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Pituitary macroadenomas (>3 cm) in young adulthood: Pathologic and proliferative characteristics



AND NEUROSURGERY

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ABSTRACT

Background: There are scarce data regarding the significance of the tumor size, hormonal activity and size of the pituitary tumor of the young; therefore, the study was designed to define the relation of the hormonal status of the large pituitary adenomas.

Objective: We compared those features with tumors of the elderly (>40) with the young patients, and analyzed the clinicopathologic and proliferative features of pituitary macro-adenomas in young adulthood (\leq 40).

Methods: 20-year archives of pituitary tumors in our clinics were reviewed and macroadenomas with diameter \geq 3 cm were included in the study. We identified 46 pituitary adenomas and immunohistochemically stained them with pituitary hormones, p53 and Ki-67. Twentyfour cases were \leq 40-year with an age range of 11–40 years (mean 28.0). Twenty-two cases were >40 with an age range of 44–78 years (mean 58.8).

Results: In the young patient group, 15 (62.5%) were functional adenomas (6 prolactinomas, six growth hormone [GH], one adrenocorticotrophic hormone [ACTH] adenoma, two multihormonal [GH + ACTH]) and nine (37.5%) were either gonadotrophic or null cell adenomas. In the elderly group, five (22.7%) were functional adenomas (two adrenocorticotrophic hormone [ACTH] adenoma, one prolactinoma, one growth hormone [GH], one multihormonal [GH + ACTH]) and 17 (77.3%) were either gonadotrophic or null cell adenomas. Ki-67 proliferation index in adenomas of the young was approximately two-folds higher than the elderly (2.7% vs. 1.2%).

Conclusion: In both groups, rare p53 positivity was identified. In conclusion, pituitary macroadenomas of the young show hormonal expression frequently with relatively high Ki-67 proliferation indices.

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1. Introduction

Most of pituitary adenomas are benign but some grow rapidly, spreading to extrasellar tissues and present neurological symptoms similar to other intracranial neoplasms [1]. Although the definition and clinical significance is not clear, some authors describe it as "the giant pituitary adenoma" [1–3].

The term 'giant adenoma' is arbitrarily based on size alone. However, these big sized tumors usually had tendency to invade cavernous sinus, sphenoid sinus, and vasculature. In our series of pituitary adenomas, using the preoperative computerized tomography (CT) and magnetic resonance imaging (MRI) studies, we differentiated the tumors with diameter >3 cm, and then classified them into two groups in regard to the age of the patients (age \leq 40 and >40) in order to identify proliferative features and immunohistochemical hormonal status of large pituitary adenomas particularly in young patients (\leq 40) and compare them with the results of the elderly (>40).

2. Materials and methods

Cases operated between 1991 and 2011 were retrospectively retrieved from the archives of Departments of Pathology and Neurosurgery, Gülhane Military Medical Academy. Data from records of the authors (BD and EG) were assessed to obtain clinical features and the information regarding the size of pituitary adenomas. Forty-six cases with a pituitary adenoma sizing over 3 cm in a single plane on preoperative images were identified (Figs. 1 and 2). Tissue specimens were totally submerged and fixed in 10% buffered formalin. Tissues were processed routinely, cut into 4 μ m thick sections, and stained with hematoxylin–eosin and reticulin.

2.1. Immunohistochemical study

All archival tissue blocks from each case were initially checked by hematoxylin–eosin stained sections to select the representative block with available tissue for immunohistochemical labeling. A 4 μm thick section from each formalinfixed and paraffin-embedded tumor was stained using the primary antibody against prolactin, growth hormone, adrenocorticotropic hormone, follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, (all monoclonal, 1:100; Cell Marque, Rocklin, CA), Ki-67 (clonal, 1:100; Neomarkers, Fremont, CA, USA) and p53 (clonal, 1:100; Santa Cruz Biotechnology, Santa Cruz, CA, USA). Immunohistochemistry was performed automatically (Ventana, Tucson, AZ, USA) using ultraview universal DAB detection kit (Roche Diagnostics GmbH, Mannheim, Germany).

2.2. Evaluation of immunohistochemistry

All immunohistochemically labeled slides of p53 and Ki-67 were manually counted (Figs. 3 and 4). Initially, immunohistochemically stained slides were scanned at low power and then the most intensely stained area was selected to count the positive cells. One thousand cells were counted for each analysis using an ocular grid. The percentage of positive cells was calculated by comparing the number of positive stained cells to total number.

The research protocol was approved by the ethical committee of Gülhane Military Medical Academy.

3. Results

There were 46 patients in the study (15 female, 31 male) and overall mean age was 42.7 years (median 40, range 11–78). Patients were classified into two groups as young adulthood (\leq 40) and elderly (>40). Of all patients involved in the study, 20 (43.5%) pituitary adenomas were hormone-active.

In the young adulthood group, there were twenty-four cases (4 female, 20 male) with a mean age of 28 (range 11–40). Of the young patients, 15 (62.5%) had functional adenomas that consisted of 6 prolactinomas, 6 growth hormone [GH] secreting adenomas, two multihormonal [GH + ACTH]



VL: 673 WW: 13

Fig. 1 – Sagittal T1 enhanced preoperative (on the left) and postoperative (on the right) MR image of the patient with a pituitary tumor of approximately 4 cm in diameter.



Fig. 2 - Coronal T1 enhanced preoperative and postoperative MR images of the same patient.

secreting adenomas and one adrenocorticotrophic hormone [ACTH] adenoma. Of the young patients, 9 (37.5%) had either gonadotrophic or null cell adenomas.

In the elderly group, there were twenty-two cases (11 female, 11 male) with a mean age of 58.8 ranging from 44 to 78. Five (22.7%) were functional adenomas, which consisted of two adrenocorticotrophic hormone (ACTH) adenomas, one prolactinoma, one growth hormone (GH), and one multihormonal (GH + ACTH) adenoma. Of the elderly, 17 (77.3%) were either gonadotrophic or null cell adenomas.

Overall, mean Ki-67 proliferation index of all macroadenomas in the study was 1.9% (range 0.1–8%). Ki-67 proliferation index in adenomas of young adulthood was approximately two-folds higher than the elderly (2.7% vs. 1.2%).

Overall, the mean percentage of p53 positivity of all macroadenomas in the study was 0.9% (range 0–10%). Except one patient with prolactinoma, all of the cases had p53 positivity less than 10% in the young patient group.

4. Discussion

Pituitary tumors constitute 8–12% of all intracranial neoplasms, but they are uncommon in the young and even rare in childhood [3]. In the literature, there are no series of large pituitary macroadenomas or giant adenomas in young patients that present their proliferative characteristics and compare them with the large adenomas of the elderly. Some studies consist of surgically and medically treated micro- and macroadenomas in young patients and present their clinical, endocrine features and surgical outcomes. In the present study, we focused on surgically treated large (>3 cm) pituitary adenomas of young adults. The available tissue enabled us to study the proliferative index and p53 status of tumor and compare them with the large adenomas of the elderly in our series (Table 1).

Pituitary adenomas diagnosed in patients at the age of 21 and younger were frequently hormonally active (80–97%) [1–3]. Nearly two-thirds of the functional adenoma cases were diagnosed as prolactinomas. Pandey et al. reported that the 95.2% of the patients under 18 years old who were operated for pituitary tumors had functioning adenomas, where 47.6% of them were prolactinomas [3]. These patients typically presented with endocrine symptoms related to their adenoma type. Considering all pituitary micro- and macro-adenomas in young patients, prolactinoma is the most common one. In their series, Pandey et al. included 72.1% macroadenomas and 9.3% giant adenomas. Higher percentage of visual deterioration (65.1%) compared to the published data in the literature is attributable to the large number of sizable adenomas in their



Fig. 3 – HE stained sections (left) were examined and the ones with remarkable tumor tissue were selected for hormone detection (prolactin) (second on the left) and further immunohistochemical procedures for Ki 67 (3rd on the left) proliferation indices and p53 expressions (right square).



Fig. 4 – Growth hormone was studied on this slice that was known to be a GH secreting tumor specimen. Third picture from the left and right square reflect the immunohistochemical reflections of Ki67 proliferation index and p53 expression, respectively.

series. Steele et al, in their study group, found out 85% functioning tumors at the age of 21 or younger [1]. Again consistent with the previously published available data, 71% of the hormonally active tumors were diagnosed as prolactinomas [1]. Cannavo et al. reported corroborative data about the hormonally active pituitary macroadenoma and microadenoma rates of 78% and 82%, respectively. Overall, 68% of them were prolactin-secreting tumors. In contrast, around one-third of the adult pituitary adenomas are non-functioning, and as the size of the tumors increases, percentage of non-functioning tumors rises [4]. The frequency of GH adenomas among the micro- and macroadenomas of children and young patients was reported as 7% in Cannavo's series. Steele et al. reported only one patient with GH secreting adenoma among 41 (2.4%) pituitary tumor cases in their series [1], where Pandey et al. reported 21.4% (9 in 42 cases) [3]. The frequency of non-functioning tumors among young pituitary adenomas is negligible.

On the other hand, there are several series of giant pituitary adenomas, which comply with young and elder patients. Their average age ranged between 36.8 and 47.9 [4,5]. Most of the giant adenomas are non-functioning and present with visual field deficits. Among the functioning giant pituitary adenomas, prolactinomas and GH adenomas are detected most frequently [1–6].

In the present study of large pituitary adenomas of young adults, 62.5% of functional (gonadotrophic cell adenomas were

included in the non-functioning portion) large pituitary macroadenomas were differentiated. Distribution of the functional macroadenomas in our series corroborated the data in the literature. The frequency of prolactinoma was 25%. They were all male patients as our institution serves a heterogeneous population of patients that usually comprises young male adults in their twenties. On the other hand, GH adenomas (25%) were also as frequent as prolactinomas. In our series, pathologic diagnosis yielded 37.5% non-functioning adenomas, half of which consisted of gonadotrophic cell adenomas. Most of the patients were older than 30 years.

In a few studies of giant pituitary adenomas, MIB-1 or Ki-67 indices were investigated [5]. In order to establish the clinicopathologic and immunohistochemical features for giant pituitary adenomas, Chacko et al. studied vascular endothelial growth factor, microvessel density (MVD), topoisomerase and MIB-1 immunohistochemically in 28 cases of pituitary adenomas with diameter of 5 cm or more [4]. They found that the MIB-1 labeling index (LI) ranged from 0.1% to 2.4% with a mean value of 0.67%. No tumor showed a MIB-1 LI greater than 3%. Furthermore, mean MIB-1 LI did not differ significantly between hormonal subtypes. In addition, our gonadotrophic adenoma rates kept up with the rate that Chacko et al. reported. They concluded that the giant pituitary adenomas, which they particularly described as those over 5 cm in any one maximum dimension, were invasive, but

(>3 cm) in young adulthood and elderly.			
	Young adulthood (≤40-year) n: 24	Elderly (>40-year) n: 22	Total n: 46
Mean age (range)	28.0 (11–40)	58.8 (41–78)	42.7 (11–78)
Male/Female	20/4	11/11	31/15
Functional adenomas	15 (62.5%)	5 (22.7%)	20 (43.5%)
Prolactinoma	6 (25.0%)	1 (4.5%)	7 (15.3%)
GH adenoma	6 (25.0%)	1 (4.5%)	7 (15.3%)
ACTH adenoma	1 (4.2%)	2 (9.1%)	3 (6.5%)
Multihormonal (GH + ACTH)	2 (8.3%)	1 (4.5%)	3 (6.5%)
Non-functioning adenomas	9 (37.5%)	17 (77.3%)	26 (56.5%)
Ki-67 proliferation index, mean (range)	2.7% (0.1–8%)	1.2% (0.1–3.5%)	1.9% (0.1–8%)
p53 expression, mean (range)	1.6% (0–10%)	0.4% (0–2.7%)	0.9% (0–10%)
GH: growth hormone; ACTH: adrenocorticotrophic hormone.			

Table 1 – Immunohistochemical subtypes, Ki-67 proliferation index and p53 expression of pituitary macroadenomas (>3 cm) in young adulthood and elderly.

meantime, they were slow growing, benign, and gonadotrophic adenomas in subtype most of the time [4].

In a series of 17 pituitary adenomas having a diameter of >4 cm, by using immunohistochemistry, Madsen et al. focused on any potential role for p53 and MIB-1, features alleged to be associated with atypical adenomas [5]. They compared those findings with non-giant, non-invasive gonadotrophic and null cell adenomas. In their study, while MIB-I labeling indices in non-giant adenomas ranged from 0.5% to 3.0% (mean 1.3%), the same entities in giant tumors showed a broad range of 0.6-6.5% with a mean value of 2.7%. Immunoreactivity for p53 was <3% in all cases of giant adenomas with a mean of 0.6%. Despite the aggressive features of massive size and cavernous sinus invasion, immunohistochemical labeling for p53 and MIB-1 were minimally increased. Their findings emphasized that, in predicting the tumor biology and behavior, it was more important to differentiate the adenoma type by IHC to determine the subtype of the hormone, rather than MIB-I LI and p53 immunostaining [5].

In the present study, the mean Ki-67 index in large adenomas of young patients was approximately two-folds higher than that of the elderly (2.7% vs. 1.2%). However, the Ki-67 indices in the young showed a wide range from 0.1% to 8%. Moreover, considerable overlap was present between young and elderly for the Ki-67 indices. No statistically significant difference was observed between groups for Ki-67 proliferation indices. To wrap up, our results concur with that of the published literature implying that most non-functioning giant pituitary adenomas are long standing, slow growing and immunohistochemical expressions do not significantly correlate with invasive behavior overall. More research is needed to determine other specific factors that indicate invasiveness in pituitary adenomas.

Conflict of interest

None declared.

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None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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