

# Clinical and neurological manifestations of non-functioning pituitary adenomas (NFPA) are it ok to suspect an early invasiveness?

## Abstract

**Introduction:** Clinically non-functioning pituitary adenomas (NFPA) are a heterogeneous set of complex adenomas with a wide variety of immunohistochemical subtypes such as silent gonadotrope, null cell adenoma, silent corticotrope adenoma, and other silent tumors of somatotrope, thyrotrope, and lactotrope lineages. The diagnosis is established by hypothalamus-pituitary MRI, which gives the volume of the tumor, and by determining the pituitary hormones, peripheral hormones when indicated, and neurologic manifestations. In NPFA, there is neither a typical hormonal hyper secretion nor a determined clinical syndrome.

**Conclusion:** The strategic location of the pituitary gland, in the case of macro adenomas, allows the compression of vital neurological structures inducing greater morbidity and mortality. The diagnosis is delayed in developing countries, and therefore, invasiveness is more frequent. The treatment consists of repetitive neurosurgeries and radiation therapies.

**Keywords:** non-functioning pituitary adenomas, diagnosis, clinical manifestations, hormonal profile, neurological complications, tumor invasion, tumor aggression, tumor size, chiasmatic syndrome

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**Abbreviations:** GH, growth hormone; TSH, thyroid stimulation hormone; MRI, magnetic resonance image; IMSS, mexican institute of social security; H-V, hardy vezzina; RE, right eye; LE, left eye; CI, confidence interval; ACTH, adeno corticotrophic hormone; POMC, pro opio melano cortin; LH, luteinizing hormone; CN, cranial nerve

## Introduction

The frequency of benign tumors of the pituitary is 10-20% of the primary intracranial tumors<sup>1</sup> with an incidence of 2.7 to 28 people out of 100,000 people a year,<sup>2-4</sup> although there is a great variance in the reported incidence of the pituitary adenomas. An early diagnosis is obtained in the case of female patients<sup>5</sup> as reported by Nabarro.<sup>6</sup> The non-functioning pituitary adenomas are a heterogeneous subset of neoplasms of monoclonal origin of the adenohypophysis,<sup>7</sup> which constitute 25-30% of pituitary neoplasias.<sup>8,9</sup> Diagnosis is usually established by detecting the predominant complications of neurological character, perhaps some degree of hypopituitarism, headache, and other clinical manifestations induced by the unpredictable biological behavior of those tumors. Prevalence of specific cellular lineage varies, but is has been calculated to be as 7 to 9 cases out of 100,000 inhabitants, including the silent gonadotrope, corticotrope, thyrotrope, oncocytic, null cell, lactotrope, and other silent cellular lineages.<sup>4,9</sup> In contrast to these data, a higher prevalence was registered in Belgium with a figure of 94 patients out of 100,000 people.<sup>10</sup>

The invasion and aggressiveness of these benign tumors are two different concepts; tumor invasion is considered when there is a predominant extension towards the sphenoid sinus and/or the

cavernous sinus, based mainly on radiologic and/or histopathological criteria, but suprasellar extension of the pituitary is not considered as an invasion criterion. Aggressiveness criteria are based on: observed clinical behavior, which can be rapidly progressive; to show a high rate of reappearance after surgery or a rapid growth, known as high mitotic index (with an index marked by MIB-1 $\geq$ 3%, as well as, a great immune reaction to p53); resistance to treatment; the precise histopathological description can be another indicator of aggressive behavior. The term infiltration is used basically when a malignant process of hypophysis is found.

The invasion of neighboring structures is frequent, and in fact, represents 25-55% of these cases [11]. The concepts of aggressiveness and invasion are different;<sup>12</sup> and are not interchangeable. Infrequently, the tumor tissue can affect, in its cavernous segment, the cranial nerves (CN) III, IV, V and VI, by compressing the adjacent neuronal tissue.<sup>13</sup> The vertical growth is established when the extension goes over the upper or lower borders of the sella turcica. The upper border of the sella is defined by a line that connects the tuberculum sellae with the back of the sella in a sagittal section. The lower border is an imaginary line that is drawn by tracing a perpendicular line from the upper border downwards at 7.24 mm. Thus, the vertical extension could be positive (upwards), or negative (downwards).<sup>14</sup> When the vertical extension is positive, the tumor might compress the axons of the optic chiasm, and also may obstruct the upper and lower vascular groups which anomalies themselves. The lower group is originated from the upper pituitary artery, and both groups (upper and lower) are branches of the posterior cerebral artery.<sup>15</sup> This phenomenon may induce ischemia (most of the time by direct compression), which

frequently reflects as defects in the visual fields and rarely, does not affect the optic chiasm.

The aim of this study was to analyze the neurological complications, other clinical problems, as well as hormone concentrations of the non-functioning pituitary neoplasia.

## Patients and methods

156 patients with non-functioning clinically pituitary adenoma were included. They had been admitted without previous treatment to the Clinical Endocrinology Department of the Specialty Hospital from the National Medical Center "La Raza" (IMSS) between January 2006 and January 2012. They were retrospectively studied after pituitary surgery was performed. The hormone determinations were carried out at least twice within a month interval. The tumor was classified according to Hardy-Vezzina (H-V) method. The neuro-ophthalmologic study was performed using the Goldmann perimetry test.

## Statistical study

Shapiro Wilk test was used to analyze the distribution of age and sex; the Barnard exact test was utilized to relate the qualitative variables, headache, and optic chiasma compression that correlates the chiasmatic syndrome with the tumor size, the cavernous sinus tumor invasion degree (classification H-V), and any adenohypophysis hormone deficiency. The statistics tests were considered significant when  $p < 0.050$  was reached.

## Results

78 women and 78 men were studied from our database of 156 patients, 50% for each gender. The average age of the patients with this pathology was  $51 \pm 15$  years old. The youngest female patient was 22 years old and the oldest 80, whereas the youngest male patient was 16 and the oldest 82. The most frequent presentation age with a non-functioning macro adenoma in the male patients, was 38 years. Age and sex had a normal distribution. The study lasted 6 years, and it was observed secondary chiasmatic syndrome due to a hypophyseal

benign tumor in 137 patients (87.82%), and no chiasmatic syndrome was found in 19 patients (12.18%).

In this group of patients, 155 had macroadenoma and 1 microadenoma ( $p < 0.001$ ). The main ophthalmologic complications included amaurosis (n=58): bilateral amaurosis in 10 patients (6.41%), right eye amaurosis was found in 20 patients (RE), and left eye amaurosis in 25 patients (LE) (16.03%). Other partial alterations such as hemianopsias and quadrantanopsias were found in 74 patients (Table 1).

A  $p$  value  $< 0.0001$  was found using the binomial exact test with CI at 95% [84.04, 94.29], when comparing against randomness. Dislalia was found in 1 patient, right palpebral ptosis in 1 patient, and headache in 41 patients (26.28%); the relationship between headache and IV-E stage of H-V classification was significant ( $p < 0.017$ ). This relationship disappeared within 6 months in 30 of the patients after neurosurgery.<sup>16</sup> A tumor extension to the III ventricle was observed in 16 cases (10.26%), diabetes insipidus in 4 patients (2.56%), and pituitary apoplexy in 11 cases (7.05%). A tumoral invasion to the sphenoidal sinus was present in 14 patients (8.97%), and to the right cavernous sinus was found in 26 patients (16.17%); CI 95% [11.26%, 23.60%],  $p < 0.0001$ . An invasion to the left cavernous sinus was noted in 28 patients (18.06%) with CI 95% [12.35%, 25.04%]  $p < 0.0001$ . Even when this diagnosis was performed by the interpretation of a magnetic resonance image (MRI), a more precise diagnosis was made by the direct surgeon's observation during surgery<sup>14</sup> (Table 2).

On the 156 patient's database, the more frequent tumor stage in 72 patients (45.51%) was IV-E, according to the Hardy-Vezina classification (45.51%); the second more frequent was IV-D stage in 48 patients (30.76%), III-Cin 9 patients (5.76%), and III-Ein 7 patients (4.48%).

Hypogonadism was present in 29 female patients and in 35 male; hypocortisolism was present in 11 female and 7 male patients. Secondary hypothyroidism developed in 81 patients and panhypopituitarism in 26 patients which represent 16.67% CI 95% [11.26%, 23.60%]  $p < 0.0001$ .

**Table 1** Alterations of the visual fields in non-functioning adenomas

| Defect | Amaurosis |        |        | Hemianopsias |        |       | Quadrantanopsias |  |
|--------|-----------|--------|--------|--------------|--------|-------|------------------|--|
|        | Bilateral | RE     | LE     | Bi temporal  | RE     | LE    |                  |  |
| N      | 10        | 23     | 25     | 50           | 16     | 5     | 3                |  |
| %      | 6.41%     | 14.74% | 16.03% | 32.05%       | 10.26% | 3.21% | 1.92%            |  |

Visual alterations in number and percentage; they include amaurosis, hemianopsias and quadrantanopsias.

**Table 2** Abnormal pituitary hormone function in non-functioning macro adenomas (Preoperative Diagnosis)

| Deficit            | Patient | %     |
|--------------------|---------|-------|
| Hypothyroidism     | 81      | 51.92 |
| Hypogonadism       | 64      | 41.03 |
| Hyperprolactinemia | 39      | 25    |
| Hypoadrenalinism   | 18      | 11.54 |
| Rise Of Acth       | 12      | 7.7   |

## Discussion

The database, which comprises 155 patients with non-functioning macro adenomas and 1 patient with micro adenoma, was analysed. Clinical, biological, and neuro-radiological data were gathered, as well as the pre and post-surgery hormone measurements, in order to realize a proper diagnostic procedure, and to choose the optimal treatment. The patients were studied by several endocrinologists, and the pituitary surgery was performed by different neurosurgeons. 156 patients' tumors were measured and the vector growth was observed; the symptoms, due to the mass effect, the hormonal study, and the impairment to any other neuronal structure were also considered. The clinical diagnosis was analyzed, which in many cases, was established

immediately before internment to the hospital. The most frequent initial symptom was a visual field defect; but the proper diagnostic approach was usually delayed by several weeks or months, until the patient arrived with a clear advanced visual field defect, which was irreversible in most of the cases. The observed hormonal abnormalities were: hyperprolactinemia registered in 39 patients (25%) whose 94 to 130 dL concentration was probably due to a shift of the dopaminergic inhibition process at the lactotrope level by a direct compression of the pituitary stalk by the tumor itself, without clinical hyperprolactinemic symptoms that also could have been caused by a biologically inactive prolactin.

Ferrante E et al.,<sup>17</sup> studied a group of 295 patients, with silent macro adenomas, and found hyperprolactinemia in 27.6% of them; Karavitaki N et al.,<sup>18</sup> also studied 226 patients and reported the existence of an association in 38.5% of them of non-functioning macro adenoma and hyperprolactinemia. Hyperprolactinemia incidence in our study is similar to the above mentioned studies.

The rise of ACTH serum levels in 12 patients (7.69%) was due to a silent corticotropinoma, probably by an abnormal processing of POCM and/or by a biologically inactive ACTH. Trouillas J et al.,<sup>19</sup> carried out a multicenter study with 410 patients of which 19 of them (4.63%) were described to have a pituitary corticotropinoma. Five of these were considered to be invasive with a high proliferation index.

Ioachimescu AG et al.,<sup>20</sup> studied two groups of patients with a corticotroph adenoma: 32 who showed a positive ACTH and 126 with a negative ACTH immune test; positive ACTH adenomas invaded the cavernous sinus in 45.5 % of the cases, and the negative ACTH did it in 30.2%. Ioachimescu AG et al.,<sup>20</sup> as well as other researcher's results matches our data as far as the invasion of the cavernous sinus is concerned. Thus, the cavernous sinus invasion associated with the presence of a silent corticotropinoma usually establishes the diagnosis of a very aggressive neoplasm, which should be suspected by a hormonal survey, at least initially, where you may observe a rise in the ACTH serum concentrations.

Panhypopituitarism, defined as the deficiency of at least three hormones, was diagnosed in 26 patients (16.67%). This is debatable since other studies report higher incidence due to different diagnostic criteria.<sup>21-24</sup> This difference may be explained by our lack of utilization of the hypothalamus-pituitary unit stimulation tests. Post-surgery hypothyroidism was confirmed in 51.92% of our patients, whose frequency is by far inferior to the studies performed prior to surgery. Concerning the hormonal therapeutic substitution for hypocortisolism, hypothyroidism and hypogonadism, it should be noted that the first two conditions are critical, and should always be kept in mind.

Headaches were present in 26.28% of our patients and the incidence was relatively low when compared with other groups where it could reach up to 41.4%.<sup>17</sup> In Chen L et al group, where 385 macro adenomas were analyzed, it was found that headache was present in 62.1% of the patients.<sup>25</sup> This could be explained by the different scales and criteria used to assess this phenomenon. Headache pathogenesis could be explained with the following issues: an increase of the intrasellar pressure, rise of the duramater tension, invasion and/or erosion of the lateral wall of the cavernous sinus, genetic predisposition,<sup>26</sup> and hypothyroidism. It has also been described the concomitant trigeminal nerve involvement by pituitary tumors.<sup>27</sup>

Patients with non-functioning pituitary adenomas have a higher mortality rate due to respiratory, cardiovascular and cerebrovascular pathologies, which are related to repeated surgeries, radiotherapy, and the inadequately treated hypopituitarism.

Unfortunately, in these non-functioning pituitary adenomas, the opportune diagnosis is delayed, especially when considering that in our series the patient's average age was 51 years. Other factors that could have influenced in this delay were low social, economic and cultural status, which in this study was found in 95% of our cases. Another issue that should be taken into account is the patient's genetic profile.

H-V and Knosp's classification gave us highly trustable information about the nature of the neoplasia's growth vector. We considered that both, the Knosp and the Hardy-Vezzina methods are highly useful to analyze the sellar, parasellar, intrasellar and suprasellar growth. The tumor's intensity (or density), the sellaturcica extension and volume are all important to establish an optimal therapeutic approach during surgery. The unusual invasion of the tumor into the sphenoidal sinus may result in the formation of cerebrospinal fluid fistula. In spite of what many authors consider, the presence of a micro adenoma does not rule out that the adenoma could be invasive into the adjacent structures, or to produce severe neurologic complications. Three patients have been reported to have microadenomas that invaded the cavernous sinus.<sup>28</sup> We had a patient with microadenoma, which in spite of its size, developed chiasmatic syndrome with RE amaurosis. Alterations of the patient's visual field, especially in macroadenomas, usually happen due to a direct compression of the optic chiasm induced by the upward vertical growth. However, in the case of microadenomas the damage to the optic nerve could happen by different mechanisms: through traction or ischemia of the optic chiasm, although it is not the usual behavior of the microadenomas.

## Conclusion

- a. The initial diagnosis of clinically non-functioning pituitary adenoma should be carried out through clinical indicators especially focused on neurologic manifestations, though the definitive confirmation is done during the post-surgery period through a tumor's immuno cyto chemical tissue study.
- b. The biological behavior of these tumors is frequently invasive and/or aggressive to the adjacent structures, independent of its size. This issue is vital in order to be able to choose the best possible therapy, as well both to control the disease and to perform the follow-up in the long term.
- c. Therefore, these tumors must be studied very carefully: clinical history, neuro-ophthalmological study, hormone determination should include LH, FSH, subunit  $\beta$ , GH, IGF-1, ACTH, cortisol, Prolactin, TSH,  $T_4$  free, and depending on gender, Testosterone, Progesterone serum levels, and also complete blood biochemistry
- d. The main biomarkers that could indicate the aggressiveness of the tumor are: Ki-67, p53, MIB-1.
- e. Neuro-imaginining study preferably with magnetic resonance imaging, and secondly by computed tomography scan of the hypothalamus pituitary unit both with and without contrast media, should be carried out in order to determine both the tumor's intensity or density and volume.

f. It is important to consider the anatomical complexity of the optic chiasm: which could be classified as prefix, postfix, lower, medium and high<sup>29</sup> as well as the normal anatomic variants of the sella turcica,<sup>30</sup> and the pituitary position which could be: upper, upper back, lateral, or inferior.<sup>14</sup>

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## Conflict of interest

The author declares there is no conflict of interest.

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