The characteristics of acromegalic patients with hyperprolactinemia and the differences with hyperprolactinemia patients

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Abstract: A substantial proportion of acromegalic patients have co-existent hyperprolactinaemia. To compare this group of population (AC+HPRL) to those of patients with merely hyperprolactinemia (HPRL), a retrospective analysis of patients was conducted. Data regarding clinical and immunohistochemical features, and outcome for patients were reviewed throughout the follow-up period. Four hundred and twenty-three patients were enrolled, with 329 in patients with HPRL and 94 in patients with AC+HPRL. Patients in the AC+HPRL group had a younger age at diagnosis (38.13±13.31 *vs.* 41.95±14.70 years; p=0.025) and a higher rate of invasion (p=0.007) than those in the HPRL group. The AC+HPRL group had higher GH levels but relatively lower PRL levels than the HPRL group before and after surgery. The rates of positive staining for GH and PRL in HPRL group were 15.20% and 93.01%, and the rates in AC+HPRL group were 84.04% and 87.23%. Patients with HPRL had a lower recurrence rate compared with patients in AC+HPRL group (p=0.018). Additionally, there were no significant correlations between the mean degree of preoperative GH or PRL and the positive rates of immunostaining (p>0.05, p>0.05). The Ki-67 indexes in HPRL group and AC+HPRL group were 3.07%±2.13 and 2.33%±1.71, respectively (p=0.001). In conclusion, acromegalic patients with hyperprolactinemia need careful and long-term follow-up following an operation.

Keywords: Acromegaly, hyperprolactinemia, GH, PRL, immunostaining.

INTRODUCTION

Acromegaly is severe endocrine disease with excess growth hormone (GH) production caused by a pituitary adenoma (Gillam *et al.*, 2006). It is common belief that patients with GH-secreting pituitary adenomas often release prolactin (PRL) (Pita-Gutierrez *et al.*, 2013). Around 16-27% of acromegalic patients have increased hormonal levels of GH and PRL (Horvath and Kovacs, 2006; Zielinski *et al.*, 2013). Andersen *et al.* (Andersen *et al.*, 1995) reported that 4-week octreotide treatment could normalise PRL levels in acromegalic patients with hyperprolactinaemia. The same pituitary cells in human pituitaries can store and secret both GH and PRL (Mulcahy and Jaffe, 1988). Nevertheless, very little information is available on the differences such as incidence, symptom, recurrence rate, immunohistochemical staining, and other characteristics of adenomas between acromegalic patients with hyperprolactinemia and patients with merely hyperprolactinemia.

In this study, we retrospectively reviewed 329 patients with merely hyperprolactinemia and 94 acromegalic patients with hyperprolactinemia. The aim of this study was 1) to assess the characteristics of acromegalic patients with hyperprolactinemia; and 2) to investigate the correlations between hormonal values, immunohistochemis staining and the clinical course by comparing the differences to patients with merely hyperprolactinemia during a long-term follow-up period. We collected data from an 8-year follow-up study and analyzed all basal hormone values, immunohistochemical staining, magnetic resonance imaging (MRI), complications, early remission and recurrence rate.

MATERIALS AND METHODS

Population

The 423 subjects were enrolled in this study. All patients were hospitalized and underwent primary trans-sphenoidal surgery at the Department of Neurosurgery, Shandong Provincial Hospital from 2002 to 2010. In this study, there were 119 males and 304 females. The range of age is from 13 to 76 (a median of 37) years. The range of follow-up period is from 15 to 76 months (median 33 months). The patients were categorized into the following groups: HPRL group (patients with hyperprolactinemia) and AC+HPRL group (acromegalic patients with hyperprolactinemia). Data were obtained from medical record database and telephone follow-up after surgery. Informed consent was obtained from each individual. The research protocol was approved by the Ethics Committee of Shandong Provincial Hospital.

Study assessments

According to Lania and Beck-Peccoz (2012), the tumor smaller than 10 mm in diameter defined as a micro adenoma, whereas the tumor larger than 10 mm defined

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as a macro adenoma. According to Knosp *et al*. (1993) and Cottier *et al.* (2000), tumors were subdivided into invasive tumors and noninvasive tumors. The serum level of PRL was measured using chemiluminescence kits (Beckman Coulter, Inc., CA, USA). The normal range of PRL in males was 2.64-13.13ng/ml in premenopausal was 3.34-26.72ng/ml, and 2.74-19.64ng/ml in premenopausal females. GH was measured using a chemiluminescence immunoassay (Roche Diagnostics GmbH, Mannheim, Germany). The normal range of GH was 0.12-7.79 ng/ml. The intra-assay variation coefficients of these assays was <10%, and the inter-assay variation coefficients of these assays was <15%. The degree of PRL and GH were re-assessed at 3 days, 3 months, and 1 year postoperatively.

Pathological evaluation

The resected tumour fragments were fixed in 10% buffered formalin, stained with routine histochemical methods for haematoxyin-eosin (H&E), embedded in paraffin blocks. Immunohistochemical analysis was also performed on specimens using specific antibodies against GH (Rabbit Polyclonal Antibody, Maxin Co. Ltd., Fujian, China) and PRL (Rabbit Polyclonal Antibody, Maxin Co. Ltd., Fujian, China). Upright fluorescence microscope (Olympus BX53, Olympus Co. Ltd., Japan) was used to record the images. The proliferative activity was assessed by Ki-67 (DAKO, Monoclonal Antibody, clone MIB-1).

Follow-up

The period from the onset of symptoms to the last entry defined as the follow-up period. The recurrences were defined as when clinical features, hormonal and residual tumor in the patients were substantially evident.

STATISTICAL ANALYSIS

Quantitative data were presented as mean ±standard deviation (Sd). Qualitative data were presented as percentages. Quantitative data were compared by Mann-Whitney U test. Qualitative data were compared using Chi-square test. Analysis performed by the SPSS 16.0 (Chicago, IL, USA). P<0.05 was considered statistically significant.

RESULTS

Demographic and tumor characteristics

Table 1 and table 2 summarize the characteristics of patients and tumor parameters. A total of 329 patients with hyperprolactinemia (240 females and 89 males; 41.95±14.70 years old ranging from 13 to 76 years) were studied. The time interval was 37.82±46.35 (range: 0.5 to 324) months. The mean value of maximal tumor diameter was 2.65±1.33 (range: 0.40 to 6.70) cm. Invasion of cavernous sinus was recognized in 41.64% of the patients. Pituitary apoplexy could be recognized in 19.45% of the patients. The AC+HPRL group consisted of 64 (68.09%) females and 30 (31.91%) males. The range of age was 17 to 61 years with a mean of 38.13±13.31 years. The mean time interval was 42.61±53.16 (range: 0.2 to 240) months. The mean value of tumor diameter was 2.74±1.27 (range: 0.50 to 6.00) cm. The invasion rate was present in 57.45% of the patients. Pituitary apoplexy could be recognized in 12.77% of the patients. The average age of patients with HPRL was meaningfully older than patients with AC+HPRL (p=0.025). However, there were statistically significant differences in the rates of invasion in different group. Obviously, the rate in AC+HPRL group was higher than HPRL group (57.45% *vs.* 41.64%, p=0.007). However, we found no differences in mean time interval, tumor size, gender and apoplexy between the two groups.

MRI findings

Among the HPRL patients, 86.63% had macro adenomas and 13.37% had micro adenomas (fig. 1). The AC+HPRL group included 89 (94.68%) macro adenomas and 5 (5.32%) micro adenomas. Overall, macro adenomas were more likely existed in patients with AC+HPRL than patients with HPRL (p=0.031).

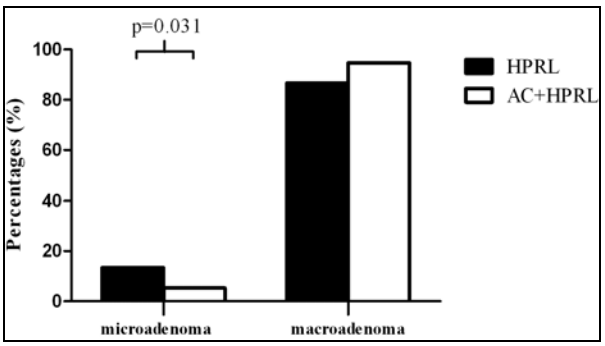

Fig. 1: The classification of tumors in the two groups

Pre-operative clinical manifestations and complications

Tumor-specific clinical features are presented in table 3. The most prevalent symptoms in HPRL were menstrual disorders (59.17%), headache/dizziness (52.28%), visual impairment (50.76%), galactorrhea (44.38%), visual field defects (40.43%) and sexual dysfunction (38.20%). However, in the AC+HPRL group, the most common symptoms were coarse facial features and broadened extremities (53.19%) followed by menstrual disorders (53.13%), headache/dizziness (48.94%), galactorrhea (44.68%) and visual impairment (34.04%). The most common clinical symptoms encountered in the two groups were menstrual disorders and headache/dizziness. Additionally, our study indicated that incidences of coarse facial features and broadened extremities in patients with AC+HPRL were higher compared with patients in HPRL group (53.19% *vs.* 0.00%, p<0.001). However, visual impairment and sexual dysfunction were also mostly associated with HPRL adenomas rather than with AC+HPRL (50.76% *vs.* 34.04%, p=0.004; 38.20% *vs.* 10.00%, p=0.004).

Table 1: Demographic and tumor characteristics of patients

Variables	Group	$\overline{x} \pm s$	$M \pm Q$	Z	p
Mean age (years)	HPRL	41.95±14.70	40.00±25.00	-2.235	0.025
	AC+HPRL	38.13±13.31	34.00±17.00		
Time interval (months)	HPRL	37.82±46.35	24.00±37.50	-1.265	0.206
	AC+HPRL	42.61±53.16	24.00±36.00		
Tumor size (cm)	HPRL	2.65±1.33	2.50±1.70	-0.454	0.650
	AC+HPRL	2.74±1.27	2.50±1.40		

Data were expressed as mean +Sd ($\overline{x} \pm s$). P<0.05 was considered statistically significant.

Table 2: Gender, invasion and apoplexy of patients

Variables		HPRL (n= 329)	AC+HPRL (n=94)	$\chi 2$	p
Gender	Male	89 (27.05%)	30 (31.91%)	0.855	0.355
	Female	240 (72.95%)	64 (68.09%)		
Invasion	+	137 (41.64%)	54 (57.45%)	7.375	0.007
	-	192 (58.36%)	40 (42.55%)		
Apoplexy	+	64 (19.45%)	12 (12.77%)	2.218	0.136
	-	265 (80.55%)	82 (87.23%)		

Data were expressed as n and %. The symbol '+' means the existence of the characteristics in the group. The symptom '-' means the deletion of the characteristics in the group. P<0.05 was considered statistically significant.

Table 3: Pre-operative manifestations and complications

	HPRL (n=329)	AC+HPRL (n=94)	p
Headache/dizziness	172/329 (52.28%)	46/94 (48.94%)	0.567
Coarse facial features /Broadened extremities	0/329 (0.00%)	50/94 (53.19%)	< 0.001
Vomiting	30/329 (9.12%)	10/94 (10.64%)	0.657
Visual impairment	167/329 (50.76%)	32/94 (34.04%)	0.004
Visual field defects	133/329 (40.43%)	30/94 (31.91%)	0.135
Menstrual disorders	142/240 (59.17%)	34/64 (53.13%)	0.384
Galactorrhea	146/329 (44.38%)	42/94 (44.68%)	0.958
Sexual dysfunction	34/89 (38.20%)	3/30 (10.00%)	0.004
Polyuria/polydipsia	10/329 (3.04%)	6/94 (6.38%)	0.134
Hypertension	22/329 (6.69%)	4/94 (4.26%)	0.387
Diabetes mellitus	8/329 (2.43%)	6/94 (6.38%)	0.094

Data were expressed as n and %. P<0.05 was considered statistically significant.

Table 4: Pre- and postoperative levels of GH and PRL

	HPRL		AC+HPRL		P [a]	
	GH (ng/ml)	PRL (ng/ml)	GH (ng/ml)	PRL (ng/ml)	GH	PRL
Before operation	2.44±1.71	165.85±88.40	23.41±15.76	131.10±73.94	< 0.001	< 0.001
3 Days after operation	2.34±1.59	65.25±47.07	13.24±10.88	33.02±15.84	< 0.001	< 0.001
3 Months after operation	2.38±1.68	62.25±49.65	13.19±11.36	31.55±16.74	< 0.001	< 0.001
1 year after operation	2.43±1.64	67.18±50.98	14.81±10.95	33.34±15.14	< 0.001	< 0.001
P [b]	0.438	< 0.001	< 0.001	< 0.001		
P [c]	0.815	0.654	0.583	0.764		

Data were expressed as mean+Sd ($\overline{x} \pm s$). P<0.05 was considered statistically significant.
P [a] Comparative analysis between the two groups at the same time point.
P [b] Comparative analysis before and 3 days after surgery.
P [c] Comparative analysis between different time points after surgery.

Hormonal levels

In patients with HPRL, the PRL level decreased from 165.85±88.40ng/ml preoperatively to 65.25±47.07ng/ml at 3 days, 62.25±49.65ng/ml at 3 months, and 67.18 ±50.98ng/ml at 1 year after surgery. However, the level of GH before and afer surgery remained within the normal range (table 4). In patients with AC+HPRL, the PRL level decreased from 131.10±73.94ng/ml preoperatively to 33.02±15.84ng/ml at 3 days, 31.55±16.74ng/ml at 3 months, and 33.34±15.14ng/ml at 1 year after surgery. GH levels decreased from 23.41±15.76ng/ml to 13.24 ±10.88ng/ml, 13.19±11.36ng/ml, and 14.81±10.95ng/ml at 3 days, 3 months and 1 year after surgery. Both preoperative and postoperative PRL were higher in patients with HPRL than patients with AC+HPRL, but the levels of GH were lower. Concerning the same hormone, there were no obvious differences among the different time.

Immunohistochemistry

The positive rates of staining for GH and PRL in HPRL group were 15.20% and 93.01%, whereas the positive rates in AC+HPRL group were 84.04% and 87.23%. There were significant differences between the GH-positive rates in the two groups ($p<0.001$), whereas the rate of PRL-positive showed no significant ($p=0.073$). In addition, there were no significant correlations between the mean degree of preoperative GH or PRL and the positive rates of immunostaining ($r=+0.084$, $p>0.05$; $r=+0.041$, $p>0.05$). The Ki-67 indexes in HPRL group and AC+HPRL group were 3.07%±2.13 and 2.33%±1.71, respectively ($p=0.001$).

Follow-up

The recurrence rate for the whole subjects after a median follow-up of 33 months (ranging from 15 to 76 months) was 8.5%. The recurrence occurred in 14 patients (4.26%) in HPRL group. However, 10 patients with AC+HPRL (10.64%) had evidence of recurrence. Therefore, the recurrence rate in the AC+HPRL group was higher compared with the HPRL group ($p=0.018$)**.**

DISCUSSION

In recent years, the frequencies of pituitary adenomas producing two or more hormones are increasing (Horvath and Kovacs, 1988; Kageyama *et al.*, 2002). Adenomas with acromegaly are often attended by secretion of PRL or TSH whereas rarely by secretion of ACTH (Nyquist *et al.*, 1994). Mixed pituitary adenomas producing two or more hormones differ in immune response, chemical composition and biological effects (Asa *et al.*, 1992). However, the latent factors causing mixed pituitary adenomas are not well studied. There were few reports so far on surgeries and immunohistochemical analysis for acromegalic patients with hyperprolactinemia or for patients with merely hyperprolactinemia. The aim of the therapy strategy for patients with acromegaly are improving manifestations, reducing hormone levels, and decreasing the recurrence rates.

In our report, the majority of patients were diagnosed in their thirties and forties. Obviously, there was significant age difference between the two groups of patients. The mean age was meaningfully older in patients with HPRL than patients with AC+HPRL. However, our results were not in accordance with the results reported by Andersen *et al.* (2003). In agreement with literature (Mindermann and Wilson, 1994; Molitch, 1997; Raappana *et al.*, 2010), we also found that a large percentage of patients were females in both groups. This may be due to the fact that females usually present evident symptoms such as menstrual disorders, or men are shy to complain about their sexual problems.

The results also showed that the rate of invasion to the cavernous sinus in the AC+HPRL group was higher than the rate in the HPRL group. Cavernous sinus invasion often occurs unilaterally. This may be associated with the surgical morbidity and mortality and a high rate of recurrence. In planning of pharmic and surgical treatment strategies, the diagnosis of cavernous sinus invasion is vital prior to surgery (Scotti *et al.*, 1988; Cukiert *et al.*, 1998; Moreau *et al.*, 1998). Tumor invasion might be explained by the in default of a bony interface in the fossa. In our study, macro adenomas were more likely existed in patients with AC+HPRL. In the literature, it has been estimated that macroadenomas are related to the cavernous sinus invasion (Cukiert *et al.*, 1998).

Excessive secretion of pituitary hormones can result in devastating metabolic complications. The hypersecretion of GH or PRL may result in multifarious manifestations, which can affect many organs. In patients with AC+HPRL, acromegaly facies and broadened extremities, menstrual disorders, headache and dizziness, galactorrhea and visual impairment are the primary manifestations. In addition, the incidence of acromegalic features, such as coarse facial features and broadened extremities, was higher in patients with AC+HPRL than in patients with merely HPRL. Because of the young age and the few characteristics of hyperprolactinemia, our study concluded that the special manifestations in AC+HPRL were result from the hypersecretion of GH. Moreover, the neurological deficits might be caused by the invasion of macro adenoma (more likely in the AC+HPRL group) into the extrasellar space. We concluded that the different clinical manifestations may be due to elevated GH and PRL levels and macro adenoma in the AC+HPRL group.

In our study, patients with AC+HPRL had elevated preoperative GH and PRL levels. Our study also confirmed that these patients often had relatively higher GH levels, which was opposite to the results reported in

the literature (Valenta *et al.*, 1987). Additionally, patients with AC+HPRL had higher degree of GH but lower degree of PRL than patients with merely HPRL before and after surgery.

Evaluation of the proliferative potential of these tumors may provide helpful information for prognosis and treatment. The Ki-67 indexes in HPRL group and AC+HPRL group were 3.07%±2.132 and 2.33%±1.71. Ki-67 is expressed in the active parts of the cell cycle (Brito *et al.*, 2008). In evaluating the extent of proliferative activity in tissue, Ki-67 method is one of the most credible methods. In our cases, patients were diagnosed by endocrine examinations and immunohistochemistry in order to display the proliferative activity of cells producing PRL or/and GH. Many GH cell adenomas are coexpressing PRL, and TSH (Andersen *et al.*, 2003). The immunohistochemical assessment of the mixed adenomas showed that cells contained GH and PRL. In accordance with the research, 79.79% (75/94) of the patients with AC+HPRL showed the positivity for both PRL and GH after immunostaining. Only 10.64% (35/329) of patients with HPRL showed the positivity for double hormone. Therefore, it is necessary for us to consider the pituitary ontogeny to find the cause. Sasaki *et al.* (1992) have studied the anterior pituitaries of fetal pig, they found PRL and GH cells presented to the same regions. In our results, the rates of positive staining for GH and PRL in HPRL group were 15.20% and 93.01%, and the rates in AC+HPRL group were 84.04% and 87.23%, respectively. There was no meaningful association between the GH or PRL levels preoperatively and the immunostaining-positive rates.

Due to the complexity of hormonal combinations in different subtypes, immunohistochemical assessment is of the essence for diagnosis. Moreover, this AC+HPRL has higher recurrence rate in the entire series. Our results also alert the clinicians that acromegalic patients with hyperprolactinaemia may require more aggressive therapy. This may suggest that the pathogenic mechanism of acromegalic patients with hyperprolactinemia is complicated. Furthermore, there was a remarkable discrepancy of recurrence rates. According to the results of our study, patients with AC+HPRL were characterized by the higher recurrence rate compared with the HPRL group. One possible explanation might be that the adenomas with both PRL- and GH-secreting could complicate management of patients with pituitary disease. We hypothesize that most of the high-risk patients may have more aggressive mixed adenomas. This study might be helpful to improve the diagnosis and treatment of acromegalic patients with hyperprolactinaemia.

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