IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 15, Issue 12 Ver. X (December. 2016), PP 89-93
www.iosrjournals.org

Phenotypical, Therapeutic And Evolutive Characteristics of Corticotroph Macro Adenomas

Ns.Fedala[1],R.Loun Is[2],Aem Haddam *[3], M.Hadid
Department Of Endocrinology Bab El Oued Hospital,
** Department Of Diabetology Bab El Oued Hospital, Algiers, Algeria*

I. Introduction

Corticotropic adenoma causes chronic hypersecretion of adrenocorticotropin (ACTH) responsible for Cushing's disease. This is the most common cause of Cushing's syndrome, or chronic excess of endogenous cortisol. Ninety percent of corticotropic adenomas are microadenomas, sometimes not visible in magnetic resonance imaging (MRI). Corticotropph macroadenomas are rare, but often cause tumor scalability issues (1) (2)

Objectif

The objective of this study is to analyze the phenotypic characteristics, therapeutic and evolutive macro adenomas corticotroph

Patients Et Methodes

Il s'agit d'une étude mono centrique retrospective descriptive de dossiers de patients présentant un macroadenome corticotrope hospitalisés au service entre 1988 et 2016 Le diagnostic d'adenome corticotrope était posé sur les éléments cliniques (Signes cliniques d'hypercortisolisme ,mélanodermie) et paracliniques spécifiques (Cycle du cortisol plasmatique , freinage faible et fort sur cortisol plasmatique ,dosage de l'ACTH plasmatique et imagerie en résonance magnétique de la région hypothalamo hypophysaire). L'exploration était complétée par un bilan de retentissement viscéral et métabolique de l'hypercortisolisme et par un bilan ophtalmologique. Tous les patients ont été opérés par voie transphénoidale . Une étude immunohistochimique était réalisée sur les pièces opératoires. En post opératoir, les patients étaient réevalués systématiquement.En fonction des résultats, un traitement complémentaire était envisagé (Reprise chirurgicale et ou radiothérapie et ou traitement anticortisolique). Un suivi régulier était éffféctué.

II. Patients And Methods

This is a retrospective mono centric descriptive study of patients with a corticotrophic macroadenoma hospitalized between 1988 and 2016 The diagnosis of corticotrophic adenoma was based on clinical features (clinical signs of hypercortisolism, melanoderma) and specific paraclinics explorations (plasma cortisol cycle,

Low and strong dose dexamethasone suppression test (cortisol after oral dexamethasone ,assay of plasma ACTH and magnetic resonance imaging of the hypophyseal hypothalamic region). The exploration was supplemented by a visceral and metabolic evaluation of hypercortisolism and by an ophthalmological assessment. All patients were operated by transsphenoidal route. An immunohistochemical study was carried out onsurgical specimens.In post-operative , patients were systematically reassessed. Depending on the results, additional treatment was envisaged (Surgical recovery and or radiotherapy and or anticortisolic treatment). Regular monitoring was carried out.

III. Results

The mean age at diagnosis was 33 ± 9.80 years (18-55).
The most affected age groups are the 3rd and 4th decades (Table I) with a Sex ratio of 6F / 1M

Table I : Distribution of Patients by Age

Age range	**Number**	**%**
≤ 20 ANS	2	7.1
]20,30]	10	35.7
] 30,40]	9	32.1
]40,50]	5	17.8
]50,60]	2	7.1

The chief complaint is dominated by the tumor syndrome and signs of hypogonadism (TableauII)
Table II: Distribution of patients according to the reason for consultation

Reason for consultation	Nbre	%
Hypogonadism (1H ,10F)	11	39.3
Ophthalmologic disorders (Decreased visual acuity) (2 M, 6F)	8	28.6
Obesity (1H,6F)	7	25
HTA, diabetes mellitus (2F)	2	7.1

The majority of patients (85.7%) had frank cushing syndrome (Table III) with signs of protein hypercatabolism and arterial hypertension in all cases.

Table III: Patient distribution according to the clinical picture

Clinical	Symptomatic cushing syndrom	Asymptomatic cushing syndrom
Nombre	24	4
%	85.7	14.3

An asymptomatic picture was observed in 10% of the cases with cutaneomucous melanoderma noted in 50% of cases. Biologically, hypercortisolism was significant and evolving with a high average of plasma ACTH (Table IV)

Table IV: Hormonal Results

Parameter	Résults	Normes
Average plasmatic Cortisol 8h (nmol/L)	**849±433**	
Average plasmatic Cortisol 00h (nmol/l)	453 ± 240	
Average plasmatic ACTH (pg/ml)	102.4 ±61.8	
Average plasmatic Cortisol after low DMZ	280 ± 100	

The endocrine evaluation found hypogonadotropic hypogonadism in two - thirds of the patients (78.8%) and the neuro - ophthalmological assessment revealed neuro - ophthalmologic involvement in almost half of the cases (Table V)

Table V: Ophthalmological Results

Ophthalmological disorders (16)	**46.42 (%)**
Isolated alteration of visual field	14.3
Reduced visual acuity + fundus abnormalities	14.3
Unilateral or bilateral blindness	17.8

Nearly half of patients had cardiovascular complications, bone and metabolic diseases (Table VI). On the radiological level, the macroadenomas had an average height of 22.5 ± 12.7 mm. 40% of patients had an average size greater than 30 mm and almost two thirds were invasive (Table VII)

Table VI: Distribution of patients according to complications

Complications	**%**
HTA (I,II,III)	73.07
*Complicated (Hypertensive retinopathy, left ventricular hypertrophy)	52.6
Anomalies of glucose tolerance	65.8
Dyslipidemia	42.3
Ostéoporosis	59

Table VII: Radiological Results				
]10,20[	60.7 (17)	0	41.17(7)	5.9 (1)
≥20	39. 3(11)	54.5 (6)	72.7(8)	36.4 (4)

Therapeutically pituitary surgery by transsphenoidal route resulted in complete tumoral excision with clinical and biological remission in 20.8%.

The presence of an adenomatous residue and the persistence of an evolutive cushing syndrome in other cases (79.1%) necessitated a therapeutic complement. Clinicobiological remission was observed after an average duration of 10 ± 0.4 years (8-15). 6 patients were referred for surrenalectomy due to a persistence scalability despite the association of all therapeutic weapons (surgical resumption, hypothalamohypophyseal radiotherapy, anticortisolic treatment)

IV. Discussion

Cushing's syndrome refers to the clinical manifestations induced by chronic exposure to excess glucocorticoids. It is a rare condition with an annual incidence of 3/million.. Cushing's disease (CD), defined as pituitary adrenocorticotropic hormone (ACTH) excess, is the most frequent cause of endogenous Cushing's syndrome with an incidence of 2/million per year. It is usually due to a microadenoma (maximal diameter <10mm) and may be difficult to visualize; in contrast, macroadenomas (maximal diameter >10mm) comprise only 4–10% of diagnosed patients (3).

Cushing's disease occurs most frequently in women of reproductive age, but it can affect males and females of any age (2). Micro-adenomas generally do not cause symptoms by local mass effect. These tumors are most often discovered when clinical manifestations of hypercortisolism resulting from hypersecretion of ACTH prompt an appropriate diagnostic work-up. Occasionally, microadenomas are found incidentally during imaging performed for other reasons (4). Macroadenomas are uncommon in patients with Cushing's disease. These tumors cause mass effect when their size exceeds 15 mm in diameter. Suprasellar extension and optic chiasm compression, local bone erosion, cavernous sinus compression and panhypopituitarism may occur as a macroadenoma enlarges (4) (5).

The most common symptom is sudden weight gain (4). Obesity, usually with a central distribution, is the most frequent sign. Any sign or symptom of cortisol excess can develop initially, but muscle weakness, bruising, hypertension, facial rounding and plethora eventually occur. Hypertension is likely to develop in patients who are more than 40 years of age (6) .

Pituitary tumors are known to compress the optic chiasm. Bitemporal hemianopsia with central visual field defects is the classic neuro-ophthalmologic finding, although other visual defects, including unilateral symptoms, can occur (4).

Cranial nerve III (oculomotor nerve) palsies are less well recognized, but they may occur in up to 25 percent of patients with pituitary macroadenomas and may be the lone presenting symptom in patients with pituitary adenomas . Pituitary tumors infrequently affect cranial nerves IV and VI.[9]The mechanism for oculomotor palsies is usually direct compression by the expanding tumor as the nerve passes through the walls of the adjacent cavernous sinus.[7] Noncompressive cranial nerve III paresis has also been reported in patients with Cushing's disease (4)(5).

Pituitary apoplexy results from infarction of a pituitary tumor or sudden hemorrhage within. This presents as a medical emergency with a headache, sudden collapse, shock, and death if not treated emergently. This tends to occur in macroadenomas

The baseline hormonal assessment of patients with macroadenomas showed a clear difference from the microadenomas, with both 0800 h ACTH and cortisol levels being significantly higher than those in microadenomas. A linear correlation between maximum tumor diameter and baseline plasma ACTH level was demonstrated by Losa et al. and a similar correlation between mean ACTH and tumor volume was reported (4)

Studies have shown that Cushing's disease caused by both microadenomas and macroadenomas is monoclonal in origin; such tumors are considered to result from sporadic mutation and subsequent clonal proliferation of neoplastic corticotroph cells (7)(8) (9). There was enhanced proliferative potential in ACTH-secreting macroadenomas in comparison with microadenomas by assaying in situ for the presence of Ki-67, a cell cycle antigen and a marker of cell proliferation. They found a trend toward a higher degree of proliferative activity in macroadenomas. In addition, the degree of Ki-67 staining was shown to correlate with aggressiveness of the neoplasm; those tumors having high Ki-67 staining were found to have more invasive proliferative activity, whereas others have correlated Ki-67 staining with maximum tumor diameter (10)(11) (12)

A pituitary tumor can transform into an ACTH-secreting carcinoma in an indolent manner. Patients with invasive pituitary adenomas require long-term surveillance to monitor for differentiation into pituitary carcinoma(7) Surgery is usually the main treatment. If the surgery doesn't remove the tumor completely or if it grows back, the 2 main options are a second surgery or radiation therapy (12) . Radiation can often take months or years to work, so medicines may be given to help control cortisol levels in the meantime (13).

Several different types of medicines can be used to help control cortisol levels or limit the effects of this hormone in the body . Unfortunately, medicines aren't always as effective in ACTH-secreting tumors as they are in some other types of pituitary tumors, and some of these drugs can have serious side effects that make them hard to take for long periods of time.

If medicines aren't helpful, or if the patient can't take them because of side effects, both adrenal glands can be removed (*adrenalectomy)*. This can usually be done with laparoscopic surgery(14)(15)(16)

The published remission rates after radiotherapy range from 23–83% for patients with Cushing's disease, without taking into consideration the size of the tumor, but this may take a variable number of years to become effective (17). In anther series , only 12.5% of patients remained in remission after radiotherapy. In another study, radiotherapy was observed to be effective in 56% of patients with macroadenomas (18) (19) (20). Different investigators have looked into which factors might predict treatment outcome . studies have reported that patients with macroadenomas showing cavernous sinus invasion and/or tumor size more than 2 cm correlated with an unfavorable outcome after surgery (19) (20) (21). They also demonstrated that baseline ACTH levels served as a good predictive index for surgical outcome, with cured patients having significantly lower levels. They also found that the size of the tumor correlated closely with the level of ACTH (14)(18)(19).

V. Conclusion

Cushing syndrome is often important in Cushing's disease and macroadenomas. Patients have significantly higher ACTH and cortisol levels. The surgical cure rate is also low, and whereas radiotherapy appears to prevent tumor progression, it infrequently led to hormonal remission.

References

[1]. Isidori AM, Kaltsas GA, Mohammed S, Morris DG, Jenkins P, Chew SL, Monson JP, Besser GM, Grossman AB . Discriminatory value of the low dose dexamethasone suppression test in establishing the diagnosis and differential diagnosis of Cushing's syndrome. J Clin Endocrinol Metab 2003; 88:5299–5306

[2]. Invitti C, Giraldi FP, de Martin M, Cavagnini F .Diagnosis and management of Cushing's syndrome: results of an Italian multicenter study. J Clin Endocrinol Metab ; 1999, 84:440–448

[3]. Woo YS, Isidori AM, Wat WZ, Kaltsas GA, Afshar F, Sabin I, Jenkins PJ, Monson JP, Besser GM, & Grossman AB . Clinical and biochemical characteristics of adrenocorticotropin-secreting macroadenomas Journal of Clinical Endocrinology and Metabolism ; 2005, 90 4963-4969

[4]. Selvais P, Donckier J, Buysschaert M, Maiter D ;Cushing's disease: a comparison of pituitary corticotroph microadenomas and macroadenomas. Eur J Endocrinol 1998 ;138:153–159

[5]. Ikeda H, Yoshimoto T, Ogawa Y, Mizoi K, Murakami O Clinico-pathological study of Cushing's disease with large pituitary adenoma. Clin Endocrinol (Oxf) 1997 , 46:669–67

[6]. Arnaldi G, Angeli A, Atkinson AB, Bertagna X, Cavagnini F, Chrousos GP, Fava GA, Findling JW, Gaillard RC, Grossman AB, Kola B, Lacroix A, Mancini T, Mantero F, Newell-Price J, Nieman LK, Sonino N, Vance ML, Giustina A, Boscaro M Diagnosis and complications of Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab ,2003 ,88:5593–5602

[7]. Losa M, Barzaghi RL, Mortini P, Franzin A, Mangili F, Terreni MR, Giovanelli M Determination of the proliferation and apoptotic index in adrenocorticotropin-secreting pituitary tumors: comparison between micro- and macroadenomas. Am J Pathol , 2000 ,156:245–251

[8]. Biller BM, Alexander JM, Zervas NT, Hedley-Whyte ET, Arnold A, Klibanski A . Clonal origins of adrenocorticotropin-secreting pituitary tissue in Cushing's disease. J Clin Endocrinol Metab 1992 , 75:1303–1309

[9]. Gicquel C, Le Bouc Y, Luton JP, Girard F, Bertagna X . Monoclonality of corticotroph macroadenomas in Cushing's disease. J Clin Endocrinol Metab , 1992 ,75:472–475

[10]. Dahia PML, Honegger J, Reincke M, Jacobs RA, Mirtella A, Fahlbusch R, Besser, GM, Chew S, Grossman AB . Expression of glucocorticoid receptor gene isoforms in corticotropin-secreting tumors. J Clin Endocrinol Metab , 1997, 82:1088–1093

[11]. Antonini SR, Latronico AC, Elias LL, Cukiert A, Machado HR, Liberman B, Mendonca BB, Moreira AC, Castro M Glucocorticoid receptor gene polymorphisms in ACTH-secreting pituitary tumours. Clin Endocrinol (Oxf) , 2002, 57:657–662
[12]. Cannavo S, Almoto B, Dall'Asta C, Corsello S, Lovicu RM, De Menis E, Trimarchi F, Ambrosi B . Long term results of treatment in patients with ACTH-secreting pituitary macroadenoma. Eur J Endocrinol 2003 , 149:195–200
[13]. Lindholm J, Juul S, Jorgensen JO, Astrup J, Bjerre P, Feldt-Rasmussen U, Hagen C, Jorgensen J, Kosteljanetz M, Kristensen L, Laurberg P, Schmidt K, Weeke J ; Incidence and late prognosis of Cushing's syndrome: a population-based study. J Clin Endocrinol Metab, 2001, 86:117–123
[14]. Blevins Jr LS, Christy JH, Khajavi M, Tindall GT Outcomes of therapy for Cushing's disease due to adrenocorticotropin-secreting pituitary macroadenomas. J Clin Endocrinol Metab , 1998, 83:63–67
[15]. Arnaldi G, Angeli A, Atkinson AB, Bertagna X, Cavagnini F, Chrousos GP, Fava GA, Findling JW, Gaillard RC, Grossman AB, Kola B, Lacroix A, Mancini T, Mantero F, Newell-Price J, Nieman LK, Sonino N, Vance ML, Giustina A, Boscaro M , Diagnosis and complications of Cushing's syndrome: a consensus statement. J Clin Endocrinol Metab 2003, 88:5593–5602
[16]. Nakane T, Kuwayama A, Watanabe M, Takahashi T, Kato T, Ichihara K, Kageyama N .Long term results of transsphenoidal adenomectomy in patients with Cushing's disease. Neurosurg , 1987 , 21:218–222
[17]. Littley MD, Shalet SM, Beardwell CG, Ahmed SR, Sutton ML Long term follow-up of low dose external pituitary radiation for Cushing's disease. Clin Endocrinol (Oxf) 1990 ,33:445–455
[18]. Jenkins PJ, Trainer PJ, Plowman PN, Shand WS, Grossman AB, Wass JA, Besser GM The long-term outcome after adrenalectomy of prophylactic pituitary radiotherapy and adrenocorticotropin-dependent Cushing's syndrome. J Clin Endocrinol Metab , 1995 ,79:165–171
[19]. Estrada J, Boronat M, Mielgo M, Magallon R, Millan I, Diez S, Lucas T, Barcelo B .The long-term outcome of pituitary irradiation after unsuccessful transsphenoidal surgery in Cushing's disease. N Engl J Med 1997 , 336:172–177
[20]. Ludecke D, Flitsch J, Knappe U, Saeger W Cushing's disease: a surgical view. J Neurooncol 2001 , 54:151–166
[21]. Sonino N, Zielezny M, Fava GA, Fallo F, Boscaro M Risk factors and long-term outcome in pituitary-dependent Cushing's disease. J Clin Endocrinol Metab , 1996 , 81:2647–2652