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Clinical Study

Clinicopathological correlates of extrasellar growth patterns in pituitary adenomas

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ABSTRACT

We reviewed clinical, imaging and histopathology details of 297 patients who underwent surgery for pituitary adenomas, with an equal distribution of functional and non-functioning tumors, to examine clinicopathological correlates of extrasellar growth. Knosp grades of 3 and 4 on MRI defined cavernous sinus invasion, Hardy grades of C and D defined significant suprasellar/subfrontal extension, and intraoperative evidence of tumor eroding through the clivus or sellar floor defined infrasellar invasion. Disease status at follow-up was known in 246 patients overall, including 35 patients who were evaluated for progression of residual disease on serial imaging. On univariate analysis, we found several statistically significant associations ($p < 0.05$) including adenoma size with age, sex and tumor protein p53 reactivity; cavernous sinus invasion with size, non-functional status, increased mitotic activity, an elevated MIB-1 proliferation index and p53 reactivity; suprasellar/subfrontal extension with p53 reactivity; and infrasellar invasion with age and tumor size. When adjusting for confounders with logistic regression, several significant associations were evident including adenoma size with male sex and p53 reactivity; cavernous sinus invasion with size and elevated MIB-1 proliferation index; suprasellar/subfrontal extension with p53 reactivity; and infrasellar invasion with adenoma size alone. Patients with early progression of postoperative residual tumor were younger with a non-significant trend towards higher MIB-1 proliferation indices. Individual patterns of extrasellar growth in pituitary adenomas are associated with unique clinical and immunohistochemical profiles. Younger patients with elevated MIB-1 values are probably at high risk for early recurrence of non-functioning tumors. Definitions of atypia must be standardized before more robust assumptions about tumor biology can be established.

1. Introduction

The results of surgical resection of pituitary adenomas, regardless of functional status, are usually rewarding although some tumors require adjuvant therapy for definitive disease control. Surgical management algorithms are, therefore, frequently frustrated by both anatomical configurations that preclude gross total adenomectomy, as well as postoperative periods that are punctuated by disease recurrences. Despite the fact that pituitary adenomas seldom demonstrate malignant potential, local and biochemical relapses contribute significantly to patient morbidity.

Attempts to understand the pathobiology of pituitary neoplasia have included estimations of cell proliferation, mitosis, apoptosis and oncogene expression, with variable conclusions with regard to aggressive tumor behavior. Subarachnoid or systemic metastasis is indisputable evidence of biological aggression, however, pituitary carcinomas are exquisitely rare. Therefore, for routine clinical practice the emphasis remains on identifying factors that relate to failure to achieve local disease control following surgical resection. Cavernous sinus (CS) invasion is the most studied of these factors, however, it is important to recognize that other anatomical factors also determine the feasibility of gross total surgical resection including tumor size and suprasellar extension, as well as infrasellar growth. Each of these factors impacts the feasibility of surgical resection in variable ways, therefore, it is not prudent to oversimplify clinical aggression in pituitary tumors. These observations have formed the basis of the current study in which we sought a holistic approach by characterizing patterns of extrasellar invasion in pituitary adenomas according to their clinical and pathological profiles.

2. Materials and methods

2.1. Patient selection

We studied clinical, radiological and operative details of 328 consecutive patients who underwent transsphenoidal or

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transcranial surgery for pituitary tumors between January 2009 and September 2013. Extensive hemorrhagic necrosis precluded meaningful immunohistochemical study of 31 tumor specimens and, therefore, we restricted our study to 297 pituitary adenomas for the final analyses.

2.2. Clinical and biochemical evaluation

All patients underwent a thorough neurological work-up including formal visual acuity and field testing. Preoperative endocrinological evaluation included routine assessments of serum growth hormone (GH), prolactin (PRL), cortisol, follicle-stimulating (FSH) and luteinizing hormones (LH) and thyroid function tests. Insulin-like growth factor-1 (IGF-1) and post glucose suppression GH levels were estimated in patients with an elevated basal GH value or clinical features of acromegaly. Cushing's disease was evaluated by suppression testing with dexamethasone.

2.3. Radiological evaluation

Radiological evaluation comprised MRI with a dedicated high resolution pituitary imaging protocol. Tumors were graded using Hardy's system. Adenoma sizes were denoted by their maximum anteroposterior, craniocaudal or transverse diameter. CS invasion was defined by Knosp grades of 3 and 4 and infrasellar invasion by definite breach of the sellar floor on intraoperative examination.

2.4. Pathological analysis

All surgically resected specimens were subjected to histopathological analysis including immunohistochemistry. Each tissue sample was fixed in 10% buffered formalin, embedded in paraffin and 5 μm sections were subjected to standard immunohistochemical examination for GH (undiluted), PRL (1:400), FSH (1:200), LH (undiluted), thyrotropin (1:100), adrenocorticotrophic hormone (1:150) and the alpha subunit (1:50; all from Biogenex, San Ramon, CA, USA).

MIB-1 (1:00) and p53 immunostaining (1:10) were performed for all specimens both from (Dako, Glostrup, Denmark). For MIB-1 proliferation indexing, approximately 1000 cells were counted under high magnification and the labeling index was expressed as the fraction of labelled nuclei with dense brown nuclear staining with appropriate positive and negative controls. An increased mitotic index was defined as $\geqslant$10 mitoses per high power field on hematoxylin and eosin staining. p53 immunopositivity in nuclei was graded as occasional and diffuse. All slides were read by a single pathologist (GC).

2.5. Outcome analysis

For non-functional pituitary adenomas (NFPA), postoperative outcomes were based on MRI performed at regular intervals >3 months after surgery. For patients with acromegaly, remission was defined as a basal GH < 1 ng/ml or a suppressed GH < 0.4 ng/ml with normal IGF-1 levels. Remission for patients with Cushing's disease was defined as a basal cortisol level of <5 μg/ml or suppression to <2 μg/ml with 1 mg dexamethasone. As we treat all patients with prolactinomas medically, none of the subjects in this cohort had primary PRL-secreting tumors.

2.6. Statistical methods

Data was analyzed with SPSS statistical software (version 20.0; IBM Corporation, Armonk, NY, USA). We calculated descriptive statistics, mean and standard deviation for continuous variables, and frequency and percentages for categorical variables. The student t-test and chi-squared test or Fisher's exact test were appropriately employed to test the significance of continuous and categorical variables, respectively. A univariate analysis was performed to calculate the odds ratio (OR) and 95% confidence interval (CI) for each factor examined that was potentially related to tumoral aggression. Logistic regression models using covariates with a p value < 0.15 were used to assess the integrity of these associations. A p value < 0.05 was considered statistically significant.

3. Results

Details of the entire cohort are summarized in Table 1. Most patients were adults and there was equal sex distribution. Less than 10% had persistent or recurrent disease following prior surgery. The majority of tumors were macroadenomas and the mean adenoma size was 27.6 ± 14.7 mm. On immunocytochemical analysis, GH and gonadotroph adenomas accounted for the majority of functional tumors and NFPA, respectively.

The results of our analysis are summarized diagrammatically in Supplementary Figure 1. The relations presented represent statistically independent predictors derived from the regression models after adjusting for confounders.

3.1. Correlations with adenoma size

On univariate analysis adenoma size was significantly associated with age, sex and p53 reactivity but not with the MIB-1

Table 1
Characteristics of the pituitary adenoma patient cohort (n = 297)

Variable	Frequency, n (%)	Mean ± SD
Age (years)	-	40.5 ± 12.2
Sex		
Male	152 (51.2)	-
Female	145 (48.8)	-
Clinical and biochemical profile		
Visual impairment	165 (55.6)	-
Hypopituitarism	120 (40.4)	-
Previous surgery	28 (9.4)	-
Adenoma size (mm)		27.6 ± 14.7
Pure intrasellar tumors (Hardy grade A/microadenomas)	88 (29.6)	-
Significant suprasellar/subfrontal extension	148 (49.8)	-
Knosp grade		
0,1,2	175 (58.9)	-
3,4	122 (41.1)	-
Infrasellar invasion	44 (14.8)	-
Surgical approach		
Transsphenoidal	276 (92.9)	-
Transcranial	21 (7.1)	-
Functional adenomas	147 (49.5)	-
GH	105	-
Cushing's disease	40	-
Crooke's hyaline change	1	-
TSH	1	-
Non-functioning adenomas	150 (50.5)	-
Null cell	39	-
Gonadotroph	82	-
Silent corticotroph	25	-
Silent GH	1	-
Silent subtype 3	3	-
MIB-1 proliferation index	-	2.9 ± 1.9%
p53 expression	67 (22.6)	-
Elevated mitotic index	42 (14.1)	-

- = not applicable, GH = growth hormone, SD = standard deviation, TSH = thyroid-stimulating hormone.