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Evaluation of the Factors Predicting the Outcome of Transsphenoidal Microsurgery in Patients with Premenopausal Microprolactinoma

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Abstract：Although cabergoline is an effective first–line treatment for prolactinoma, transsphenoidal microsurgery remains useful for the treatment of microprolactinoma. We investigated the factors that predict the outcome of transsphenoidal microsurgery and also evaluated indications for this method in patients with prolactinoma. We reviewed the cases of 21 premenopausal patients with prolactinoma, who had undergone magnetic resonance imaging (MRI). The clinical characteristics, preoperative prolactin level, adenoma size, MIB–1 labeling index, and cavernous sinus invasion were evaluated. Cavernous sinus invasion was graded according to Knosp's MRI classification. The preoperative prolactin level (P=0.0268) and grade of cavernous sinus invasion (P=0.0284) were statistically significant predictors of a surgical cure for patients with prolactinoma. As a result, transsphenoidal microsurgery is considered to be an effective therapy for appropriately selected premenopausal patients with prolactinoma. We believe that patients with either low Knosp's grade (0 or 1) and/or a preoperative prolactin level of <100 ng/ml would benefit most from transsphenoidal microsurgery as a first–line treatment.

Key words：**Prolactinoma, Microadenoma, Cabergoline, Grade, Premenopausal, Transsphenoidal microsurgery**

Introduction

Dopamine agonist cabergoline is used as the first–line treatment for prolactinoma because of its efficacy and safety.[1)–8)] Studies of the remission rate of microprolactinoma in response to microsurgery report rates ranging from 38% to 91%.[9)–13)] However, most of these reports evaluated remission by computed tomography (CT). Dopamine agonists comprise long–term therapy, with occasional resistance and side effects such as nausea, dizziness, and fatigue.[4)14)–16)] We believe that (except regarding the matter of surgical cost) transsphenoidal microsurgery thus remains a useful treatment for microprolactinoma. We investigated factors, in particular magnetic resonance imaging (MRI), which are predictive of microsurgery outcome and evaluated indications for transsphenoidal microsurgery in patients with prolactinoma.

Subjects and Methods

We retrospectively studied 21 premenopausal patients with prolactinoma who had undergone transsphenoidal microsurgery during the period from 1994 to 2004. All patients had undergone MRI. Postoperative follow–up periods ranged from 23 to 135 months (median, 61 months). As statistical analysis was performed to ascertain the prognostic importance of the following variables：age, duration of amenorrhea, preoperative prolac-

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Table 1. Clinical characteristics of patients with prolactinoma

Case (no.)	Age (yrs)	Duration of amenorrhea (months)	Pre－op. PRL (ng/ml)	Grade	MIB-1 LI (%)	Size	Post-op. medication*
1	36	36	49	0	1.5	0	－
2	21	7	98	0	6.2	1	－
3	27	14	94.6	0	6.6	0	－
4	26	12	40	0	1.6	1	－
5	30	48	193.3	0	2.7	0	＋
6	18	36	655	1	5.9	1	＋
7	21	72	145	1	1.6	0	－
8	36	36	452	1	3.3	2	－
9	20	24	390	1	3.7	0	－
10	27	8	88	1	3.7	0	－
11	25	60	247	1	5.8	1	＋
12	35	168	288	1	1.1	0	－
13	35	180	678	1	1.4	2	＋
14	24	10	732	1	1.2	1	＋
15	36	36	135.2	1	1.3	2	－
16	33	6	102	2	2.0	0	＋
17	19	22	5,070	2	1.4	2	＋
18	31	6	559	2	3.2	2	＋
19	20	12	1,037	2	5.4	2	＋
20	23	7	394	2	6.1	0	＋
21	22	6	218	2	4.6	0	＋

Pre-op. PRL, prolactin ; MIB-1 LI, MIB-1 labeling index ; Post op., postoperative.
Size:0, intrasellar; 1, suprasellar extension beneath the optic chiasm; 2, reaching and/or extending beyond the optic chiasm.
*－ : After surgery the serum prolactin level had been normalized without medication during the follow-up period.

Table 2. Comparison of postoperative medication and clinical parameters with Fisher's exact test

		Post-op. medication (n)		Fisher's *P* value
		－	＋	
Age (yrs)	0	3	6	
	1	3	1	
	2	4	4	0.394
Duration of	0	3	6	
Amenorrhea (months)	1	4	2	
	2	3	3	0.490
Pre-op. PRL	0	2	0	
	1	3	0	
	2	3	4	
	3	2	7	0.035*
Grade	0	4	1	
	1	6	4	
	2	0	6	0.015
MIB-1 LI	0	5	5	
	1	5	6	1.000
Size	0	6	4	
	1	2	3	
	2	2	4	0.640

Post-op., postoperative ; Pre-op., preoperative.
Age : Group 0, 18-24 yrs ; Group 1, 25-29 yrs ; Group 2, 30-36 yrs.
Duration : Group 0, <1 yr ; Group 1, 1 to <3 yrs ; Group 2, >3 yrs.
Pre－op. prolactin (PRL) level : Group 0, <50 ng/ml ; Group 1, 50-100 ng/ml ; Group 2, 101-300 ng/ml ; Group 3, >300 ng/ml.
MIB-1 LI : Group 0, < 3 % ; Group 1, > 3 %. *P<0.05

Table 3. Univariate logistic regression analysis of various preoperative parameters

	Post-op. medication (mean+/− SD)		*P* value	R (contribution)
	+ n=11	− n=10		
Age	25.45±5.89	28.5±6.72	0.2674	0
PRL	898.66±1412.28	178.03±146.11	0.0347	0.29
MIB-1 LI	3.61±1.99	3.06±2.03	0.5169	0
Duration of ammenorhea (months)	35.73±51.42	41.30±48.61	0.4567	0
Size			0.2897	0
Grade			0.0284	0.31

Post-op., postoperative ; PRL, preoperative prolactin value ; MIB-1 LI, MIB-1 labeling index ; n, number

tin level, adenoma size, MIB-1 labeling index, and the extent of the tumor in the cavernous sinus. Postoperative remission was defined as a normal prolactin level with no need for medication after surgery.

Tumor invasion of the cavernous sinus was evaluated according to Knosp's MRI classification.[17] Grade 0 denotes a normal cavernous sinus with no lateral tumor extension. In grade 1, the tumor passes the medial tangent of the intra- and supracavernous internal carotid arteries (ICAs) but it does not go beyond the midline of the ICAs. In grade 2, the tumor extends beyond the midline, but not beyond the lateral tangent of the ICAs. In grade 3, the tumor extends beyond the lateral tangent of the ICAs.

Statistical analysis

All statistical analyses were performed with the version 12.0 SPSS software program (SPSS, Inc., Chicago, IL, USA). *P* values <0.05 were considered statistically significant.

Results

The clinical data are listed in Table 1. Five cases were identified as grade 0, 10 as grade 1, and six as grade 2. Grade 3 was not identified in this study. Of the Grade 0 patients, 20% took medication after surgery, as did 40% of the Grade 1 patients and all of the Grade 2 patients. Surgical remission was observed in 100% of patients with preoperative prolactin levels <100 ng/ml and in 78% of patients with those <200 ng/ml. All patients exhibited normal prolactin levels after microsurgery, resumed regular menses, or became pregnant during the study.

Table 4. Spearman's rank correlation coefficient

		Correlation coefficient	
		r	*P* value
PRL	vs. grade	0.631	0.002
PRL	vs. size	0.471	0.031
Grade	vs. size	0.251	0.35
MIB-1 LI	vs. grade	0.196	0.396

PRL, preoperative prolactin value;MIB-1 LI, MIB-1 labeling index.

We used Fisher's exact test to investigate whether each studied parameter influenced the requirement for medication after surgery (Table 2). The preoperative prolactin level ($P=0.035$) and grade ($P=0.015$) significantly correlated, with no requirement for postoperative medication. We performed univariate comparisons between putative predictor variables and the requirement for postoperative medication (Table 3). Preoperative prolactin level ($P=0.0347$) and grade ($P=0.0284$) were again found to be statistically significant factors. We then investigated the correlations between each parameter with the Spearman correlation coefficient (Table 4). Grade versus preoperative prolactin level ($r=0.631$, $P=0.002$) and preoperative prolactin level versus adenoma size ($r=0.471$, $P=0.031$) showed statistically significant correlations. Grade and preoperative prolactin level were strongly correlated. Accordingly, we used two types of multivariate logistic regression analysis. One included a grading parameter, while the other did not. We performed a multivariate logistic regression analysis including the grading parameter (Table 5). Grade was the only statistically significant outcome factor ($P=0.0284$, odds ratio=9.98). We also performed an adjusted multivariate analysis excluding the grading pa-

Table 5. Multivariate logistic regression analysis

	β	S.E.	*P* value	R	Odds ratio	(95% C.I.)
*Grade	2.3004	1.0495	0.0284	0.31	9.98	(1.28, 78.05)
#pre－op. PRL	1.7788	0.8031	0.0268	0.32	5.92	(1.23, 28.58)

*：*P* value generated from logistic regression for qualitative variables with adjustment for age, duration of amenorrhea, pre-operative PRL value, grade, MIB-1 LI, and size.
#：*P* value generated from logistic regression for qualitative variables with adjustment for age, duration of amenorrhea, pre-operative PRL value, MIB-1 LI, and size. Grading parameter is excluded.
β, estimated regression coefficient ; S.E., standard error; R, contribution ; C.I., confidence interval ; pre-op. PRL, preoperative prolactin level.

rameter (Table 5), and the preoperative prolactin level was found to be a statistically significant factor (P=0.0268, odds ratio=5.92).

Discussion

Prolactinoma is frequently treated with dopamine agonists, which reduce the tumor size and normalize serum prolactin level. During the 1970s and 1980s, bromocriptine was the established drug for the treatment of prolactinoma. However, bromocriptine can have side effects, particularly nausea and vomiting. Moreover, it must be used as a life-long therapy.[16] Many patients have therfore opted for transsphenoidal microsurgery. The results have been good, with a particularly high cure rate (70%－90%) for microadenoma.[9)10)13)18)-20)] In the late 1990s, cabergoline, a selective dopamine D2 receptor agonist came into use for the treatment of prolactinoma, thus resulting in less frequent side effects and longer lasting benefits.[2)-4)6)-8)] Mild to severe adverse effects of cabergoline include dizziness, headache, nausea, postural hypotension, and fatigue; these side effects were reported in 13%－39.5% of patients undergoing cabergoline therapy.[6)8)] However, only 3%－4% of the patients discontinued cabergoline, a very low rate compared to that for bromocriptine (12%).[6)7)] Many hospitals have recently made cabergoline their first-line treatment for prolactinoma. However, we believe that some problems remain with this treatment. Like bromocriptine, it is a life-long therapy, and some prolactinomas are resistant to cabergoline therapy.

Microprolactinoma occurs more frequently in adolescent and young women.[21)] Cabergoline is very effective and well tolerated in patients with microprolactinoma or macroprolactinoma.[21)] However, appropriate selection of patients with microprolactinoma will allow for a complete cure by surgical management. Colao et al.[15)] reported recurrence rates 2 to 5 years after termination of cabergoline of 31% in patients with microprolactinoma and 36% in patients with macroprolactinoma. They also reported an 8.8% drug resistance rate in patients with prolactin levels that did not normalize (10 of 155 microprolactinomas; 14 of 117 macroprolactinomas). Another study reported that 64% of patients with microprolactinoma treated with dopamine agonist therapy (cabergoline or bromocriptine) experienced recurrence after a termination of therapy.[14)] Ferrari et al.[3)] treated patients with macroprolactinoma with cabergoline and reported normoprolactinemia in 52 of 85 patients (61.2%) and tumor shrinkage in 41 of 62 patients (66.1%). In another report, tumor shrinkage was observed in 93% of the patients with macroprolactinoma and in 74% of patients with microprolactinoma.[22)]

Although cabergoline is very effective and safe in the treatment of prolactinoma, cabergoline resistance and relapse after cabergoline withdrawal remain problematic. When the indications for microsurgery are properly evaluated, we believe that transsphenoidal microsurgery remains a useful treatment for microprolactinoma. To obtain good results with transsphenoidal microsurgery, a preoperative evaluation of the factors predicting surgical outcome is necessary. The present and previous studies have determined that the preoperative prolactin level, tumor size (Hardy classification), and lateral tumor extension are valid predictors of the surgical outcome.[11)-13)23)24)] Tyrrell et al.[13)] reported that 92% of patients with preoperative prolactin levels <100 ng/ml experienced initial surgical remission; however, only 37% with preoperative prolactin levels >200 ng/ml achieved surgical

remission. Other studies have reported remission rates of from 73%－82% in patients with preoperative prolactin levels ＜200 ng/ml.[9)11)24)-26)]

Tumor size is an important factor for the prediction of surgical success. Patients with microadenoma or Hardy classification grades of I or II tend to have successful outcomes.[9)10)12)13)23)24)27)] Preoperative prolactin level correlated with adenoma size.[11) 13) 23)-25)] The present study showed a weak correlation between preoperative prolactin level and adenoma size (r＝0.471, *P*＝0.031). We therefore were unable to statistically show that adenoma size is a good predictor of the surgical outcome.

Most early microsurgical reports concerning the surgical outcome for microprolactinoma were performed with CT or CT and MRI.[9)-13)23)24)] However, it is difficult to preoperatively determine the extent of tumor invasion in the cavernous sinus by CT. In the present study, we reviewed only MRI cases and found that the best predictive factor of surgical success was Knosp's MRI grading system.[17)] The surgical findings indicate that Knosp's MRI grade correlates highly with tumor invasion of the cavernous sinus. This grading system was the best statistical predictor of surgical success in the present study (odds ratio＝9.98; 95% confidence interval, 1.28－78.05; *P*＝0.0284). With the use of monoclonal antibody KI－67, Knosp et al.[17)] also showed a good statistical correlation between MRI grade and tumor cell proliferation rate. In the present study, we were unable to show any correlation between Knosp's MRI grade[17)] and MIB-1 labeling index (r＝0.196, *P*＝0.396). However, our data were limited, and an investigation of more cases with the MRI grading system and MIB-1 labeling index is thus required.

In conclusion, cabergoline is an effective medication therapy and it should remain as the primary treatment for macroprolactinoma. However, in appropriately selected patients, transsphenoidal microsurgery is also effective for the treatment of microprolactinoma. In such cases, we believe that Knosp's MRI grading system[17)] is the best predictor of surgical success. Transsphenoidal microsurgery is recommended for patients who show either a low grade (0 or 1), a preoperative prolactin level of ＜100 ng/ml or both.

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