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Non-Functional Pituitary Adenomas, Epidemiology, Diagnosis, Management and Outlook: Experience of the Diabetology-Endocrinology Department of the Mohammed VI University Hospital, Marrakech

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Abstract **Original Research Article**

Introduction*:** Non-functioning pituitary adenomas (NFPAs) are benign tumors of the anterior pituitary gland that do not secrete biologically active hormones. They represent about 15–30% of diagnosed pituitary adenomas. This study aims to analyze the clinical and paraclinical features of NFPAs and discuss management strategies. ***Methods*:** This retrospective study involved 28 patients diagnosed with NFPAs between January 2018 and December 2024 at Mohamed VI University Hospital, Marrakech. Clinical, biological, and imaging data were collected and analyzed. ***Results*:** A female predominance was observed (sex ratio 4:10), with a mean age of 40.7 years. The main clinical signs were headaches and visual disturbances. Hormonal insufficiency was found in 80% of patients, with corticotropic insufficiency being the most common. MRI revealed macroadenomas in 67.8% of cases. The primary treatment was surgery, with radiotherapy used in some cases. ***Discussion: NFPAs are often associated with hormonal deficiencies and compressive symptoms. Surgery remains the gold standard, sometimes followed by radiotherapy. Genetic mutations, such as those in the MEN1 and CDKN1B genes, offer potential future therapeutic targets. ***Conclusion*:** NFPAs require multidisciplinary management and careful follow-up to prevent complications. Although the prognosis is generally favorable, ongoing monitoring is essential to detect recurrences and manage hormonal deficiencies.

Keywords: Non-Functioning Pituitary Adenomas, Hormonal Insufficiency, Surgery, Radiotherapy, MRI Imaging, Endocrinology.

INTRODUCTION

Non-functioning pituitary adenomas (NFPAs) are benign tumours of the anterior pituitary gland that do not produce biologically active hormones. They account for around 15 to 30% of diagnosed pituitary adenomas and are generally discovered incidentally or in the setting of compressive complications and clinical signs of pituitary hormone deficiency [1, 2]. From an immunohistochemical point of view, more than 45% of adenomas show staining for gonadotropins or their subunits and are therefore termed gonadotropic adenomas, whereas 30% of these adenomas show no hormonal staining and are termed null cell adenomas [1].

The aim of this study was to analyse the clinical and paraclinical features of non-functioning pituitary adenomas and to identify the relative peculiarities of management and emerging perspectives for this pathology.

PATIENTS AND METHODS

This is a retrospective descriptive study of all patients with a non-functional pituitary adenoma who consulted a day hospital or were hospitalised in the Endocrinology and Metabolic Diseases Department of the Mohamed VI University Hospital, Marrakech, over a 4-year period from January 2018 to December 2024, i.e. a total of 28 patients.

We selected patients for whom non-secreting pituitary adenoma had been confirmed on clinical, biological and anatomopathological criteria.

The epidemiological, clinical, therapeutic and evolutionary characteristics of the patients were analysed retrospectively on the basis of medical records and a previously established data sheet.

Hypothalamic-pituitary nuclear magnetic resonance imaging was performed in all patients. The

macroadenoma (diameter greater than 1 cm) was characterised by T1 hypointensity. Microadenomas were less than 1 cm in diameter.

Data collection was carried out taking into consideration the overall ethical rules relating to respect for confidentiality and protection of patient-specific data.

RESULTS

Our series includes 28 patients with non-functioning pituitary adenoma, we noted a large female predominance, with a sex ratio of 4/10. The mean age of the patients in our series was 40.7 years, with extremes ranging from 11 to 67 years. The age group most affected was between 40 and 60. The main warning signs in our series of patients were headaches and reduced visual acuity.

Of the 28 patients, 12 (43%) consulted for a tumour syndrome involving headache and AVB, while galactorrhoea was indicative of AHNS in 4 cases (14.3%), decreased libido was found in 2 patients (7.1%), and staturo-ponderal retardation and intracranial hypertension syndrome in one patient (3.5%).

The clinical manifestations in our patients were presented as follows: spontaneous galactorrhoea was identified in 4 patients and induced galactorrhoea in 3, decreased libido and erectile dysfunction in 8 patients, major asthenia in 6 patients, cycle disorders such as spaniomenorrhoea or amenorrhoea in 4 patients, and hypoglycaemic malaise in 4 patients.

To confirm the diagnosis of a non-functioning pituitary adenoma, a complete hypophysogram was performed, revealing corticotropic insufficiency in 20 patients (71.4%), thyrotropic insufficiency in 12 patients (42.8%), gonadotropic insufficiency in 8 patients (28.6%) and disconnection hyperprolactinaemia in 5 patients (17.8%). Morphological exploration based on hypothalamic-pituitary MRI revealed macroadenomas in 67.8% of cases (Image1), microadenomas in 32.1% of cases and one case of apoplectic pituitary macroadenoma.

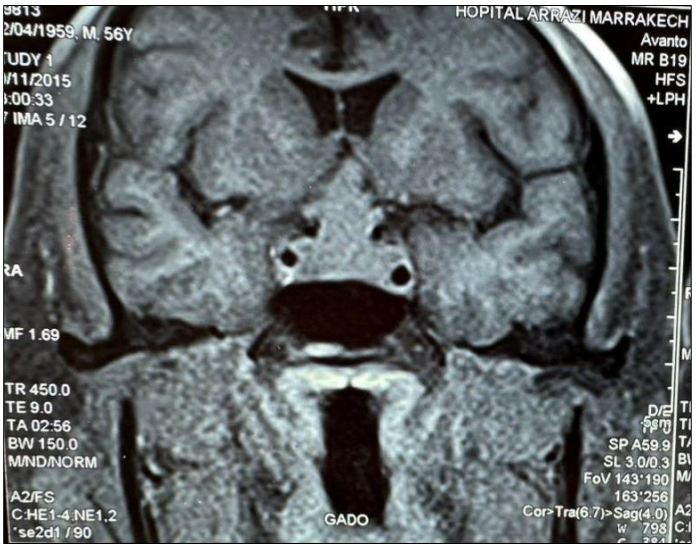

Image 1: Coronal T1 sequence of a pituitary MRI suggesting: a sellar and suprasellar lesional process in T1 isosignal, measuring 19x24x12.3 mm, hourglass shape with intense and homogeneous enhancement after injection of Gadolinium

Table 1: Main results

Epidemiological data	
Average age 40.7 ans	
Sex-ratio	4H/10F
Données cliniques	
Tumour Syndrom	43%
Galactorrhea	28.6%
Menstrual cycle disorders	14,3%
Decreased libido and erectile dysfunction	7,1%
Données biologiques	
Disconnection hyperprolactinemia	17.8%
Corticotropic axis dysfunction Thyreotropic Gonadotropic	71.4% 42.8% 28.6%

Données radiologiques	
Macro-adenoma	67.8%
Micro-adenoma	32.1%
Pituitary apoplexia	3.5%

DISCUSSION

NFPAs arise from monoclonal proliferation of cells of the anterior pituitary gland. Although they are said to be 'non-secreting', these tumours may express low-level hormonal markers, detected only by immunohistochemistry. They are often classified according to their cellular origin:

- Gonadotropic: the most common, expressing FSH and/or LH.
- Null cell adenomas: showing no hormonal expression.
- Plurihormonal: expressing several hormones without functional activation.

NFPAs affect both sexes equally and are generally diagnosed between the 4th and 6th decade of life [5], unlike in our study where there is a clear female predominance with a sex ratio of 4/10.

In 10% of cases, immunostaining is negative ('cell-free adenoma'). Exceptionally, GH, PRL, TSH or ACTH may be positive despite the absence of secretion; these cases are known as somatotrophic adenomas, lactotrophic adenomas, thyrotropin adenomas or adrenocorticotropic adenomas [1].

A distinction is made between: true non-functional adenomas without hormonal secretion (rarer), gonadotropic adenomas. non-functional or silent pseudo-adenomas with low hormonal secretion (prolactin, GH, TSH, ACTH or alpha subunit) but no clinical effect [4].

Clinically, NFPAs may manifest as a tumour syndrome, which has been found in 43% of cases; these rates are close to those reported in the literature [5-9], pituitary insufficiency in 80% of cases and, exceptionally, a hyperstimulation syndrome [1-5].

Diagnosis is based on clinical signs which, according to various studies, may manifest themselves in several situations, such as pituitary tumour syndrome in 50-80% of cases, with intense headaches resistant to analgesic treatment and visual field alteration such as bitemporal hemianopia secondary to chiasmatic compression [1], galactorrhoea, which may be a sign of disconnection hyperprolactinaemia, and biological investigations suggesting anteropituitary insufficiency secondary to compression of normal pituitary cells, or pituitary apoplexy, which is a medical emergency characterised by haemorrhage or necrosis of the adenoma.

A full hormonal work-up is essential to rule out other secreting adenomas. In asymptomatic patients, normal levels of TSH, ACTH, prolactin, FSH and LH are observed. Anteropituitary insufficiency affecting the different axes has been observed in several studies, gonadotrophic deficiency being the most widespread (>80% of cases), followed by somatotrophic deficiency; thyrotrophic and corticotrophic deficits are found in 20 to 50% of cases, moderate hyperprolactinaemia or disconnection hyperprolactinaemia has also been demonstrated [1-3]. In our study, disconnection hyperprolactinemia was found in 17.8% of cases. Pituitary adenomas can produce very small quantities of hormones (PRL, GH, ACTH, TSH) at levels that have no clinical consequences and do not release peptides with no biological activity [4, 5].

Pituitary MRI is the gold standard. NFPA appear as well-demarcated lesions, isointense in T1 and hyperintense in T2, a pituitary macroadenoma (>10mm) in the majority of cases [1-8]. In our study, macroadenomas were found in 67.8% of cases and microadenomas in 32.1%. Calcifications or haemorrhagic remodelling are rare but may be present, as in our study they were present in 3.5% of cases.

The management of NFPAs depends on their size, their compressive effects and their clinical course. The gold standard treatment is surgery, which will allow more or less complete eradication of the tumour and an anatomopathological and immunohistochemical study. Surgery is either trans-sphenoidal or transcranial, reserved for large tumours with suprasellar extension [6-8]. Radiotherapy is used in cases of recurrence or when surgical resection is incomplete. Medical treatment based on somatostatin analogues, dopaminergic agonists or their combination is indicated in cases of incomplete tumour resection and may be tested in some cases to reduce tumour size [6].

Anatomopathological and immunohistochemical studies confirm the diagnosis of NFPA. Immunohistochemistry is used to determine the nature of the adenoma: gonadotropic (FSH, LH, SU, chromogranin A antibodies) or silent somatotropic and/or lactotropic (GH, PRL antibodies) or corticotropic (ACTH, cytokeratin antibodies). Pathology reports should also establish proliferation status by systematically testing for three types of cell cycle marker: Ki67, mitosis index and p53 [1-3].

The main post-operative complications include: post-surgical pituitary insufficiency, tumour recurrence, and persistent visual disturbances in the event of prolonged compression.

The biochemical hormonal assessment at 3 months post-op concerns the recovery of preoperative pituitary deficits and the definitive nature of deficits discovered post-op. The investigation is then repeated to adapt, if necessary, replacement therapies in the event of functional warning signs or an increase in the size of any residue [1-7].

Post-operative MRI is essential in NFPA because of the frequent absence of clinical symptoms despite progression. The first MRI is performed at 3 or 6 months; a 6-month interval minimises interpretation difficulties due to postoperative remodelling. A second MRI is systematically performed one year after the operation. These two MRI scans serve as a reference for subsequent follow-up [1-8].

Advances in functional imaging and molecular biology are opening up new prospects for the early diagnosis and therapeutic strategy of NFPA. Genetic studies have identified recurrent mutations, such as those in the MEN1 and CDKN1B genes, offering potential targets for future treatments [7].

CONCLUSION

Non-secreting pituitary adenomas represent a complex clinical entity requiring personalised, multidisciplinary management. They are often discovered late in the course of visual complications, hence the importance of careful questioning and clinical examination, as well as extensive paraclinical investigations. Although their prognosis is favourable in the majority of cases, careful monitoring is essential to detect and treat associated complications.

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