4

Pituitary Adenomas – Clinico-Pathological, Immunohistochemical and Ultrastructural Study

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1. Introduction

Pituitary adenomas (PA) constitute about 10% of intracranial neoplasm. Most of them have its origin in adenohypophysis (Cury et al., 2009; Rosai, 1989). They occur most often in adults between the ages of 30 and 60 years, and may have slightly higher incidence in females in early life (20-45 years) and in males in later life (35-60 years) (Davis et al., 2001; McDowell et al., 2011). The majority of pituitary adenomas have a sporadic origin; familial cases represent 5% of all pituitary tumors (Vandeva et al., 2010; Tichomirowa et al., 2009). Couldwell and Cannon (2010) report strong evidence of genetic contribution for predisposition to symptomatic pituitary tumors.

Pituitary adenomas clinically manifest by signs of hypopituitarism, this is caused by the compression of the gland by the tumor which may affect fertility, the compression of other adjacent structures may cause headache and if the optic chiasm is affected visual alterations; secretion of one or more specific hormones can take place (Galland & Chanson, 2009; Melmed, 2010). However, up to 30% of adenomas do not secrete hormones (Cury et al., 2009; Martinez, 1986; Moreno, 2005).

Pituitary adenomas have been classified as: microadenomas (<10mm diameter) and macroadenomas (> 10 mm diameter), according to its size assessed by tomography and magnetic resonance; staining affinity (acidophilic, chromophobic or basophilic); hormonal activity or secretion of growth hormone (GH), prolactin (PRL), thyroid stimulating hormone(TSH), adrenocorticotrophin hormone (ACTH), follicle stimulating hormone (FSH), and luteinizing hormone (LH); and ultrastructural characteristics (Galland & Chanson, 2009; Nosé, 2011). Hardy (1973) classified pituitary adenomas in four grades according to its size and local invasion degree:

Grade I: Microadenomas, measuring less than 10mm in diameter, they minimally alter the radiographic appearance of the sella.
Grade II: Macroadenomas are bigger than 10mm in diameter, they enlarge the sella or exhibit suprasellar expansion, but not cause destruction.
Grade III: Invasive adenomas, locally eroded the sella, and show suprasellar outgrowth.
Grade IV: Strongly invasive adenomas, that destroys adjacent bony structures and with suprasellar outgrowth, including bone, hypothalamus, and the cavernous sinus.

This classification remains valid using computed tomography scanning and magnetic resonance imaging.

Histologically pituitary adenomas are dense cellular tumors, composed by cells with solid nuclei, rounded and uniform. These cells can be arranged in big groups (diffused pattern), around sinusoidal vessels (sinusoidal pattern), or covering connective-vascular axes (papillary pattern). In all PA types, atypia and mitotic cells are rare. Despite the histologically benign aspect, pituitary adenomas may have an invasive behavior (Chang, 2010; Lau, et al., 2010; Li-Ng, 2008; Melmed, 2010; Scheithauer, 1986; Zada et al., 2011;). This factor is not necessarily indicative of malignancy, because tumor growth is slow and metastases are rare. The histological aspect is not different from the rare carcinoma cases (Colao et al., 2010; Crocker, 1978; Kaltsas et al., 2005; Schteithauer et al., 2005; Tena-Suck et al., 2006;).

In most patients the pathologist cannot provide information about the PA behavior, if will be aggressive based on the histological appearance of adenomas, this is because tumors with variations in the size, shape and nuclear density and the presence of bi-or multinucleated cells do not necessarily had a poor prognosis.

The functional classification of pituitary adenomas based on its hormonal activity, assessed by immunohistochemistry technique, and associated with the transmission electron microscopy analysis, has allowed the characterization of neoplastic cells in detail and proposes the classification of the adenomas in 14 different types, this allows a better correlation with the clinical manifestations that the old classification of chromophobe, acidophilic and basophilic pituitary adenomas (Horvath & Kovacs, 1992; Horvath, 1994; Kovacs & Horvath, 1986).

The aim of this investigation is to present a review of different cases of pituitary adenomas studied in the Laboratory of Experimental Neuropathology of National Institute of Neurology and Neurosurgery, correlating the local invasion degree, clinical manifestations, histological aspects, immunohistochemical and ultrastructural features, with the biological behavior, especially with the invasive potential.

2. Methods

One hundred and twenty two cases of pituitary adenomas were studied. They were classified by their local invasion degree according with Hardy classification (Hardy, 1973), endocrine symptoms (clinically functioning and clinically non functioning pituitary adenomas) and by their hormonal secretion, assessed by immunohistochemistry. The evolution of the disease at the time of diagnosis, tumor regrowth, bromocriptine treatment, and time of outcome of the patients, were evaluated to analyze the PA biological behavior.

2.1 Histopathological analysis

The biopsies were divided in two parts; the first one was fixed in phosphate-buffer saline (PBS)-formalin solution, alcohol dehydrated and paraffin-embedded. Five μm sections were stained with hematoxilyn-eosin and Masson's trichrome (Prophet & Arrington, 1992) for PA treated with bomocriptine. In each hematoxylin-eosin stained section was analyzed nuclear pleomorphism and mitosis figures.

2.2 Immunohistochemistry

In other sections, immunohistochemistry (Bratthauer et al., 1994) was performed. Slides of each case were deparaffinized, rehydrated, and rinsed in PBS. Later on, endogenous peroxidase was blocked with 0.25 % H_2O_2/distilled water for 15 min., and blocking with 3% BSA in PBS (Albumin, Bovine, Sigma-AldrichCo. St. Louis USA). The slides were incubated for 1 h in ready to use monoclonal antibodies of pituitary hormones: prolactin, growth hormone (GH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), thyroid stimulating hormone (TSH) (BioGenex, San Ramón, CA) and adrenocorticotropic hormone (ACTH, DAKO, Carpinteria, Ca, at a 1;100 dilution). Normal postmortem pituitaries were used as positive controls for pituitary hormones. To assess the proliferative index of pituitary adenomas Ki-67 antibody was used (Santa Cruz Biotechnology, inc. Santa Cruz CA. USA at 1:100 dilution). After that the sections were washed, and incubated for 30 min. with the secondary antibody (biotinylated anti-Ig, BioGenex, San Ramón, CA). After washing in PBS the sections were incubated for 30 min with peroxidase-conjugated streptavidina complex (BioGenex, San Ramón, CA). The reaction was developed with diaminobenzidine (DAB) using a Dako kit detection system (Dako enVision System Peroxidase. Dako Carpinteria, CA) according to manufacturer's instructions and the sections were hematoxylin counterstained. The immunodetection was analyzed under a wide-field microscope Olympus H2 (Tokyo, Japan). The immunoreactivity to different hormones in tumor cells were estimated as positive or negative, and the Ki-67 labeled index (LI) was assessed by counting the percentage of number of positive / nuclear cells in five 40x fields. Statistics analysis were done to associate Ki-67 labeling index (LI), disease evolution time, and outcome, in functional PA and in non-functional PA, hormone secretion, invasion degree, and tumor regrowth.

2.3 Ultrastructural analysis

The second part of biopsy was processed for its use in electron microscopy to assess the fine structure of PA. The tissues were fixed in 2.5% glutaraldehyde in 0.1 M phosphate-buffer-saline (PBS pH 7.4) and postfixed in 1% tetroxide osmium in the same buffer, dehydrated in alcohol, and embedded in Epon. One-micron thick sections were stained with toluidine blue and examined by light microscopy. Ultrathin sections at the silver/grey area of the spectrum of interference colors were stained with uranyl acetate and lead citrate and examined under Zeiss EM 10 transmission electron microscopy.

2.4 Statistical analysis

Statistical analysis was performed by using the SPSS 13.0 software. ANOVA test and X^2, Kurskal-Wallis were used to evaluate differences and association respectively, among evolution time and follow up with grades of invasion. Bivariate analysis was accomplished by means of Fisher's exact test for association among functional and non-functional PA, or hormonal immunodetection with recurrences. U Mann-Whitney's test was used to assess evolution time and follow up differences among functioning and non-functioning PA. To evaluate differences in Ki-67-LI detection among invasion grades, X^2 Kurskal-Wallis test was done; among functioning and non-functioning PA with recurrences U Mann-Whitney's test was used; and the association of Ki-67-LI detection with hormonal immunodetection, U Mann-Whitney's test was accomplished. P value less than .05 were considered significant.

3. Results

One hundred and twenty two pituitary adenomas were studied between 1988 and 1992. They were organized according to their characteristics, by means of transsphenoidal or transcranial-frontal technique, and the tumors were removed in 60 to 100%. Tumors mainly affected young adult population with a mean age of 41.4 yr. Sixty five (53.3%) were male, mean age of 43.6±14.8 yr (range, 17-71 yr) and 57 (46.7%) were female, mean age of 39.3±14.4 yr (range, 13-75 yr). Twelve patients were under 20 yr (9.8%). Six males with mean age of 18.8 ± 2.4 yr, and 6 females with mean age of 16.1 ± 2.5 yr. Clinically they were 11 functioning PA and 1 non-functioning PA (Table 1).

Grade	Gender	Age (yr)	Evolution Time (yr)	F	NF	Symptoms	IHQ
II	M	17	1	X		Hypogonadism	Prl
II	M	20	2	X		VA Ha Ac	GH
II	F	23	4	X		VA Ha Am-Gal	Prl-TSH
II	M	24	6	X		Cush	Neg
II	M	18	4		X	VA Ha	Prl
III	F	14	2	X		VA Am	Prl
III	M	20	8	X		Gal-Am Gig	Prl-GH
III	F	23	8	X		VA Ha Am-Gal	Prl-ACTH
IV	F	18	4	X		VA Ha Am	Prl
IV	F	18	4	X		VA Ha Am-Gal	Neg
IV	F	13	2	X		VA Am	Prl
IV	M	20	2	X		VA Ac	Prl-GH

F= functioning pituitary adenoma; NF= non-functioning pituitary adenoma; VA= visual alterations; Ha= headache; Am= amenorrhea; Gal= Galactorrhea; Gig= gigantism; Ac= acromegaly; IHQ= immunohistochemical detection.

Table 1. Pituitary adenomas in young cases under 20 years old at the onset of symptoms. The age column is the age at diagnosis.

Twenty two cases (18%) were classified as I and II invasion grades tumors, and 66 cases (54.1%) were in extensive invasion phase (IV grade). The disease evolution time before the first surgery was 2.9±2.3 yr (range, 2 months to 10 years). Of the 122 patients thirty eight patients continued to attend their review appointments (31%). The average follow up time of the patients was 11±7.4 yr (range, 1-27 yr); from 1 to 5 yr, and from 15 to 20 yr, were the most frequent. Only one patient (0.8%) was considered healthy; four deaths have been reported. The remaining patients stopped coming to the Institute to control appointments. Thirty nine (31.9%) cases out of the 122 had recurrence; 23 (58.9%) belong to grade IV PA. In grade III and IV, two patients with recurrences were observed (Table 2).

Grade	Cases n	Gender Female n(%)	Mean Age F/M	Evolution Time Years (mean)	Follow up time Years (range)	Recurrences		
						Cases n (%)	1	2
I	2	1 (50)	33/31	1.5	1	0		
II	20	4 (20%)	39/45	2.1	10.6 (1m-20yr)	6 (15.3%)	6	
III	34	23 (67%)	40/34	3.4	12.1 (2-20)	10 (25.6%)	7	3
IV	66	29 (44%)	39/44	3	10.3 (1-27)	23 (58.9%)	21	2

Table 2. Pituitary adenomas classification by grades of invasion according to Hardy (1973). Disease evolution time, follow up time, and recurrences in each grade are shown.
F= females; M= males; m= month.

3.1 Immunohistochemistry

Prolactin was the most frequent hormone detected by immunohistochemistry (54 cases, 44.2%) (Table 3). Prolactin hormone expression was found in combination with others hormones: 10 were in combination with GH (8.1%), 4 (3.2%) with TSH; 3 (2.4%) with ACTH, and 1 (0.81%) with LH. Fifteen (12.3%) cases were positive for gonadotroph hormones, 5 (4%) for growth hormone, 2 (1.6%) for ACTH, 1 (0.82%) for TSH, 1 (0.82%) multihormonal (HC-FSH-TSH), and 26 (21.3%) cases were negative for all hormones (Fig. 1).

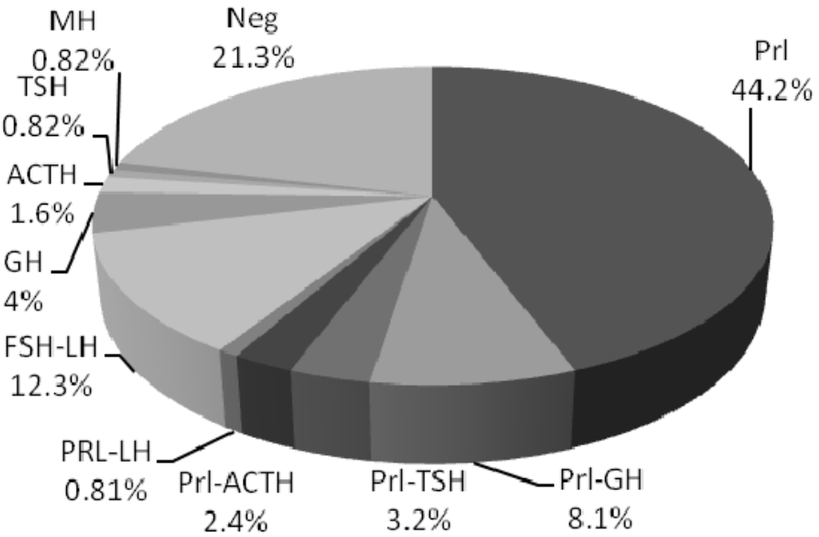

Fig. 1. Pituitary adenoma classification according to their hormonal content assessed by immunohistochemistry.
Prolactin hormone expression was the most frequent detected. Prl= prolactin hormone; GH= Growth hormone; TSH= Thyroid stimulating hormone; ACTH= adrenocorticotropin hormone; LH= luteinizing hormone; FSH= follicle stimulating hormone; MH= multihormonal; Neg= negative.

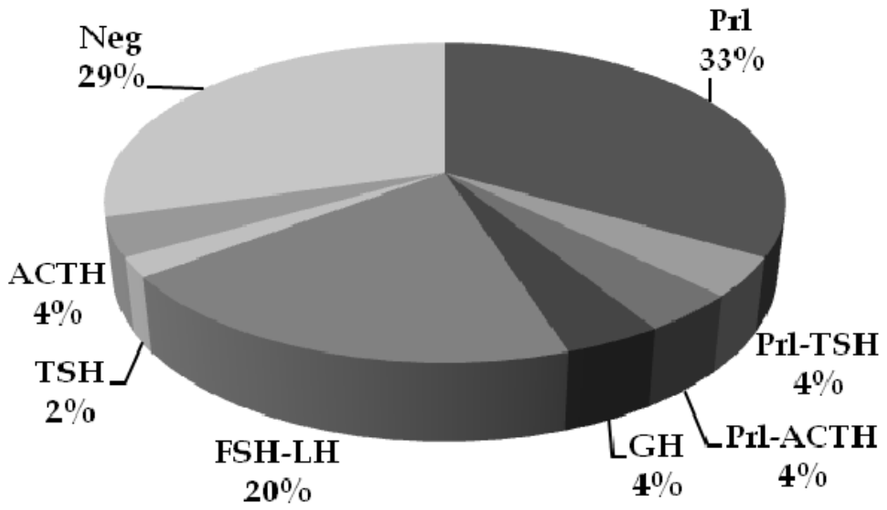

Fig. 2. Classification of non-functioning pituitary adenomas.
Immunohistochemical detection of hormonal expression in non-functioning pituitary adenomas. Prl= prolactin hormone; GH= Growth hormone; TSH= Thyroid stimulating hormone; ACTH= adrenocorticotropin hormone; LH= luteinizing hormone; FSH= follicle stimulating hormone; Neg= negative.

There were 51 (41.8%) non-functioning PA, 17 (33%) were Prl positive by immunohistochemistry, 15 (29%) were negative, and 10 (19.6%) were positive for gonadotrophic hormones (Fig. 2).

Non-functioning PA presented visual alterations and headache as clinical manifestations. There was 58.2% of clinically functioning pituitary adenomas. The most frequent clinical manifestations were: amenorrhea, galactorrhea, and libido diminished. Acromegaly was found in GH positive pituitary adenomas and one patient with gigantism was found (Table 1). Ki-67-LI was high in IV grade tumors (Table 3, Fig. 3).

Grade	Cases #	F	NF	Prl # (%)	Ki-67-LI Median (range)
I	2	2	-	2 (100)	ND
II	20	10	10	11 (55)	10.7 (10-16)
III	34	21	13	22 (64.7)	6.8 (1-20)
IV	66	38	28	37 (56)	25.4 (2-35)

Table 3. Pituitary adenomas classification according to their endocrine symptoms: Clinically functioning pituitary adenomas (F) and clinically non-functioning pituitary adenomas (NF). Prolactin hormone expression detected by immunohistochemistry (Prl). Number and percentage of positive cases, in each grade. Ki-67 Labeled Index (Ki-67-LI) in each grade. ND= No determined.

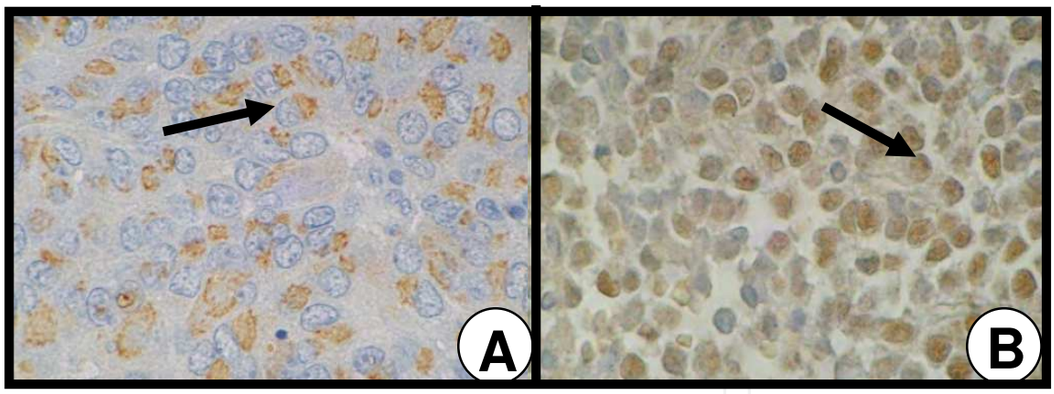

Fig. 3. Immunohistochemical detection

Photomicrograph of pituitary adenomas stained with immunohistochemical technique. Antibodies against prolactin hormone (A), and Ki-67 (B). Prolactin detection is present in the cytoplasm and Ki-67 can be seen in nucleus. Arrows show the immunodetection. (original magnification X 400).

3.2 Statistical analysis

There was no significative statistic difference in disease evolution time (F=1.0, p=0.351) and follow up (F=0.1, p=0.885), compared between invasion degrees. Neither the evolution time (p=0.146) nor the follow-up time (p=0.678) differed between functioning PA and non-functioning PA, however disease evolution time was lightly higher in III and IV invasion degrees. Evolution time (X^2=2.4, p=0.287) and follow up time (X^2=0.1, p=0.939) did not have association with the invasion grade.

No association was found among recurrence and functioning PA (p=0.526), and with hormone immunodetection (Prl p=0.595; GH p=0.377; FSH p=0.635).

Ki-67-LI was higher in IV grade (median value: 24.5%; range 2-35) in comparison with grade II (median value 6.8%; range 1-20; X^2=6.4, p=0.029); Grade III PA has an intermediate value (median value 10.7%; range 10-16). There was no statistic difference of Ki-67-LI between functioning PA and non-functioning PA (p=0.893) or between PA with recurrence and PA without recurrence (p=0.253). There was no association of Ki-67-LI with hormone secretion type (Prl p=0.121; GH p=0.100; FSH p=0.5).

3.3 Histopathological analysis

Histologically 98.4% show high cellular density, discrete nuclear pleomorphism, and dense nuclei, between 7 and 10 μ of diameter (Fig. 4A). Neither necrosis areas nor mitotic figures were observed. Only two cases of IV grade invasion degree, which were prolactin secretor PA, show nuclear pleomorphism, pseudoinclusions, bi- or multinucleated cells, and mitotic figures (Fig. 4B and 4C).

There were 11 prolactinomas (15.2%) treated with bromocriptine before surgery for a period of 2 months to 3 years. The drug decreased tumor size and serum prolactin levels, the menstruation was restored, galactorrhea stopped and fertility returned. Histologically interstitial fibroses was observed in these tumors (Fig. 4D). Ultrastructuraly the cells showed

smaller endoplasmic reticulum and Golgi complex; lysosomes were more frequent observed and there were scarce secretory granules.

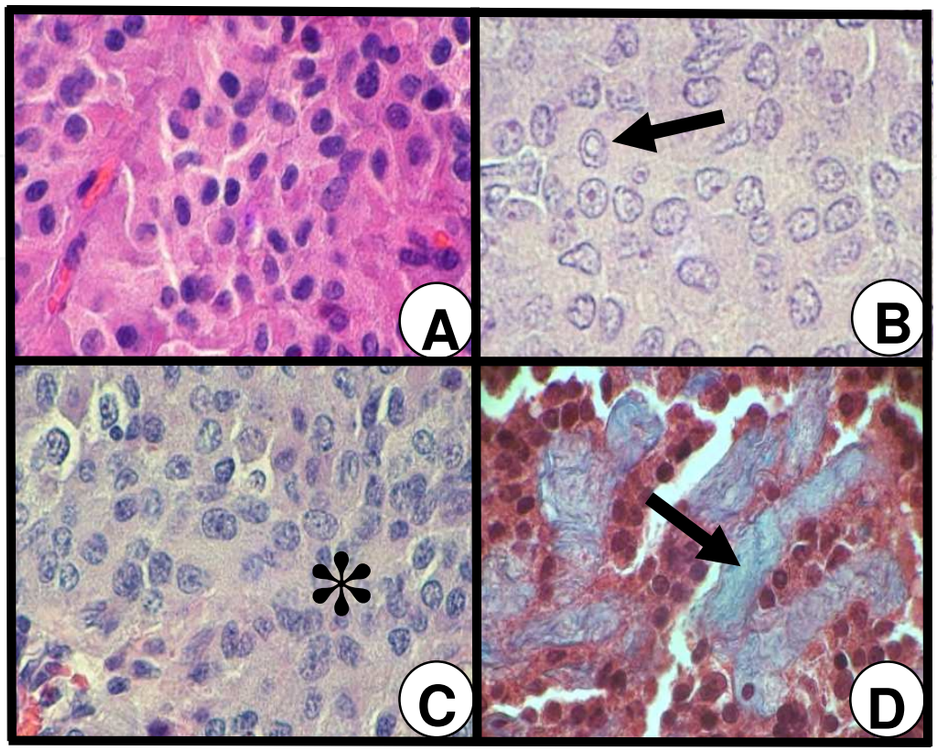

Fig. 4. Photomicrograph of pituitary adenomas with hematoxilyn-eosin stain (A-C), and with Masson's trichrome stain for collagen fibers (D). (A) PA showing solid pattern with homogeneous size cells. (B-C) PA showing nuclear pleomorphism (asterisk) and pseudoinclusions (arrow). (D) Bromocriptine treated PA which shows interstitial fibrosis (arrow). (Original magnification: X400).

3.4 Ultrastructure

3.4.1 Prolactin adenomas

The most frequent type of pituitary adenomas was the prolactinoma (59%). All prolactinomas were sparsely granulated. The tumor show polyhedral cells with irregular nucleus, and prominent nucleolus. In the cytoplasm abundant, lamellar, rough endoplasmic reticulum and well development Golgi complex, was observed. There were scarce secretory granules, with size between 100-300 nm in diameter; some of them were localized between lateral cell surfaces which are known as misplaced exocytosis, the morphologic mark of prolactin secretor PA (Fig. 5).

3.4.2 Growth hormone adenomas

Adenoma secreting only growth hormone had an incidence of 4%. Ultrastructuraly this tumor was sparsely granulated. The cells showed pleomorphic and eccentric nucleus, with scarce and dilated endoplasmic reticulum. Fibrous bodies with type II filaments were

observed, some of them with secretory granules inside it, whose size was between 221 nm and up to 769 nm in diameter (Fig. 6A).

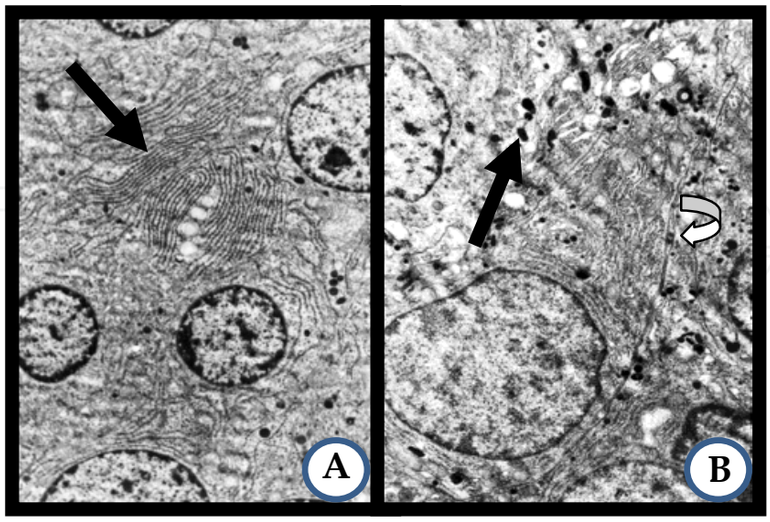

Fig. 5. Electronmicrographs of sparsely granulated prolactin adenoma grade II. (A) Lamellar endoplasmic reticulum (arrow). X 6,076; (B) fused secretory granules (black arrow) and misplaced exocytosis (white curved arrow). X9,750. Uranyl acetate-lead citrate.

3.4.3 GH secreting adenoma and prolactin hormone adenoma

Ten cases (8%) of pituitary adenomas with prolactin hormone and growth hormone secretion were found. Ultrastructuraly it was observed a monomorphous tumor, formed by only one cell type. All cells were scarcely granulated with secretory granules with 178 nm of diameter, few mitochondrias, lamellar endoplasmic reticulum and folded cell membranes;

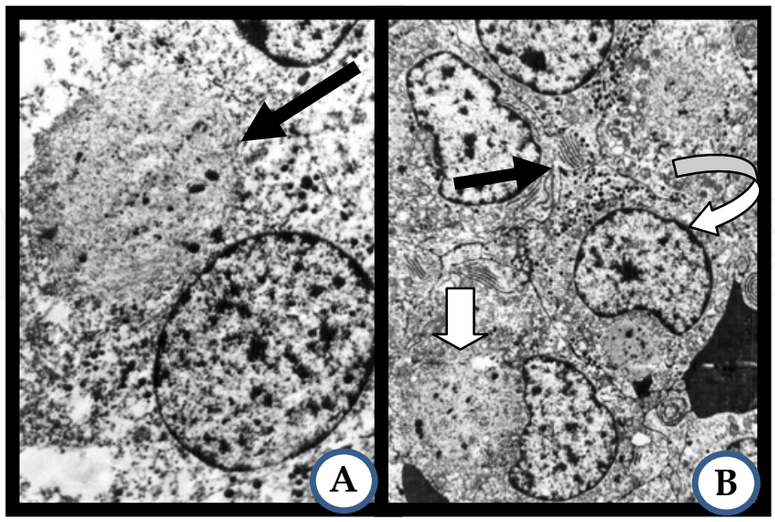

Fig. 6. Electronmicrograph of grade IV, GH PA, with their hall-mark fibrous body (arrow) X10,350. (A); grade III PA, prolactin and GH secreting, with lamellar endoplasmic reticulum (black arrow), crescent moon nuclei (curved arrow), and fibrous body of type II filaments (white arrow). X5,137. (B). Uranyl acetate-lead citrate.

nucleus show rounded or crescent moon shape in which concave area fibrous bodies were observed (Fig. 6B).

3.4.4 Gonadotroph adenomas

These adenomas were the most abundant (12%) after prolactinomas (44%) and the negative types for immunohistochemistry (21%). This tumor was formed by polyhedral cells, with poorly developed cytoplasm. Nuclei had rounded contours, some of them with irregular shapes and eccentric nucleoli attached to the electron-dense perinuclear chromatin. Rough endoplasmic reticulum was scarce and dilated, and secretory granules were few and small (153 nm in diameter). Big Golgi complex was observed with dilated cisterns (Fig. 7A). In two IV grade cases, smooth endoplasmic reticulum, mixed with mitochondria and pleomorphic secretory granules were detected; there was a vacuolated Golgi complex which was arranged in a honey comb complex, the hall-mark of this adenoma type (Fig. 7B).

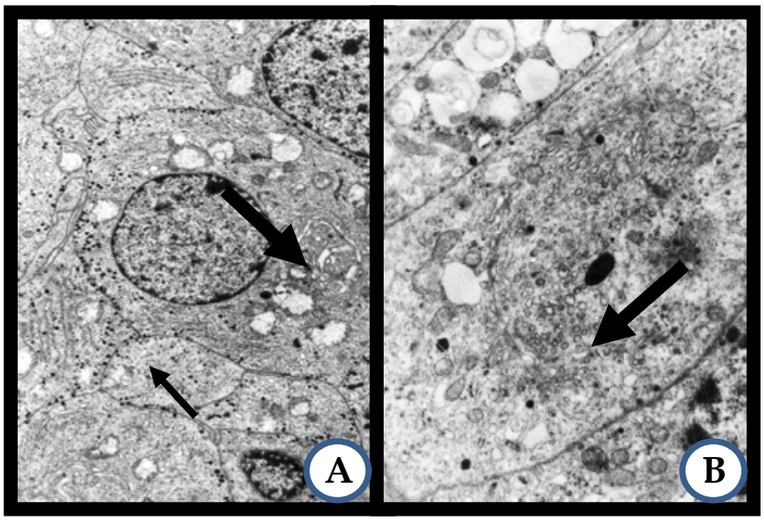

Fig. 7. Electronmicrograph of grade III gonadotroph PA. (A) This tumor showed big Golgi complex with dilated cisterns (arrow), small secretory granules located along the cell membrane (thin arrow). X 6,370; (B) Golgi shows a honey comb complex (arrow). X15,600. Uranyl acetate-lead citrate.

3.4.5 Negative pituitary adenomas

This type of tumors was negative for all hormones with the immunohistochemistry technique. Under transmission electron microscopy, poorly developed cells were observed with scarce rough endoplasmic reticulum, few secretory granules with 100-200 nm of diameter and small Golgi complex. In some cases it was observed numerous mitochondria, which is known as oncocytic transformation (Fig. 8A).

3.4.6 Corticotroph adenoma

There were 2 cases (1.6%) of ACTH secreting pituitary adenomas. This tumor showed polyhedral or elongated cells with poorly developed cytoplasm. The cell boundaries were clearly marked, elongated nuclei with irregular contours, and prominent nucleoli (8B);

secretory granules were scarce and small (104 nm). In one case proliferation of type I filaments were perceive with secretory granules inside it (Fig. 8C).

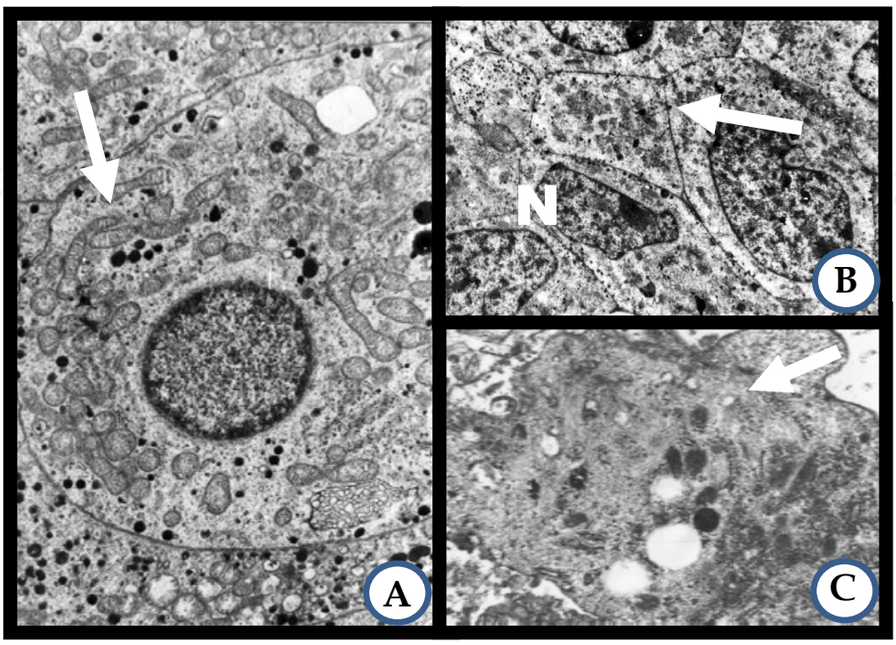

Fig. 8. (A) Electronmicrography of grade IV immunonegative PA. This tumor showed sparsely granulated cells with abundant mitochondria (arrow). X9,900 ; (B) Corticotroph cell adenoma grade III which consist of closely-apposed, angular cells, with marked cell boundaries (arrow), and nucleus with irregular shape (N). X6,370 ; (C) Cytoplasm with abundant type I filaments were observed (arrow). X8760. Uranyl acetate and lead citrate.

4. Discussion

Pituitary adenomas are heterogeneous tumors, this is because their different types of cells. The analysis of them had take into account several characteristic, the aim of these is to explain its behavior, although until now, has not been understood.

Pituitary adenomas comprise nearly 15% of intracranial neoplasms and are the most common lesions in the sellar region (Valassi et al., 2010). There is a report of 84.6% PA in a study of 4,122 tumors of sellar region (Saeger et al., 2007). In a 10-year study conducted at the National Institute of Neurology and Neurosurgery, in Mexico City, from 2,041 central nervous system tumors and covers, 26.2% were PA (personal communication). Here we present a study of 122 case of PA which occurred between 13 and 75 yr old, with peak of incidence from 20 and 60 years (100 cases; 81.9%), 10 yr earlier than other series (Davis et al., 2001). There was a slightly higher incidence in men; however women had earlier age at diagnosis (since 13 yr) than men (since 17), with higher frequency between 20 and 48 yr (men between 30 and 60 yr; 68%).

Pituitary adenomas incidence are rare in young people under 20 yr and mostly are prolactinomas (86%) or corticotropinomas (10%) (Mindermann & Wilson, 1994). In this study was found 12 patients under 20 yr (9.8%); Nine (75%) were prolactinomas, one of which was Prl-ACTH positive, two Prl-GH, one Prl-TSH. From these 12 cases, one (8.3%) was GH immunopositive and in 2 PA the hormone expression was no detected. In table 1 it can be

observed, that in some patients the age at diagnosis (age column) is over 20 yr, although the patients reported that the beginning of the symptoms was some years before (evolution time).

In general, tumor size correlates with functional activity (clinically functioning and clinically non-functioning pituitary adenomas), and in women has been observed that, prolactinomas and also in ACTH clinically functioning pituitary adenomas, the diagnosis is carry out at early stages. (Kontogeorgos, 2006). In our work we found 71 (58.1%) functioning PA; 44 (61.9%) were in female of which only 5 (11%) were grade I and II PA and 39 (88.6%) were classified in III and IV grades. Out of this 39 PA, 29 (74%; 13 in grade III and 16 in grade IV) were prolactin immunopositive. In this case, women functioning adenomas, which produced prolactin hormone, were detected at an advance stage of invasion.

In this study must of the PA were in a invasive phase (grade III and IV), and the disease evolution time in these patients was higher than in I and II grades, even though there was no statistical association with clinical manifestation (functioning or non-functioning PA) or hormonal activity assessed by immunohistochemistry. Similar long evolution time (from 10 days to 20 years), has been reported in a Brazilian serie which was greater than the Italian and US series (Drange et al, 2000; Ferrante et al., 2006). This may be due to the class of population that assist to this Institute, which are used to endure the symptoms of the disease for a long time before seeking medical treatment, or do not have the right information to perceive them at an early stage, also before turning to adequate health service they look for alternative therapies. As it has been suggested by other authors, the clinical signs might be underestimated or not correctly diagnosed (Drange et al., 2000; Ferrate et al., 2006). In our experience, patients as first choice went to the ophthalmologist, because of the visual alterations, and by the computed tomography or magnetic resonance imaging scans, sellar alterations were observed. Nowadays incidental detection of PA tumors has been increased due to radiological evaluations performed for unrelated reasons (Saeger et al., 2007). In this analysis we can observed that the functionality was not related to tumor size, but with time the patient will assit to the health center.

Non-functioning pituitary adenomas are a diverse and heterogeneous group, where glycoprotein hormones, null cell adenoma and oncocytoma are included (Laws et al., 1982; Moreno et al., 2005). They are usually diagnosed as macroadenomas due to absence of clinical manifestations, which cause tumor growth in long time. Non-functioning PA account between 15% and 45% of pituitary tumors (Asa & Kovacs, 1992; Milker-Zabel et al., 2005). It has been reported that 95-100% of non-functioning pituitary adenomas are macroadenomas, and the frequency of recurrence varies between 19% and 34.8% in different studies (Aurer & Clarici, 1985; Reddy et al., 2011); up to 79% has hormone expression, evaluated by immunohistochemistry (Moreno et al., 2005), being gonadotroph hormones and/or their α- β- subunits the most common (Cury et al., 2009, Hanson et al., 2005). In our study 51 (42%) tumors were non-functioning PA, of which 38 (74.5%) were men, this is consistent with other studies (Asa & Kovacs, 1992; Cury et al., 2009; Ferrante et al., 2006; Milker-Zabel et al., 2005). Out of 51 non-functioning pituitary adenomas, 15 (29.4%) showed recurrence and 41 (80%) were macroadenomas. In 71% of non-functioning PA hormone expression was found, being prolactin the most frequent hormone detected by immunohistochemistry (33%), followed by gonadotroph hormones (20%); there were 29% of immunonegative PA in accordance with Turner report (Turner et al., 1999). It is important to point out that 13 cases of non-functionig PA were female, 7 of grade III and 6 of grade IV.

There were no adenomas classified in grades I and II. In our case, in women non-functioming pituitary adenomas could be related with the size.

In pituitary adenomas recurrences are common problems. The large size and the invasive behavior of these tumors cause difficulties in their removal (Paek et al., 2005). It has been reported that about 50% of patients have tumor remnants, and tumor re-growth can be presented at 10 years after neurosurgery (Reddy, 2011; Sassolas et al., 1993). Generally larger tumors recurred more frequently than smaller adenomas after surgery (Gopalan et al., 2011; Saeger et al., 2007). In our work the tumors were removed between 60% and 100%, by means of transcranial-frontal or transsphenoidal technique, and in III and IV grades the recurrences were higher, with secondary recurrences in 5 patients (three in III grade and 2 in IV grade). The time of interval between surgery and recurrence ranged from 1 to 11 years in both clinically functioning PA and non-functioning PA. In non-functioning pituitary adenomas Reddy et al. (2011) showed relapse/re-growth in 10 or more years after the initial surgery, and found significant increase in re-growth rates when remnant pituitary tumors are observed on the first post-operative scan or if the patient is younger age at initial surgery.

The follow up time of the patients is an important factor for their outcome (Dekkers et al., 2008). In our work 38 (31%) patients were found with a mean of 11 yr of follow up (range 1-27 yr), 12 of them were non-functioning PA with 10.3 yr of follow up (range, 1-27 yr). Reddy et.al. (Reddy, 2011) reports an average of 6.1 yr (range, 1-25.8) of follow up in 29 patients with non-functioning PA out of 155, of which 54 (34.8%) had recurrence, with 20% of relapse after 10 years of surgery; they suggest that it is necessary to track patients beyond this time.

In this study, few patients continued to attend for monitoring appointments. This could be because the patients who come to this health institution live outside of Mexico city, and sometimes it is difficult for them to travel to the city. Other patients are sent to other hospitals for continue their treatment, or they have no financial means for the follow up. Patients, who maintain their treatment and attendance to appointments for periodic reviews, have good outcome, with a improve of their visual impairments and hormonal levels, treated by hormonal substitution. It has been observed that patients with pre-operative anterior dysfunction recover function after surgery and the cases who presented with visual disturbance improve their vision with a second surgery (Chang et al., 2010; Müslüman et al., 2011).

An important factor in the biological behavior of pituitary adenomas is their proliferative capacity, which could be assessed by counting mitoses and the immunostaining of nuclei for proliferation markers as Ki-67. Mitoses figures are rare in non-invasive pituitary adenomas (3.9% of cases), they are more frequent in invasive PA (21.4%) and are greater in carcinomas (66.7%) (Pernicope et al., 2001). In our study there were found 2 cases (1.6%) with mitoses, which is not different from that reported in other studies, including the recently established rare subtype spindle cell oncocytoma of the pituitary gland (Matyja et al., 2010; Saeger et al., 2007).

Ki-67 is the most important proliferation marker; it is expressed in early G1, S, G2, and M phases of the cell cycle. This marker is associated with tumor proliferation, invasiveness, and prognosis (Cattoretti et al., 1992; Petrowsky et al., 2001). In pituitary adenomas the value of Ki-67 is controversial, in relation to the aggressive behavior (de Aguiar et al., 2010; Zhao et al., 1999), and in pituitary carcinoma appear to predict rapid disease progression (Dudziak et al., 2011). In a study performed in 44 pituitary macroadenomas, visual field defect and recurrence show correlation with Ki-67 LI, no statistical differences were

observed in Ki-67 LI in relation to the Hardy´s classification (Paek et al., 2005). In other study in a series of 20 radically resected pituitary macroadenomas (11 functioning, 9 nonfunctioning) MIB-1(antibody of Ki-67 antigen) did not show a significant difference of expression between recurrent and non-recurrent adenomas (Ruggeri et al., 2011). Yarman (2010) assessed Ki-67 expression in growth hormone-secreting pituitary adenomas and showed no correlation with the invasive character. In other study it has been observed that Ki-67 LI was marginally higher in clinically functioning adenomas than clinically non-functioning adenomas. They also found significant difference in the MIB-1 LI in tumors with a maximum diameter of more than 4cm at a MIB-1 LI of ≥2%, however this difference was not statistically significant at a higher MIB-1 LI cut off value of >3% (Chacko et al., 2010). On the other hand, there is other report in which no significant difference in MIB-1 LI was found between functioning and non-functioning PA (Scheithauer et al., 2006). In our results, Ki-67 LI was significantly higher in IV grade PA than those of II grade which is different to that reported by Paek (2005); however there was no statistic difference of Ki-67 LI between pituitary adenomas with recurrence or without recurrence. About functionality we did not found differences between functioning and non-functioning pituitary adenomas which differs with Scheithauer report (2006).

Ultrastructural analysis of pituitary adenomas is an important tool for the detailed characterization of this type of tumors, particularly in problematic cases, because it is the initial basis of adenoma classification. With transmission electron microscopy it can be confirmed the endocrine nature of PA and their functional differentiation, which can be identified based on their ultrastructural markers of each hormonal type. Despite the utility of electron microscopy analysis in the evaluation of these tumors, diagnostic cannot be made on ultrastructural grounds alone, it should be done taking into consideration histology, immunohistochemistry and electron microscopical morphologic features, as well as findings from imaging studies and the symptoms (Kontogeorgos, 2006). Both clinical and histopathological factors are important for the diagnostic and outcome of patients.

In our study we observed the ultrastructural features of the different types of PA according to their hormonal expression, and in relation to clinical manifestations. Ultrastructural analysis was very useful in mixed secretory adenomas, as growth hormone and prolactin secreting PA where cells with fibrous bodies, hall-mark of GH pituitary adenoma. In this way, ultrastructural findings of most PA are consistent with the immunophenotype, however there are occasional cases with ultrastructural features less well differentiated like the rare carcinomas (Scheithauer et. al., 2001).

5. Conclusion

Pituitary adenomas are a heterogeneous group whose behavior has not been understood yet. In our study must of the tumors were in a extensive invasive phase, they affected young adult population and in this series of cases people under 20 years were founded. The disease evolution time and recurrence frequency was high in the advanced grades. The diagnosis of these tumors was not related with the clinical manifestations, according to the time taken by the patients to consult a doctor. The good outcome of patients depends on the follow-up, which has a very low rate for different reasons.

Pituitary adenomas have benign histological aspect, however can be aggressive, and may have one or more recurrences, as has been shown in this analysis. These neoplasms seem to

have, a natural evolution, a potential to invasion, sparing the nervous tissue and without seeding to distant organs.

Although there are no parameters or experimental tests that serve as clear markers of disease progression, the data that have been obtained as a result of the evaluation of hormone expression and clinical evaluation, have important information that can be associated with pathogenicity of PA. Currently, there are new molecular techniques, as proteomic technique that allows us to investigate the proteins involved in the disease process.

The setup of registry on pituitary tumours constitutes a useful tool to analyze clinical experience, improve therapeutic strategies and patient's care. It also contributes for teaching medical students and develops clinical research.

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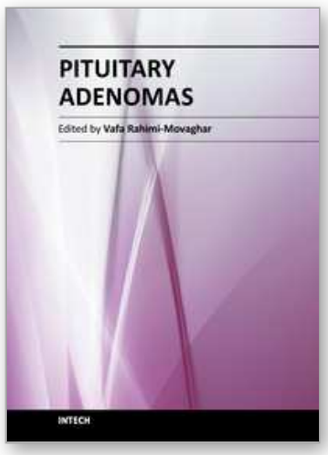

Pituitary Adenomas

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Pituitary Adenomas is a comprehensive book about the most common pathology of the pituitary gland in the sellar region. The book chapters include epidemiology, symptoms and signs, clinical, imaging, immunohistochemical and ultrastructural pathological diagnosis, therapeutic approaches and outcome of the functional and non-functional pituitary tumors. Therapies include medications, endoscopic transphenoidal and open surgeries; radiotherapy includes gamma knife radiosurgery. Visual symptoms has important and characteristic patterns which has discussed in one specific chapter. Endocrine secretion is another characteristic in 40% of pituitary adenomas. Therefore, another chapter presents it. Stereotactic radiosurgery and endoscopic surgery both have special role in recent decades. Thus, they have considered specifically, too. Authors expect to give excellent insight in pituitary adenoma to the book readers.

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