Endocrinol Diabetes Nutr. 2017;xxx(xx):xxx–xxx

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

REVIEW ARTICLE

# Clinically non-functioning pituitary adenomas: Pathogenic, diagnostic and therapeutic aspects

**Moises Mercado**[a,b,*], **Virgilio Melgar**[b], **Latife Salame**[a], **Dalia Cuenca**[c]

[a] *Experimental Endocrinology Unit, Hospital de Especialidades, Centro Médico Nacional S.XXI, IMSS, Mexico City, Mexico*
[b] *Neurological Center, American British Cowdray Medical Center, Mexico City, Mexico*
[c] *Department of Medicine, American British Cowdray Medical Center, Mexico City, Mexico*

Received 6 April 2017; accepted 29 May 2017

**KEYWORDS**
Nonfunctioning pituitary adenomas;
Gonadotropinomas;
Null cell adenomas;
LH;
FSH;
Hypopituitarism

**Abstract** Clinically non-functioning pituitary adenomas (NFPAs) are among the most common tumors in the sellar region. These lesions do not cause a hormonal hypersecretion syndrome, and are therefore found incidentally (particularly microadenomas) or diagnosed based on compressive symptoms such as headache and visual field defects, as well as clinical signs of pituitary hormone deficiencies. Immunohistochemically, more than 45% of these adenomas stain for gonadotropins or their subunits and are therefore called gonadotropinomas, while 30% of them show no immunostaining for any hormone and are known as null cell adenomas. The diagnostic approach to NFPAs should include visual field examination, an assessment of the integrity of all anterior pituitary hormone systems, and magnetic resonance imaging of the sellar region to define tumor size and extension. The treatment of choice is transsphenoidal resection of the adenoma, which in many instances cannot be completely accomplished. The recurrence rate after surgery may be up to 30%. Persistent or recurrent adenomas are usually treated with radiation therapy. In a small proportion of these cases, drug treatment with dopamine agonists and, to a lesser extent, somatostatin analogs may achieve reduction or at least stabilization of the tumor.


**PALABRAS CLAVE**
Adenomas clínicamente no funcionantes;
Gonadotropinomas;

**Adenomas hipofisarios clínicamente no funcionantes: aspectos patogénicos, diagnósticos y terapéuticos**

**Resumen** Los adenomas hipofisarios clínicamente no funcionantes son los tumores más frecuentes de la región selar. Dado que estas lesiones no resultan en un síndrome de hipersecreción hormonal, se manifiestan por síntomas compresivos como cefalea y alteraciones campimétricas, así como por manifestaciones clínicas de hipopituitarismo, o bien son descubiertos de forma

* Corresponding author.
*E-mail addresses:* mmercadoa@yahoo.com, moises.mercado@endocrinologia.org.mx (M. Mercado).

http://dx.doi.org/10.1016/j.endinu.2017.05.009


Please cite this article in press as: Mercado M, et al. Clinically non-functioning pituitary adenomas: Pathogenic, diagnostic and therapeutic aspects. Endocrinol Diabetes Nutr. 2017. http://dx.doi.org/10.1016/j.endinu.2017.05.009

Adenomas de células nulas;
LH;
FSH;
Hipopituitarismo

incidental (en particular los microadenomas). Inmunohistoquímicamente, más del 45% de estos adenomas inmunotiñen para gonadotropinas o sus subunidades, por lo que se los conoce como gonadotropinomas; mientras que el 30% de los casos no inmunotiñe para ninguna hormona y se los denomina adenomas de células nulas. El abordaje diagnóstico de los adenomas hipofisarios clínicamente no funcionantes debe incluir la evaluación de los campos visuales y la medición de las hormonas de la hipófisis anterior, así como una resonancia magnética nuclear para establecer el tamaño y la extensión del tumor. El tratamiento de elección es la resección transesfenoidal del adenoma, que en ocasiones no se logra completamente. La tasa de recurrencia después de la cirugía puede ser de hasta el 30%. Los adenomas persistentes o recurrentes suelen ser tratados con radioterapia. Una proproción pequeña de estos pacientes puede responder de forma favorable a agonistas dopaminérgicos y, en menor medida, a análogos de la somatostatina.


## Introduction

According to the most recent report of the Central Brain Tumor Registry of the United States (CBTRUS), 15.5% of all central nervous system (CNS) neoplasms are pituitary tumors, third only to meningiomas (37.1%) and glioblastomas (15.6%).[1] In young adults, aged 20–34 years, over 30% of CNS tumors are in fact pituitary adenomas (PA).[1] These figures are similar to those reported by a meta-analysis, whereby the prevalence of pituitary adenomas in autopsy and radiological studies was found to be 16.7% and 22.5%, respectively.[2] It most be noted however, that many of these adenomas are small, incidentally found asymptomatic lesions.[2–5] The age-adjusted incidence rate of PA is estimated to be 3.4 cases per 100 000 inhabitants per year.[2]

Among community-dwelling studies, clinically non-functioning pituitary adenomas (NFPA) account for a mean of 33% of all PA, ranking second only to prolactinomas that represent 47% (Table 1).[6–11] NFPA are the most common type of adenomas when taking into account only macroadenomas, whereas prolactinomas predominate when both micro- and macroadenomas are considered in the analysis. Since they do not result in a hormonal hypersecretion syndrome, the diagnosis of NFPA is either made incidentally or relies on the detection of symptoms and signs of mass effect such as headaches and visual abnormalities due to optic chiasm compression as well as pituitary hormone deficiencies.[3,12,13] The prevalence of NFPA varies between 60 and 100 cases per million inhabitants, with a bimodal peak incidence between the ages of 25–45 and 60–70 years and a standardized incidence rate of 1.02–1.08 per 100 000; there is no gender predominance.[4,9,11,13,14]

## Pituitary tumorigenesis

Pituitary adenomas are benign, epithelial neoplasms, arising from a single cell clone that has undergone one or several mutational events.[15–17] A small proportion of these tumors, approximately 5%, occur in the context of hereditary syndromes such as type 1 multiple endocrine neoplasia (MEN1) caused by inactivating mutations of the menin gene,[18] the Carney complex resulting from inactivating mutations in the regulatory alpha-subunit of protein kinase-A (PRKARA1)[19] or the familial isolated pituitary adenoma syndrome (FIPA) due to loss of function mutations of the aryl hydrocarbon receptor binding protein gene (*AIP*).[20] Although in these hereditary syndromes the molecular abnormalities leading to tumor formation have been relatively well characterized, in the vast majority of pituitary adenomas occurring sporadically these molecular changes are only infrequently found as somatic events.[21] In fact, NFPA are far less frequent than functioning lesions in these hereditary syndromes. Data from a multicenter European study shows that among 324 cases of MEN1, 136 harbored pituitary adenomas, of which 116 (85.3%) were secreting tumors and only 20 (14.7%) were non-functioning adenomas.[22] NFPA have not been reported to occur in the context of the Carney complex, whereby the vast majority of pituitary lesions are GH-secreting adenomas.[23] Similarly, the majority of patients belonging to FIPA kindreds harbor GH and to a lesser extent, PRL secreting adenomas; less than 10% have NFPA.[24]

Thus, the oncogenic mechanisms responsible for the development of sporadic pituitary adenomas in general and of NFPA in particular are likely to involve multiple, simultaneously or sequentially occurring abnormalities in cell cycle regulation.[15–17] Some of these abnormalities may take place at an epigenetic level, through the silencing (by hypermethylation of CpG islands) of genes like p16, that encodes a Cyclin D inhibitor that normally prevents a cell with damaged DNA from progressing beyond the G1 phase of the cell cycle.[25] The pituitary tumor-transforming gene (*PTTG1*) localized in the short arm of chromosome 5 encodes a protein known as securin that regulates the separation of sister chromatids and modulates the DNA-repair actions of p53 (26). *PTTG1* mRNA is overexpressed in a significant proportion of both, secreting and non-secreting pituitary adenomas[27] and correlates with markers of aggressive biological behavior such as the Ki-67 index.[28] In a recently published whole-exome sequencing study of 7 patients with NFPA, no *MEN1*, *PRKRA1* or *AIP* germline mutations could be identified in DNA from peripheral mononuclear cells, and although 24 somatic genetic variants were found in tumoral DNA, including genes such as *PDGF* (platelet derived growth

Please cite this article in press as: Mercado M, et al. Clinically non-functioning pituitary adenomas: Pathogenic, diagnostic and therapeutic aspects. Endocrinol Diabetes Nutr. 2017. http://dx.doi.org/10.1016/j.endinu.2017.05.009