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Clinical characteristics and surgical outcome of prolactinoma in patients under 14 years old

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Abstract

Prolactinoma is one of the most common pituitary tumors, but relatively uncommon in patients under 14 years old. Surgery is the second-line treatment for prolactinoma when patients show resistance or intolerance to medical therapy. There are only a few published series of children who underwent surgery treatment. This study is performed to investigate the clinical manifestation and surgical outcome of pituitary prolactinoma in patients under 14 years old who are resistant or intolerant to medical therapy of dopamine agonist.

Thirty-six cases were included in a retrospective review of patients under 14 years old operated for prolactinoma between December 1987 and December 2015. Preoperative radiological and endocrinal evaluation was performed on every patient. All patients received operation with trans-sphenoidal approach.

Based on enhanced pituitary magnetic resonance imaging (MRI) taken 2 months after the surgery, total resection was achieved in 16 patients (44.4%) and subtotal resection in 20 (55.6%). Thirty-four cases (94.4%) showed remarkable decrease of prolactin (PRL) level 7 days after surgery, and 16 (44.4%) returned to normal. All patients were followed up for 2 years. Tumor regrowth or recurrence occurred in 5 patients and secondary treatment was applied, including drug treatment in 2 patients, second surgery in 2, and radiotherapy in 1.

Trans-sphenoidal pituitary surgery is an effective treatment for prolactinoma in patient under 14 years old. There is no significant difference between the patients under 14 years old and adults for prolactinoma in characteristics and treatment.

Abbreviations: CT = computed tomography, DA = dopamine agonist, MRI = magnetic resonance imaging, PRL = prolactin, PUMCH = Peking Union Medical College Hospital.

Keywords: adolescent, child, prolactinoma, surgery, trans-sphenoidal approach

Highlights

- Trans-sphenoidal pituitary surgery is an effective treatment for prolactinoma patients under 14 years old who resistant to or intolerant of medical therapy.

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1. Introduction

Prolactinoma is one of the most common pituitary tumors, but patients under 14 years old are relatively uncommon. The first-line treatment for prolactinoma in both adults and children is dopamine agonist therapy. While surgery is indicated when patients are resistant to or intolerant of bromocriptine or cabergoline. There are only a few published case series of surgical treatment on prolactinoma in childhood and adolescence.[1,2] In the department of neurosurgery of Peking Union Medical Hospital (PUMCH), we collected 36 cases of prolactinoma under 14 years old that took surgical treatment between December 1987 and December 2015, and analyzed the clinical presentation, treatment, and prognosis in these young patients.

2. Patients and methods

2.1. Patient population

In a retrospective review of prolactinoma patients under 14 years old at PUMCH between December 1987 and December 2015, 26 out of 735 cases were resistant to dopamine agonist (DA) therapy, which is defined as inability to induce prolactin (PRL) normalization after 3-months DA therapy (with increasing doses up at least to 15 mg bromocriptine per day or 3 mg cabergoline per week).[3] Ten out of 735 cases were intolerant of DA therapy, which is defined as hindrance on drug compliance due to adverse side effect, the intolerance rate reported here is much lower than that reported in adult patients before.[4,5] Among the 10 patients

with DA therapy intolerance, 8 reported dizziness, 2 reported headache, 7 reported nausea, vomiting, or constipation, and 4 reported persistent low blood pressure. The symptoms are consistent with that reported in pediatric prolactinoma patients.[2]

Those 36 patients, 11 men and 25 women, underwent prolactinoma surgery at PUMCH and were thus included in this study. Upon admission, the average course of disease was 35.5 months, 2 patients had undergone radiotherapy, another 2 had undergone surgery but developed recurrence. One patient developed recurrence in 14 months, and the other one developed recurrence in 15 months. This study was approved by the institutional review boards of PUMCH. Prior written informed consent was obtained from every patient and their parents.

2.2. Preoperative evaluation

Radiological evaluation was performed on every patient, magnetic resonance imaging (MRI) in 33 cases, computed tomography (CT) in 3 cases. Based on the pneumatization of sphenoid sinus, 18 cases (50.0%) are classified as full-sellar type, 10 cases (27.8%) as pre-sellar type, and 8 cases (22.2%) as conchal type. Serum PRL level was also measured on every patient (normal range: men: 2.64–13.13 ng/mL, women: <30 ng/mL).

2.3. Surgery

Based on the evaluation of tumor size, growth direction, presence of invasiveness and sphenoid sinus development, trans-sphenoidal approach was adopted for all patients, 10 cases under microscope, 17 under endoscope, and the remaining 9 with both. For patients with full-sellar and pre-sellar type sphenoid sinus, surgeries were performed with conventional method, and the rest were guided by neuro-navigation.

2.4. Follow-up

Thirty six cases were all followed up for 24 months via outpatient clinic visit. Symptoms, pituitary MRI, and serum PRL level were assessed for the follow-up.

3. Results

3.1. Clinical presentation

On preoperative evaluation, among the 11 men and 25 women enrolled, 23 women had menstrual disturbances and/or amenorrhea, 18 women had lactation, 9 men and 8 women had vision loss, 7 men and 8 women had headache and/or dizziness, 3 men and 3 women had visual field defect, 5 men had gynecomastia. Weakness, nausea, and vomiting were also reported.

3.2. Preoperative evaluation

Based on radiological evaluation, 4 cases (11.1%) had microadenoma (tumor diameter ≤10 mm), 27 cases (75.0%) had macroadenoma (10 mm < tumor diameter ≤ 40 mm), the remaining 5 cases (13.9%) had giant adenoma (tumor diameter ≥40 mm). Nine cases (25.0%) were diagnosed as invasive pituitary adenoma (Knosp grade ≥3).[2]

Serum PRL level of the 36 patients ranged from 60.5 to 27,341.0 ng/mL, with a mean PRL level of 2946.9 ng/mL. Among all, 31 patients with macroadenoma (26/27) or giant adenoma (5/5) had a PRL level over 200 ng/mL, while 4 patients with microadenoma (4/4) and 1 patient with macroadenoma (1/27) <200 ng/mL.

3.3. Surgical results

Based on enhanced pituitary MRI taken 2 months after the surgery, total resection of the pituitary adenoma was achieved in 16 cases (44.4%), while the remaining 20 cases (55.6%) were sub-total resected because of the invasion of cavernous sinus.

PRL levels were measured 7 days after surgery. PRL level decrease was shown in 34 cases. In 16 cases, postoperative serum PRL level returned to normal. PRL level in 2 cases remained elevated or higher than the level before surgery (Table 1). Average postoperative serum PRL level of 36 patients was 128.6 ng/mL. Patients with postoperational hyperprolactinemia were treated with DA therapy again.

3.4. Pathology

The diagnosis of pituitary prolactinoma was confirmed histologically. Immuno-histological staining revealed PRL (+) in 31 patients (86.1%). Staining for P53 in 11 cases was all negative. Ki-67 index was obtained in 13 cases, 3 of them had a Ki-67 index ≥3%, all 3 were men with giant adenoma. Four cases of microadenoma and 6 cases of macroadenoma had a Ki-67 index <3%.

3.5. Complications

Complications were observed in 12 patients. Temporary diabetes insipidus occurred in 6 patients. Other complications include dizziness and/or headache in 5 cases, fever in 4 cases because of the infection, electrolyte disturbance in 2 cases, weakness in 1 case, and sleepiness in 1 case.

3.6. Follow-up

Thirty six cases were all followed up for 24 months. Twenty three patients showed remarkable clinical improvement after surgery. Nine patients showed mild remission. There is no obvious clinical improvement in the remaining 4 patients.

Table 1

Postoperative serum PRL levels and MRI evaluation in 36 patients with pituitary prolactinoma.

	PRL level			Post-op MRI	
	Normal*	Reduced**	High***	Total resection	Subtotal resection
Microadenoma	3	1	0	3	1
Macroadenoma	13	14	0	13	14
Giant adenoma	0	3	2	0	5

MRI = magnetic resonance imaging, PRL = prolactin.

* Normal means that PRL level between 2.64 and 13.13 ng/mL.

** Reduced means that PRL level decreased by ≥50% after surgery.

*** High means that PRL concentration remained elevated or higher after surgery.

Based on pituitary MRI and serum PRL level during follow-up, 4 patients who underwent subtotal resection showed regrowth, and 1 patient with total resection showed recurrence. Two of them chose medical therapy and 2 underwent another surgery. Only 1 patient chose radiotherapy. Besides, all 5 patients featured a postoperative serum PRL levels >10 ng/mL, while no recurrence was observed in the 8 cases with postoperative PRL level <10 ng/mL.

4. Discussion

In our study, trans-sphenoidal surgery was performed on 36 medically refractory patients with 16 total resections and 20 subtotal resections. Among all 36 cases, no perioperative death was observed, and 24 showed no postoperative complications. In 3 out of 4 cases with microadenoma and 13 out of 27 cases with macroadenoma, serum PRL levels returned to normal, while no cases with giant adenoma showed normal PRL level after surgery. During 2 years follow-up, 23 patients showed remarkable clinical improvement, while only 4 patients showed regrowth, and 1 patient showed recurrence. Our study demonstrated that trans-sphenoidal surgery is an effective way for those patients under 14 years old with medically refractory prolactinoma with the proof of postoperative PRL level and MRI findings, combined with low recurrence and regrowth rate.

Pituitary prolactinoma is the most common form of pituitary adenomas in childhood and adolescence and more common in adolescence with a sex ratio around 1:2.3 (male:female) in our study. Clinical presentation includes menstrual disturbance, lactation and amenorrhea in women, and erectile problems and gynecomastia in men. Amenorrhea in young female patients is usually mistaken as late menarche by their parents, and menstrual disturbance in adolescents can hardly draw enough medical attention. Symptoms in men are even harder for parents to recognize. Therefore, the diagnosis of prolactinoma in patients under 14 years old is often delayed.

The diagnosis of prolactinoma was made based on clinical presentation, radiological evidence of pituitary adenoma, and obvious elevation of serum PRL. Prolactinoma is the most common reason of hyperprolactinemia, but still, sellar lesion other than prolactinoma (including other forms of pituitary adenoma and vacuole turcica) and other possible reasons like inflammation should be excluded.[6] Generally, prolactinoma is diagnosed when serum PRL level is >200 ng/mL. And serum PRL level >250 ng/mL usually indicates macroprolactinoma. For patients with PRL level under 200 ng/mL, diagnosis should be made with consideration on clinical presentation and sellar MRI.[6]

In patients with no indication for emergency operation (acute pituitary apoplexy, rapid progress of vision loss, leakage of cerebrospinal fluid) or drug resistant, medical therapy of dopamine agonist (DA) is the first-line treatment for prolactinoma.[7] In the majority of patients with prolactinoma, DAs are effective in suppressing serum PRL levels, restoring fertility, terminating lactation, and reducing tumor size. Bromocriptine, cabergoline, and quinagolide are most widely used DA drugs, and are recommended for patients in childhood and adolescence. Comparing with bromocriptine, cabergoline is more effective in lowering PRL levels, reducing tumor size, and have less adverse effects.[3] Thus, it is preferable as the first-line drug in adult patients. Currently, bromocriptine is used as initial therapeutic agent in China, while cabergoline has not been approved for clinical application yet. The efficacy of quinagolide is not clear due to a lack of large-scale clinical trials. Current challenge of medical therapy is that some patients are resistant to DAs. Drug resistance rates of bromocriptine, cabergoline, and quinagolide are 24%, 11%, 13%, respectively.[8] Clinical investigation shows that individuals react differently to different DAs, and different patients react differently to the same DA.[9]

Surgical treatment is indicated when patients are resistant to or intolerant of medical therapy.[10] Trans-sphenoidal pituitary surgery is preferred among all approaches, due to its safety, minimal invasion, and maximal reservation of the normal function of the remaining pituitary.[4]

Furthermore, radiotherapy is considered when medical treatment or surgery is invalid. As a third-line treatment, radiotherapy is not efficient in hormone level control, and may lead to multiple complications. Possible complications of radiotherapy include hypopituitarism, diabetes insipidus, visual disorders, cognitive disorders, and death.[11]

The prognosis of pituitary prolactinoma in childhood and adolescence depends on multiple factors such as tumor invasion,[12] tumor size, postoperative serum PRL levels, degree of surgical resection, pathological type of tumor, and sensitivity to DAs.

In long-term follow-up, the cure (defined as a reduced to normal serum PRL level) rate of microadenoma is around 62%, while that of macroadenoma is only 16%. Meanwhile, recurrence is still observed in cured patients in long-term follow-up.[13] Amar et al[14] suggested that serum PRL level <10 ng/mL after 1 week from surgery predicts a long-term endocrinal cure in patients with prolactinoma. In contrast, an endocrinal cure is not likely to be achieved in patients with normal PRL >10 ng/mL. In our study, 8 cases had an early postoperative PRL level <10 ng/mL, with no recurrence at follow-up. In all cases with recurrence or regrowth, early postoperative PRL levels were >10 ng/mL.

Postoperative residual tumor is one of the main causes of recurrence.[15] Residual tumor is relevant to the size, morphology, invasion, blood supply of the original tumor as well as the surgical technique of surgeons.[16] In patients with residual disease or uncontrolled PRL level, postoperative DA therapy is recommended to reduce recurrence.[17]

5. Conclusions

Trans-sphenoidal pituitary surgery is an effective treatment for prolactinoma in patient under 14 years old. There is no significant difference between the patients under 14 years old and adults for prolactinoma in characteristics and treatment.

Author contributions

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