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The characteristics of and surgical treatment for pituitary adenomas in patients under 14 years old

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ABSTRACT

To investigate the clinical characteristics of pituitary adenomas in patients under 14 years old.

A total of 140 children and adolescents with pituitary adenomas were admitted to Peking Union Medical College Hospital (PUMCH) from December 1987 to December 2014, and their clinical manifestations, hormone secretions, images, pathological types, surgical complications and follow-up characteristics were analyzed. Fifty-eight (41.4%) males and 82 (58.6%) females with a mean age of 12.5 years old (range, 6–14 years old) were included. Regarding tumor type, adrenocorticotropic hormone (ACTH), prolactin (PRL), growth hormone (GH), non-functioning and multiple-secreting adenomas accounted for 35.7%, 25.7%, 12.2%, 25.7%, and 0.7% of the tumors, respectively. Microadenomas, macroadenomas and giant adenomas accounted for 33.6%, 60.0% and 6.4% of the patients, respectively. Approximately 19.3% of the adenomas included in our study were invasive. Trans-sphenoidal approach surgery (TSS) was commonly used and accounted for 97.9% of the cases in our study. Total resection was achieved in 93.6% of the patients, and subtotal resection was performed in the remaining patients. Finally, 113 patients underwent full-term follow-up until 2 years after surgery, and tumors recurred in 32 patients.

TSS is the most commonly used surgical procedure in patients younger than 14 years old. No significant differences in surgical outcomes, mortality during the perioperative period or complications were observed between patients younger than 14 years old and similar patients in the general population.

1. Introduction

Pituitary adenomas are rare in patients younger than 14 years old, in whom they account for only approximately 3–5% of all intracranial tumors and 2–6% of all pituitary adenomas [1]. Pituitary adenomas have a strong influence on growth and development in children and adolescents and can cause growth retardation, visual impairment, and osteoporosis in addition to primary amenorrhea in females and sexual dysfunction in males. The clinical characteristics and types of pathology of pituitary adenomas observed in children and adolescents are different from those found in adults. We investigated 140 pituitary adenoma patients younger than 14 years old at PUMCH from December 1987 to December 2014 to summarize their characteristics and treatment methods.

2. Material and methods

A total of 140 children and adolescents with pituitary adenomas were admitted to Peking Union Medical College Hospital (PUMCH) from December 1987 to December 2014, and their clinical manifestations, hormone secretions, images, pathological types, surgical complications and follow-up characteristics were analyzed. We do the data analysis with a description. This study was approved by the Ethics Committee of Peking Union Medical College Hospital, and written informed consent was obtained from all patients.

3. Symptoms and signs

One patient (0.7%) displayed no symptoms during a physical examination. The remaining 139 patients (99.3%) exhibited one or more significant symptoms, such as headache and/or dizziness, menstruation disorders and/or amenorrhea, weakness, impaired vision, and signs of Cushing syndrome, lactation, and visual field defects (Table 1).

4. Results

A total of 140 pituitary adenoma patients aged 6–14 years old participated in this study. These included 58 (41.4%) males and 82

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Table 1
Manifestations of 140 pituitary adenoma patients under 14 years old.

Manifestation	Cases	Rate (%)
Headache and/or dizziness	54	38.6
Menstruation disorders/amenorrhea	54	38.6
Cushing syndrome	50	35.7
Impaired vision	47	33.6
Weakness	26	18.6
Lactation	24	17.1
Visual field defects	16	11.4
Gigantism	13	9.3
Acromegaly	13	9.3
GH level changes	8	5.7
Polydipsia and polyuria	8	5.7
Nausea and vomiting	6	4.3
Sweating	5	3.6
Polyphagia	4	2.9
Dark skin	4	2.9
Fever	2	1.4
Unconsciousness	2	1.4
None	1	0.7

(58.6%) females. Fifty cases (35.7%) involved ACTH adenomas, which had an average course (duration of pre-diagnosis symptoms) of 45.5 months; 36 cases (25.7%) involved PRL adenomas, which had an average course of 35.5 months; 17 cases (12.2%) involved GH adenomas, which had an average course of 29.3 months; 36 cases (25.7%) involved non-functioning adenomas, which had an average course of 32.6 months; and 1 case (0.7%) involved a multiple-secreting adenoma (PRL + GH) with a course of 1 month. Thirty-six patients (25.7%) who received bromocriptine therapy were insensitive or intolerant to the drugs before undergoing surgery. Fourteen patients (10.0%) had a recurrence after a first operation performed at another hospital and were then admitted to PUMCH.

4.1. Radiology

One hundred twenty-five patients (89.3%) underwent magnetic resonance imaging (MRI) of the sellar region (Table 2), and the other 15 patients (10.7%) underwent computed tomography (CT) scans. Forty-seven cases (33.6%) consisted of microadenomas ($\leq$10 mm), 84 cases (60.0%) consisted of macroadenomas (10 $<$ d $\leq$ 30 mm), and 9 cases

Table 2
MRI presentations of 140 pituitary adenoma patients under 14 years old.

MRI	Cases	Rate (%)
T1		
Iso-intensive signal	54	43.2
Low signal	43	34.4
High signal	23	18.4
Mixed signal	5	4.0
T2		
Iso-intensive signal	39	31.2
Low signal	25	20.0
High signal	54	43.2
Mixed signal	7	5.6
Enhanced T1		
Obvious enhancement	12	9.6
Circulation enhancement	10	8.0
Homogeneous enhancement	14	11.2
Inhomogeneous enhancement	46	36.8
Low enhancement	19	15.2
No enhancement	24	19.2
Invasion status		
Invasive	27	19.3
Non-invasive	113	80.7

(6.4%) consisted of giant adenomas ($>$ 30 mm). Furthermore, 27 cases (19.3%) involved invasive adenomas with a knosp$\geq$3, and 113 cases (80.7%) involved non-invasive adenomas. Almost 35 patients had a conchal-type sphenoid sinus anatomy.

4.2. Laboratory tests

Before the operation, 18 patients had hypothyroidism, 4 had a low IGF-1 level, 11 had adrenal insufficiency, and 41 were hypogonadal. Laboratory tests were conducted at 3–10 days after the operation in 122 patients (87.1%). Seven (21.2%) of the 33 patients with non-functioning pituitary adenomas had abnormal thyroid hormone levels, 9 (27.3%) had abnormal sex hormone levels, 5 (15.2%) had abnormal PRL levels, 7 (21.2%) had abnormal ACTH levels, and 5 (15.2%) had abnormal GH levels. The GH-axis was above normal in 11 patients (64.7%) and maintained at a normal level or increased in 3 patients (17.6%). The PRL-axis was above a normal level in 12 patients (42.9%), and PRL levels were increased in 2 patients (7.1%). After the operation, the ACTH-axis was above normal in 10 patients (22.7%), and 4 patients (9.1%) had increased ACTH levels. The only patient with multiple-secreting pituitary adenoma exhibited decreased hormone levels.

4.3. Surgery

The surgical methods used in the 140 patients were selected based on characteristics of the tumors, including size, invasiveness, and growth. Before 2000, we used a microscope, and thereafter, we used an endoscope. A standard vision evaluation was performed using a visual chart, and the visual field was evaluated by a dynamic field instrument before and after the operation. TSS was conducted in 137 (97.9%) patients, and navigation was used during the operation in 2 of these patients. Only 3 patients (2.1%) were treated using the trans-frontal approach. The MRI results were reviewed 3 days after the operation as an evaluation standard. Total resection of the tumors was achieved in 131 cases (93.6%), and subtotal resection was achieved in the other 9 cases (6.4%).

Almost all patients with one or more symptoms reported that their feelings of discomfort were improved after the operation. A total of 124 patients without pre-operative visual field defects showed no change after the operation, while 15 of the 16 patients who exhibited a symptom of a visual field defect reported visual improvement, and 1 was not changed.

All tumors were subjected to pathological examinations after the operation, and all cases were confirmed to be pituitary adenomas. Next, 109 of the tumors (77.9%) were subjected to immunohistochemical examination, with 47 cases (33.6%) analyzed for p53 labeling and 51 cases (36.4%) used to determine the Ki-67 index. These results are shown in Tables 3 and 4.

4.4. Complications

Forty-seven patients (33.6%) experienced serious complications after the operation. The transient diabetes insipidus was the most frequent complication, occurring in 25 cases (17.9%), while 17 patients (12.1%) presented with headache and/or dizziness, 15 (10.7%) presented with fever, 6 (4.3%) presented with electrolyte disturbances, 4 (2.9%) presented with leakage of cerebrospinal fluid, 2 (1.4%) presented with pituitary hypofunction; and poor appetite, palpitation, weakness, drowsiness and vomiting were observed in 1 patient each (0.7%).

4.5. Follow-up

The full follow-up plan was followed by 113 patients (80.7%) and

Table 3
Immunochemistry results in 109 primary pituitary adenoma patients.

Immunochemistry	PRL	GH	FSH	LH	TSH	ACTH	p53	Ki-67 index
Positive	64 (58.7)	53 (48.6)	13 (11.9)	29 (26.6)	8 (7.3)	60 (55.0)	8 (17.0)	19 (37.3)
Negative	45 (41.3)	56 (51.4)	96 (88.1)	80 (73.4)	101 (92.7)	49 (45.0)	39 (83.0)	32 (62.7)

PRL: prolactin; GH: growth hormone; FSH: follicle-stimulating hormone; LH: luteinizing hormone; TSH: thyroid-stimulating hormone; ACTH: adrenocorticotropic hormone.

included examinations performed at 3–10 days, 3 months, 12 months and 24 months after the operation. MRI and laboratory tests were conducted in each examination. Sixteen patients (14.2%) required a second operation due to the recurrence of tumors. Seven (28.0%) of the 25 patients with invasive tumors who completed the full follow-up process had a recurrence within 1 year after the operation. Nine (10.2%) of the 88 patients with non-invasive tumors had a recurrence within 2 years. Three (33.3%) of the 9 sub-resection patients who completed the full follow-up process had a recurrence within 1 year of the operation. Thirteen (12.5%) of the 104 total resection patients who completed the full follow-up process had a recurrence within 2 years.

5. Discussion

In our study, the number of females exceeded that of males, and the most common pituitary adenoma was ACTH-secreting adenoma (35.7%). PRL-secreting adenomas (25.7%), non-functioning adenomas (25.7%), GH-secreting adenomas (12.2%) and multiple-secreting adenomas (0.7%) were also identified, similar to previous studies [2,3]. PRL-secreting adenoma is not a rare disease, and because bromocriptine is the first choice for therapy in this tumor type, few of these patients required an operation for resection. Because no systematic studies of patients over 14 years old have been conducted to date, we compared our results to those obtained in the general population. Molitch [4] concluded that non-functioning pituitary adenomas accounted for 15–54% of tumors, similar to our findings. GH-secreting adenomas accounted for 8–16% of tumors, also similar to our findings. ACTH-secreting adenomas accounted for 2–6% of tumors, and this was lower than the proportion found in our study ($p < 0.05$). PRL-secreting adenomas account for 32–66% of tumors, similar to our results. Finally, multi-secreting adenomas are rare, accounting for 1% of tumors, similar to our findings. Therefore, our results are similar to those found in the general population, with the exception of ACTH-secreting adenomas.

The clinical manifestations of pituitary adenomas vary among patients younger than 14 years old [5]. In our study, the main manifestations included headache and/or dizziness, menstruation disorders and/or amenorrhea, Cushing syndrome and impaired vision. Other presentations were also observed, such as weakness, lactation, visual field defects, gigantism and acromegaly. Kane et al. [2] and Webb and Prayson [6] found that headache and impaired vision are the main presentations, while Cushing syndrome is unique to ACTH-secreting adenomas, and gigantism and acromegaly are unique to GH-secreting adenomas. Although manifestations are important for establishing a diagnosis during the early stage, parents who lack medical knowledge tend to delay medical consultation. Hence, some patients have already suffered from the tumor for 10 years when they are first admitted to outpatient care.

Other than manifestations, laboratory tests and radiology examinations are also important for achieving a diagnosis, especially in functioning adenomas, and may allow the type of the tumor to be identified. MRI may present iso-intensive or long T1 signals and long T2 signals, and enhanced lesions may also be detected. In our study, 77.6% of the patients had iso-intensive or long T1 signals, 43.2% of the patients had long T2 signals, and 80.8% of the patients exhibited signal enhancement. Radiology plays an important role in evaluating tumor size, invasion, and diagnosis and in guiding the choice of surgical method [7]. Pituitary adenoma in childhood and adolescence should be distinguished from craniopharyngioma and germ-cell tumors in the sellar region, which usually present with normal signals on MRI. Additionally, calcification is more frequent in craniopharyngioma.

The therapeutic effects of drugs and surgery are different in pituitary adenomas found in children and adolescents. ACTH-secreting adenomas are more sensitive to surgery (80%˜90%) [8]; therefore, surgery is the first choice of treatment in these tumors. As in adults, drug therapy is the first choice in PRL-secreting adenomas, and 36 patients (25.7%) used bromocriptine before undergoing surgery. However, drug treatment had no effect in these patients. GH-secreting adenomas are usually large in size, and this makes them insensitive to drug treatment. Surgical procedures are effective in 83% of these cases [9]. Drug therapy is not effective in non-functioning adenomas, and surgery is therefore the first choice if treatment in these patients. TSS is considered the best method for treating pituitary adenoma due to its minimal trauma, short operation time and reduced complication rate [10]. In our study, total resection was achieved in 131 cases (93.6%), and subtotal resection was achieved in the other 9 cases (6.4%).

The most commonly reported complication after TSS is diabetes insipidus, which accounts for 18.3% of cases, while permanent diabetes insipidus occurs in 1.4–2% of patients [11]. Diabetes insipidus was also the most common complication in our study, in which it occurred in 25 cases (17.9%). Pituitrin was an effective treatment in these patients. Ciric et al. [11] found that the rate of leakage of cerebrospinal fluid was 0.6–5.3%. Four patients (2.9%) experienced this complication in our study, and it was effectively treated with bedrest. One patient (0.7%) had pituitary hypofunction and was treated with hormone replacement therapy. However, regular re-examination was required in this case. Other complications resolved after therapy.

Pathological examination is essential for diagnosing the type and atypism of pituitary adenomas [12]. In our study, 109 patients underwent immunohistochemical examinations. The p53 and Ki-67 indexes were sufficient to predict the fission status and atypism of the observed tumors. Twenty-two patients were p53-positive or had a Ki-67 index $\geq 3\%$. We compared the tumor size, invasiveness and operation reports in these patients to those obtained in patients who were p53-negative with a Ki-67 index $< 3\%$ and found that the rate of invasion was higher in the former group, which had more macroadenomas. There was no significant difference between these groups regarding the operative range. A greater number of giant adenomas was observed among patients who were p53-negative with a Ki-67 index $< 3\%$.

Pituitary adenomas in children and adolescents have a recurrence rate of 10–25% [2,9,13]. In our study, 113 patients completed follow-ups at 3–10 days, 3 months, 12 months and 24 months after the operation, and the recurrence rate within 2 years in this group was 14.2%,

Table 4
Size, invasion characteristics and resection in 51 tumors analyzed by p53 or Ki-67 staining.

p53 or Ki-67 staining	Total number	Tumor size			Invasion status		Range of resection	
		Giant adenoma (≥ 3 cm)	Macroadenoma (1–3 cm)	Microadenoma (< 1 cm)	Invasive	Non-invasive	Total resection	Subtotal resection
p53(+) or Ki-67 index ≥ 3%	22 (43.1)	2 (9.1)	17 (77.3)	3 (13.6)	13 (59.1)	9 (40.1)	21 (95.5)	1 (4.5)
p53(-) or Ki-67 index < 3%	29 (56.9)	7 (24.1)	13 (44.8)	9 (31.0)	8 (27.6)	21 (72.4)	29 (100.0)	0 (0.0)
p		< 0.05			> 0.05		> 0.05	

similar to previously published rates. The operative method, whether subtotal resection was achieved, and the invasiveness of the tumors played important roles in the 2-year recurrence rate.

Besides craniopharyngioma and germ-cell tumors, the physiologic enlargement of the pituitary gland due to puberty in adolescents and hypothyroidism in infants should also be considered, so a detailed examination before the operation is necessary.

6. Conclusion

TSS is the most commonly used surgical procedure in patients younger than 14 years old. No significant differences in surgical outcomes, mortality during the perioperative period or complications were observed between patients younger than 14 years old and similar patients in the general population.

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Author contribution

Yi Zhao wrote the report and analysed the data. Wei Lian design the study and the conception. Xing Bing and Renzhi Wang collected the data and made the decision to submit the article for publication.

Declaration of Competing Interest

There are no sources of support to report. The authors report no conflicts of interest concerning the materials and methods used in this study or the findings described in this paper.

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References

[1] M.F. Keil, C.A. Stratakis, Pituitary tumors in childhood: an update in their diagnosis, treatment and molecular genetics, Expert Rev. Neurother. 8 (2008) 563–574.
[2] L.A. Kane, M.C. Leinung, B.W. Scheithauer, E.J. Bergstralh, E.R. Laws Jr., R.V. Groover, K. Kovacs, E. Horvath, D. Zimmerman, Pituitary adenomas in childhood and adolescence, J. Clin. Endocrinol. Metab. 79 (1994) 1135–1140.
[3] S. Kunwar, C.B. Wilson, Pediatric pituitary adenomas, J. Clin. Endocrinol. Metab. 84 (1999) 4385–4389.
[4] M.E. Molitch, Diagnosis and treatment of pituitary adenomas: a review, JAMA 317 (2017) 516–524.
[5] D. Theodros, M. Patel, J. Ruzevick, M. Lim, C. Bettegowda, Pituitary adenomas: historical perspective, surgical management and future directions, CNS Oncol. 4 (2015) 411–429.
[6] C. Webb, R.A. Prayson, Pediatric pituitary adenomas, Arch. Pathol. Lab. Med. 132 (2008) 77–80.
[7] P. Famini, M.M. Maya, S. Melmed, Pituitary magnetic resonance imaging for sellar and parasellar masses: ten-year experience in 2598 patients, J. Clin. Endocrinol. Metab. 96 (2011) 1633–1641.
[8] U.J. Knappe, D.K. Ludecke, Transnasal microsurgery in children and adolescents with Cushing's disease, Neurosurgery 39 (1996) 484–492.
[9] T. Mindermann, C.B. Wilson, Pediatric pituitary adenomas, Neurosurgery 36 (1995) 259–268 discussion 269.
[10] L.J. Orvidas, J.L. Kasperbauer, F.B. Meyer, D. Zimmerman, Pediatric transseptal transsphenoidal pituitary surgery, Am. J. Rhinol. 14 (2000) 265–271.
[11] I. Ciric, A. Ragin, C. Baumgartner, D. Pierce, Complications of transsphenoidal surgery: results of a national survey, review of the literature, and personal experience, Neurosurgery 40 (1997) 225–237.
[12] M. Yamaguchi-Okada, N. Inoshita, H. Nishioka, N. Fukuhara, S. Yamada, Clinicopathological analysis of nonfunctioning pituitary adenomas in patients younger than 25 years of age, J. Neurosurg. Pediatr. 9 (2012) 511–516.
[13] M.D. Partington, D.H. Davis, E.R. Laws Jr., B.W. Scheithauer, Pituitary adenomas in childhood and adolescence. Results of transsphenoidal surgery, J. Neurosurg. 80 (1994) 209–216.