0.0%)	0/4 (0.0%)	2/46 (4.3%)
IIa	0	0/17 (0.0%)	1/6 (16.7%)	0/5 (0.0%)	0/4 (0.0%)	1/46 (2.2%)
IIb	4/14 (28.6%)	11/17 (64.7%)	2/6 (33.3%)	1/5 (20.0%)	0/4 (0.0%)	18/46 (39.1%)
III	8/14 (57.1%)	6/17 (35.3%)	3/6 (50.0%)	4/5 (80.0%)	4/4 (100.0%)	25/46 (54.3%)
NA	5	1	0	0	0	6

NA not available, *ACTH* adrenocorticotrophic, *GH* growth hormone, *TSH* thyroid stimulating hormone, *PRL* prolactin

Table 4 Comparison among patients with different anatomic-origin SPA subtypes

Subtypes n/N (%)	I (N = 02)	IIa (N = 01)	IIb (N = 18)	III (N = 25)	NA (N = 06)	Total
Sex						
Female	2/2 (100.0%)	0/1 (0.0%)	11/18 (61.1%)	17/25 (68.0%)	2/6 (33.3%)	32/52 (61.5%)
Male	0/2 (0.0%)	1/1 (100.0%)	7/18 (38.9%)	8/25 (32.0%)	4/6 (66.7%)	20/52 (38.5%)
Clinical manifestations						
Headaches	1/2 (50.0%)	0/1 (0.0%)	15/18 (83.3%)	8/25 (32.0%)	3/6 (50.0%)	15/52 (28.8%)
Visual symptoms	1/2 (50.0%)	1/1 (100.0%)	6/18 (33.3%)	11/25 (44.0%)	4/6 (66.7%)	23/52 (44.2%)
CDI	0	0	2/18 (11.1%)	0	0	2/52 (3.8%)
Tumor size (max diameter)						
< 10 mm	0/2 (0.0%)	0/1 (0.0%)	8/15 (53.3%)	6/23 (26.1%)	0/4 (0.0%)	14/45 (31.1%)
≥ 10 mm	2/2 (100.0%)	1/1 (100.0%)	7/15 (46.7%)	17/23 (73.9%)	4/4 (100.0%)	31/45 (68.9%)
NA	0	0	3	2	2	7
Imaging (tumor origin)						
Intrasellar	2/2 (100.0%)	0/1 (0.0%)	7/18 (38.9%)	6/25 (24.0%)	0/6 (0.0%)	18/52 (34.6%)
Suprasellar	0/2 (0.0%)	1/1 (100.0%)	11/18 (61.1%)	19/25 (76.0%)	6/6 (100.0%)	34/52 (65.4%)
Diagnosis						
TSS	1/2 (50.0%)	0/1 (0.0%)	5/18 (27.8%)	10/25 (40.0%)	2/6 (33.3%)	18/52 (34.6%)
TCS	1/2 (50.0%)	1/1 (100.0%)	13/18 (72.2%)	15/25 (60.0%)	4/6 (66.7%)	34/52 (65.4%)
Repeat surgery	0/2 (0.0%)	0/1 (0.0%)	5/18 (27.8%)	2/25 (8.0%)	1/6 (16.7%)	8/52 (15.4%)
Postoperative condition						
Intact pituitary gland	0/2 (0.0%)	1/1 (100.0%)	15/18 (83.3%)	24/25 (96.0%)	NA	40/46 (87.0%)
Intact pituitary stalk	2/2 (100.0%)	0/1 (0.0%)	10/18 (55.5%)	24/25 (96.0%)	NA	36/46 (78.3%)
Postoperative CDI	0 (0.0%)	1/1 (100.0%)	10/18 (55.5%)	2/25 (8.0%%)	0/6 (0.0%)	13/52 (25.0%)
Follow-up/						
Tumor residue	1/2 (50.0%)	0/1 (0.0%)	1/15 (6.7%)	4/21 (19.0%)	2/5 (40.0%)	8/44 (18.2%)
Tumor recurrence	0/2 (0.0%)	0/1 (0.0%)	1/15 (6.7%)	1/21 (4.8%)	0/5 (0.0%)	2/44 (4.5%)
NA	0	0	3	4	1	8

MRI magnetic resonance imaging, *NA* not available, *CDI* central diabetes insipidus, *TSS* transsphenoidal surgery, *TCS* transcranial surgery

symptoms commonly appeared in patients with PRL-secreting and nonfunctioning SPAs. In addition, symptoms of hormone excess were the main complaints for the majority of patients with ACTH-, TSH- and GH-secreting SPAs. In addition, more than half of female patients with PRL-, TSH- and GH-secreting adenomas suffered menstrual changes, including amenorrhea and menstrual dysregulation (Table 3).

A total of 83.3% of patients with type IIb SPA complained of headaches, but only 32.0% of patients with type III SPA had this symptom. In addition, 33.3% and 44.0% of patients with type IIb and III SPA, respectively, had visual symptoms. Interestingly, there were 2 patients presenting with central diabetes insipidus, and both of their adenomas were type IIb (Table 4).

Imaging examination

Several of the earlier published articles reported some patients whose sellae lesions were found with techniques other than MRI. There were 2 (3.8%) patients [4, 5] whose suprasellar lesions were detected by pneumoencephalography, and 4 (7.7%) [6, 15] were identified by brain CT. All other 46 (88.5%) patients received pituitary MRI.

Based on preoperative imaging examination, all 52 (100.0%) patients were identified with sellar lesions. There were 34 (65.4%) patients whose tumors were suspected to be of suprasellar origin because their lesions on the imaging pictures were shown to be completely in the supradiaphragmatic region according to the appearance of an intact DS between the mass and the pituitary gland. However, the tumors of the other 18 (34.6%) patients were suspected to originate from the intrasellar area due to the lack of a clear DS on the images, and their mass seemed to derive from the intrasellar region, which invaded upward into the suprasellar space (Table 4).

Interestingly, all type IIb and type III SPAs derived from the supradiaphragmatic space, but only 64.7% and 73.1% of these two types were suspected to have suprasellar origins based on their preoperative imaging presentations,

respectively (Table 4). In addition, the preoperative diagnosis of 4 cases was considered to be craniopharyngioma due to calcification on their imaging pictures [7, 13, 25, 35]. There was only one patient with type IIa SPA that originated from the subdiaphragmatic part of the pituitary stalk; it was initially indicated to be of suprasellar origin based on preoperative MRI [34]. In total, among the 46 patients whose tumor origins were finally confirmed by surgery, the tumor origins of 14 (30.4%) patients were wrongly indicated on presurgical imaging.

Surgery and postoperative condition

All 52 patients underwent surgery, and their diagnoses were confirmed by intraoperative inspection and postoperative histopathology. There were 8 (15.4%) patients who first received transsphenoidal surgery (TSS), but no intrasellar lesions were found (Table 4). Then, transcranial surgery (TCS) was performed for 6 of these patients [15, 23, 27], extended TSS was performed for the other 2 patients [26], and all achieved successful tumor resection. Among the 52 cases, the diagnoses of 34 (65.4%) patients were confirmed and their tumors were finally removed by TCS; the remaining 18 (34.6%) patients were treated by TSS (Table 4).

Presurgical imaging provided the initial estimate of the tumor origin. TCS was more likely to be selected initially for patients with tumors of suspected suprasellar origin than those with tumors of suspected intrasellar origin (70.6% vs. 22.2%, $p = 0.0013$). However, no significant difference in tumor size was found among the different surgical approaches ($p = 0.1071$) (Table 5).

According to intraoperative exploration and postoperative MRI, postoperative information was available for 46 patients. Compared with those of intrasellar origins (type I and IIa), SPAs of suprasellar origin (type IIb and III) showed a higher rate of complete preservation of pituitary gland after surgery (33.3% vs. 92.9%, $p = 0.0289$). The pituitary stalk was partially or totally removed in 9 (47.4%) of

Table 5 Surgical selection and postoperative conditions

	n/N (%)		*p* value
	Surgical approach		
Suspected tumor origin	TCS	TSS	
Suprasellar origin	24/34 (70.6%)	10/34 (29.4%)	
Intrasellar origin	4/18 (22.2%)	14/18 (77.8%)	0.0013*
Tumor size	TCS	TSS	
Macroadenomas	20/31 (64.5%)	11/31 (35.5%)	
Microadenomas	5/14 (35.7%)	9/14 (64.3%)	0.1071
	Pituitary gland integrity		
Tumor origin	Yes	No	
Suprasellar (type IIb and III)	39/42 (92.9%)	3/42 (7.1%)	
Intrasellar (type I and IIa)	1/3 (33.3%)	2/3 (66.7%)	0.0289*
Surgical approach	Yes	No	
TCS	26/27 (96.3%)	1/27 (3.7%)	
TSS	19/24 (79.2%)	5/24 (20.8%)	0.0876
	Pituitary stalk integrity		
Tumor origin	Yes	No	
Non-stalk origin (type I and III)	25/27 (92.6%)	2/27 (7.4%)	
Stalk origin (type II)	10/19 (52.6%)	9/19 (47.4%)	0.0036*
Surgical approach	Yes	No	
TCS	22/27 (81.5%)	5/27 (18.5%)	
TSS	19/24 (79.2%)	5/24 (20.8%)	0.9999
	Post-operative CDI		
Tumor origin	Yes	No	
Non-stalk origin (type I and III)	3/27 (11.1%)	24/27 (88.9%)	
Stalk origin (type II)	11/19 (57.9%)	8/19 (42.1%)	0.0011*
Surgical approach	Yes	No	
TCS	5/28 (17.9%)	23/28 (82.1%)	
TSS	9/24 (37.5%)	15/24 (62.5%)	0.1304

TCS transcranial surgery, *TSS* transsphenoidal surgery, *CDI* central diabetes insipidus

p values indicate statistical significance, *$p = 0.05$

patients with SPAs of stalk origin (type II) during tumor resection, but was damaged in only 2 (7.4%) patients from those with SPAs of non-stalk origin (type I and III). So, type II SPAs showed a significantly lower rate of integrity of pituitary stalk than the other two subtypes (I and III) after surgery (52.6% vs. 92.6%, $p = 0.0036$). In addition, 57.9% of patients with type II SPA experienced central diabetes insipidus (CDI) after surgery. However, for patients with type I and III SPA, the incidence (11.1%) of postoperative CDI was significantly lower ($p = 0.0011$). There were no significant differences in the intact rates of the pituitary gland ($p = 0.0876$) and pituitary stalk ($p > 0.9999$) between TCS and TSS. No significant difference in the incidence of postoperative CDI was shown between these two surgical approaches ($p = 0.1304$) (Table 5).

Follow-up data

Based on the 44 cases whose follow-up data were available, tumor residue was found in 8 (18.2%) patients (Table 4). Four of these patients received radiation therapy [9, 12, 15], 1 chose medical therapy [15] and the other 3 maintained regular follow-up without any therapy [8, 12]. For the other 36 cases whose tumors were successfully and completely removed, only 2 patients [4, 20] had tumor recurrence, and one died three years after surgery [4].

Discussion

This study reviewed a special series of patients with pituitary adenomas. Due to all of them presenting with a "suprasellar mass", their lesions were all called "suprasellar pituitary adenomas (SPAs)". In fact, SPAs included not only pituitary adenomas of suprasellar origin but also those of intrasellar origin that invade the suprasellar space. Thus, SPAs can be defined as pituitary adenomas completely or partially located in the suprasellar region. Only SPAs of suprasellar origin can be classified as EPAs. According to the anatomic classification [34], SPAs are further divided into subtype I, IIa, IIb and III.

There are three possible causes of SPAs based on previous studies [6, 19, 28]: (1) tumors originating from the pars distalis of the adenohypophysis and extending superiorly through the DS, which become type I SPAs; (2) tumors originating from the pars tuberalis, which leads to type IIa and IIb SPA; and (3) tumors originating from residual cells of Rathke's pouch, which are scattered in the suprasellar space and ultimately become type III SPAs (Fig. 1).

Type I and IIa were both adenomas of intrasellar origin, and they were more easily ignored and rarely reported because they are not generally considered special. And in our study, the search keyword "suprasellar" might have missed some reports on these cases because they were not usually recorded as "suprasellar masses". Besides, all SPAs were confirmed by surgical exploration. So, the real prevalence of SPAs might be underestimated.

Generally, prolactinomas accounts for up to 60% of all pituitary adenomas, nonsecreting (14–55%) and GH-secreting (8–15%) adenomas were as follows, whereas ACTH-(2–6%) and TSH-secreting (1%) adenomas were relatively rare [36, 38]. This differed from the proportion of each hormone-secreting types of SPAs. Medication is generally indicated for prolactinomas and only a few of patients with inadequate tumor shrinkage may require surgery [36, 37]. Thus, as a surgical series, our study showed a smaller proportion of prolactinomas in SPAs. An interesting finding in our study was that ACTH-secreting SPAs showed a very high relative prevalence. This may due to that patients with severe Cushing's syndrome are more likely to be identified and the difficulty of localization diagnosis [38] may increase the doctors' attention and lead these cases more likely to be discovered, and subsequently, to be published. But further study is needed on the possible mechanism.

The most common symptoms in SPAs patients were visual symptoms, although the prevalence might be underestimated because many patients did not receive a visual field test according to the descriptions in previous literatures. This could be explained that the suprasellar masses were more likely to compress the optic nerve and chiasm [38]. So, the visual field assessment is necessary, and besides, the visual condition will affect surgical decisions [36].

A study of a large series of sellar masses [39] shows that the prevalence of headaches in patients with nonadenomatous lesions (57%) was higher than that with pituitary adenomas (27–38%). However, the prevalence of headaches in patients with type IIb SPAs seemed much higher. This may due to that type IIb adenomas easily stretch the dural of the DS, which could result in headaches but the real mechanisms remain unclear [40].

Interestingly, menstrual changes were very common in female patients with SPAs. The high prevalence of menstrual disorders might be attributed to a stalk effect [41] because the particular location of SPA makes it more likely to involve the pituitary stalk. Besides, a cohort of pituitary stalk lesions [42] shows that more than half of patients present secondary hypogonadism. But due to the lack of details on hormone evaluation in previous case reports, it was difficult to explore the real cause.

The pituitary MRI have a sensitivity of 99% to identify a sellar or parasellar lesion [39] and can provide information about tumor size and surrounding extensions, consequently affecting the selection of treatment and surgical options [43]. However, the etiologies of sellar lesions are broad, including pituitary tumors, cysts, nonpituitary tumors, developmental lesions, infectious and inflammatory masses as well as

vascular lesions [39, 44, 45]. Although MRI can provide some clues for differential diagnosis, endocrine evaluation is also essential [38, 43]. Since nearly two-thirds of SPAs presented hormone hypersecretion, a thorough endocrine assessment could provide a strong evidence to distinguish them from other diseases.

However, more than one-third of suprasellar-origin SPAs were wrongly thought to have an intrasellar origin based on MRI. And the relationship between pituitary stalk and tumor could not be clearly identified on radiological pictures. Hence, it was difficult to determine the origin of SPAs by relying on imaging presentations alone, but surgery plays a very important role in this [33, 34].

TCS was more likely to be performed on patients with suspected suprasellar-origin adenomas because the best way to remove a large suprasellar tumor was craniotomy in the last few decades [46]. With the development of endoscopic equipment, for large pituitary adenomas or suprasellar lesions, an extended endoscopic transsphenoidal approach can be a safe and efficient substitute for TCS [47, 48]. Although only a few patients received extended endoscopic TSS in the previous reports [31–33], 9 patients underwent this approach in our center, and almost no severe complications appeared. Therefore, endoscopic TSS should be considered an ideal surgical approach for treating SPAs. Furthermore, endoscopic inspection can provide a broad and clear view to confirm the tumor origin [33].

The etiology of pituitary stalk lesions is very broad, but it is rarely caused by pituitary adenoma [42]. CDI is a very common symptom, which is diagnosed in 51% of patients with pituitary stalk lesions [42] and up to 68.8% of patients with stalk thickening [49]. Interestingly, initial CDI in patients with type II SPAs was very uncommon, although these tumors were also infundibular masses. In fact, CDI could be caused by local inflammation or destruction of the hypothalamic-neurohypophyseal axis but is uncommon in pituitary adenomas [50]. So, this feature may provide some clues for differential diagnosis. Unfortunately, many patients experienced pituitary stalk injuries during surgery and then suffered postoperative CDI, especially for type II SPAs. Pituitary stalk is responsible for delivering signaling factors and its integrity is crucial for normal functioning of pituitary[43, 49]. Therefore, for type II SPAs, the tumor must be carefully separated from the normal tissue during the operation, so as to preserve the integrity of the pituitary stalk as much as possible. Besides, the surveillance of CDI and fluid management are also important after surgery.

Limitations

There were several limitations in our study. Due to its retrospective nature, selection bias was unavoidable. Due to recall bias, some information, such as clinical symptoms and hormone tests, could be incomplete or inaccurate. Therefore, the clinical features of the SPAs may not have been estimated comprehensively. There may be some potential SPA patients who were not identified because they did not receive surgery or draw enough attention, so the real prevalence of SPA may have been underestimated. In addition, due to the small sample size and the age of some of the reported cases, more studies are needed to verify the results in our study, especially by enrolling additional and updated cases in the future. Since the majority of patients with SPAs received TCS, more research is needed on the application of extended endoscopic TSS.

Conclusions

Suprasellar pituitary adenomas (SPAs) are pituitary adenomas that are completely or partially located in the suprasellar region, including intrasellar pituitary adenomas that invade the suprasellar space and ectopic suprasellar pituitary adenomas. Based on the anatomic origin, a SPA can be classified into four subtypes: intrasellar pituitary (I), pituitary stalk (IIa and IIb) and suprasellar peri-infundibular (III). Only type IIb and III SPAs were real ESPAs, and type III was the most common anatomic subtype. The most frequent hormone types of SPAs were nonfunctioning and ACTH-secreting adenomas. Headaches were not specific symptoms but were very common in patients with type IIb SPAs. CDI was rare in these patients. However, visual field tests should be essential examinations because visual symptoms were the most common symptoms among the SPA patients. In addition, hormone tests and enhanced pituitary MRI were also necessary for differential diagnosis. Because MRI is not a reliable method for identifying the tumor origin, surgery is therefore necessary. Extended endoscopic transsphenoidal surgery might be a safe and efficient way to remove these SPAs, but more studies are needed to verify this conclusion. For type II SPAs, the pituitary stalk is vulnerable, and physicians should be vigilant for postoperative CDI.

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Compliance with ethical standards

Conflict of interest The authors have no conflict of interest.

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