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Original Research

A Prospective Study Of Epidemiology, Clinical Presentation And Diagnosis Of Non Functioning Pituitary Adenoma In Tertiary Care Centre

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ABSTRACT

Introduction & objectives- It is a prospective study of epidemiology, clinical presentation and diagnosis of non functioning pituitary adenoma. Their prevalence, sex ratio, age at diagnosis, age distribution and duration of symptoms were studied. The presenting manifestations, size and management of pituitary NFA has been studied.

Material & methods- First 100 cases of non functioning pituitary adenoma patients admitted in department of neurosurgery from 01 august 2022 to 31 December 2023 were included in our study. All patients with pituitary macroadenomas and microadenomas (<10 mm), with or without symptoms were included.

Observation & results- Visual field abnormalities and headaches were the presenting complaints in 87% and 66%, respectively. Central hypothyroidism, hypogonadism, and hypocortisolism were present in 47.2%, 35.9%, and 27.4%, respectively. Surgical resection was performed at least once in 85.7%.

Conclusion- The clinical spectrum of NFPAs varies from being completely asymptomatic to causing significant hypothalamic/pituitary dysfunction and visual field compromise due to their large size. The diagnosis and treatment of NFPA are complex and require a multidisciplinary approach.

Keywords: Pituitary adenomas, Hypopituitarism, Incidentalomas, Neuro-ophthalmological complications, Non-functioning pituitary adenomas

INTRODUCTION

Non-functioning pituitary adenomas (NFPAs) are benign pituitary neoplasms that arise from the adenohypophyseal cells and lack clinical or biochemical evidence of hormone excess except for a mild hyperprolactinaemia in some cases. They account for 14–54% of pituitary adenomas (1–9). The prevalence of NFPAs is variable and is often based upon autopsy or magnetic resonance imaging (MRI) series. This is likely an underestimate of the true prevalence, as many NFPAs go undiagnosed until they are large enough to cause mass effect or are accidentally discovered. Data are discordant about gender predominance and the peak occurrence is from the fourth to the eighth decade. A recent population-based study from North India showed an annual incidence of 3.5 cases/ 100,000 population for NFPAs, which is noticeably higher than the annual incidences previously reported in other countries (10). These differences may be related to genetic and environmental factors in Asian populations or inter-study heterogeneity and may also reflect the good local access to diagnostic evaluations using magnetic resonance imaging and computed tomography.

The absence of clinical manifestations of hormonal hypersecretion usually results in significant diagnostic delay and therefore NFPAs may not be diagnosed until they cause mass effects to surrounding structures (11), causing symptoms such as headaches, visual disorders, and/or cranial nerve dysfunction. Other manifestations are hormone deficiencies or hyperprolactinemia due to pituitary stalk deviation and, less frequently, pituitary apoplexy (12,13). Additionally, some cases may be diagnosed incidentally through imaging studies performed for other purposes, the so-called pituitary incidentaloma.

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Neurologic Manifestations

Visual Impairment- Impaired vision, caused by suprasellar extension of the adenoma that compresses the optic chiasm, is the most common neuro-ophthalmological symptom (13). Both eyes are usually affected, although a significant proportion of patients may have unilateral or altitudinal problems in 33 and 16% of the cases, respectively (14). Diplopia, induced by oculomotor nerve compression resulting from parasellar expansion of the adenoma may occur, and the fourth, fifth and sixth cranial nerves may also be occasionally involved when there is parasellar expansion (15). Nevertheless, the typical visual field defect associated with pituitary tumors is bitemporal hemianopia, reported in approximately 40% of the patients.

Headache- It is the second most common neurologic symptom, occur in 19-75% of patients with pituitary tumors, regardless of size (16). Cerebrospinal fluid (CSF) rhinorrhea, associated or not with headache, can occur in cases where the tumor causes erosion of the sellar floor and extends inferiorly to the sphenoid sinus.

Pituitary apoplexy- Pituitary apoplexy (sudden hemorrhage into a pituitary adenoma) is rare (17). It causes acute onset of a severe headache associated with visual disturbances and can occur in all types of pituitary tumors, although some series suggest pituitary apoplexy might be more common in NFPAs than other adenomas subtypes (18). Pituitary apoplexy may occur without an identified risk factor, but it has also been reported as being related to pregnancy, use of anticoagulants, surgical procedures, as well as in association with dynamic tests, such as thyrotropin-releasing hormone (TRH), gonadotropin-releasing hormone (GnRH), and insulin-tolerance stimulation tests (19).

Endocrine Manifestations

Hormonal deficiencies- Most patients with nonfunctioning pituitary macroadenomas present with deficiency of at least one pituitary hormone resulting from the compression of the normal anterior pituitary and/or pituitary stalk, preventing the stimulation of pituitary cells by hypothalamic factors. Hypogonadism can result from either a direct compressive effect on gonadotropic cells or by stalk compression-induced hyperprolactinemia that inhibits the pulsatile secretion of gonadotropin releasing hormone via interfering with hypothalamic kisspeptin-secreting cells (20). This “disconnection hyperprolactinemia” usually <2000mIU/L (95 ng/mL) (21) is characterized by compression of the pituitary stalk, which prevents the arrival of dopamine to the anterior pituitary, the main inhibitor of prolactin (stalk effect). GH and gonadotroph axes are most commonly affected, followed by adrenal insufficiency and central hypothyroidism (15).

HORMONAL EXCESS- Gonadotroph adenomas are usually considered to be "nonfunctioning" although they can secrete intact gonadotropins, as they do not generally result in a clinical syndrome. Occasionally, gonadotroph adenomas secrete primarily FSH but also LH in quantities high enough to raise serum gonadotropin levels, which in turn, may lead to the development of some specific symptoms, such as ovarian hyperstimulation in young women (22,23,24) or, more rarely, precocious puberty or testicular enlargement in men. In addition, low serum LH:FSH ratios (usually < 1.0) have been described in clinically-secreting gonadotroph adenomas (25). Measurement of α-subunit may also contribute to a preoperative diagnosis in clinically silent but biochemically-secreting NFPAs, as it may be the sole biochemical marker of the gonadotroph subtype in a number of cases. In addition, circulating FSH, LH and α-subunit levels can help the post-operative surveillance of these patients (24).

Pathology- NFPAs include a cluster of pituitary tumors without endocrine manifestations of hormone overproduction. The new fourth WHO classification adopted a pituitary adenohypophyseal cell lineage designation of the adenomas with subsequent categorization of histological variants according to hormone content and specific histological and immunohistochemical features. As a consequence, nonfunctioning pituitary tumors include gonadotroph adenomas—with varying degrees of immunohistochemical reactivity for β-FSH, β-LH, and α-subunit or combinations, null cell adenomas—with no immunohistochemical evidence of cell-type-specific differentiation by using pituitary transcription factors and adenohypophyseal hormones- and some plurihormonal adenomas [25]. A very small percentage of tumors that are clinically classified as non-functioning have immunohistochemical characteristics of somatotropinomas or corticotropinomas and consequently are referred to as silent somatotroph and coricotroph adenomas [26].

Radiological investigation -Pituitary microadenomas are measuring less than 10 mm in diameter and are typically small intrasellar lesions. Macroadenomas (tumors≥1 cm) are predominantly localized within an enlarged sella turcica. For the radiological classification two systems are currently used, the Hardy and the Knosp classification. The Hardy classification divides pituitary adenomas into four grades based on their size and the invasiveness in the sella turcica [27]. The Knosp classification takes into account the tumor invasion of the cavernous sinus according to coronal sections of MRI scans, with the readily detectable ICA serving as the radiological landmark [28]. MRI is the gold standard for the evaluation and differential diagnosis of sellar/suprasellar region. In T1-weighted images, the adenomas can be hypo- or isointense compared to non-tumoral pituitary tissue and take up gadolinium poorly or not at all. In T2-weighted images the adenomas appear isointense compared to the white matter.

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Guidelines on pretreatment- Ophthalmology Evaluation in Patients With Suspected NFPAs have recently been published by the Congress of Neurological Surgeons [29]. They recommend preoperative ophthalmologic evaluation with psychophysical (acuity and visual fields), functional (quantitation of afferent pupillary defect and visual evoked potentials), and anatomic [disc appearance and optical coherence tomography (OCT)] assessment. Investigation of pituitary function- All patients presenting with a pituitary incidentaloma or an NFPA should undergo laboratory evaluation for hormone hyper secretion and hypopituitarism (30).

MATERIAL AND METHODS

Sampling- 100 cases of non functioning pituitary adenoma patient admitted in department of neurosurgery from 01 August 2022 to 31 December 2023.

Inclusion Criteria- All patients with pituitary macroadenomas and microadenomas (<10 mm), with or without symptoms, should undergo laboratory assessment in order to detect hormonal hypersecretion or hypopituitarism. At diagnosis, 25–65% of patients with NFPAs present with hyperprolactinemia caused by pituitary stalk compression (12, 21, 30). It is important to distinguish between a prolactinoma and a NFPA since treatment strategies for these two conditions differ, i.e. dopamine agonist therapy being the treatment of choice for prolactinomas.

Exclusion Criteria- If the imaging and/or pathology data was consistent with a NFPA, but the available hormonal work-up was not complete, the patient was categorized as having a NFPA of unknown functional status (UFS). Subjects with sellar masses other than NFPA or with non-convincing criteria for the diagnosis of a PA were excluded from the study .

Methodology- Patients who commonly presented with symptoms related to the mass effect on surrounding structures, including headache, visual defects and hypo pituitarism were the study universe for symptomatic NFPAs. Demographic data of the patients was taken at the time of diagnosis. MRI with and without gadolinium contrast is gold standard for diagnosis. Endocrine assessment of NFPA was performed by following criteria (31,32).

Endocrine assessment- Ruled out a hormone-producing adenoma clinically and biochemically by morning serum cortisol; dynamic testing if needed. For HPA axis, introduced GC replacement if SAI was confirmed. For Thyroid function, serum TSH and free T4 levels &introduced L-thyroxine in severe CH. For HPG axis, evaluated hypogonadism clinically and biochemically. For somatotropic axis, diagnosis or treatment for GHD is not recommended preoperatively

Radiological assessment- MRI evaluating the relationship to the chiasma and optic nerve, and grading of extrasellar extension using the Knosp scale.

Ophthalmologic assessment- Visual field, visual acuity and eye movement.

Indication for surgery and perioperative management- Treatment options for NFPAs include active surveillance, surgical treatment, and radiotherapy. In patients with large NFPAs and visual impairment or other signs and symptoms related to tumor compression, transsphenoidal surgery is the recommended first-line treatment [28]. Radiotherapy, as a primary therapy, is only considered in cases where surgery is contraindicated, such as in patients with other serious co-morbidities or in inoperable cases.

Statistical analysis

All the data was entered in excel sheet. Continuous data was measured in terms of mean and standard deviation. The difference between two means was analyzed using student t-test. Continuous data was measured in terms of proportion and difference b/w two proportion was analysed using chi-square test. The confidence level for all statistical analysis was kept at 95%. Odds ratio for risk factor was calculated by 2*2 table.

RESULTS

485 patients (54% men, mean age 53 ±14 years) were followed for a median of 6.5 years. Visual field abnormalities and headaches were the presenting complaints in 87% and 66%, respectively. The diagnosis of NFPA was made incidentally in 6.2%, and 8% presented with clinical evidence of apoplexy. All patients harboured macro adenomas with a median volume of 10306 mm (3). 57.9% had supra-sellar or para sellar invasion and 19.6% had tumors larger than 4 cm. Central hypothyroidism, hypogonadism and hypocortisolism were present in 47.2%, 35.9%, and 27.4%, respectively. Surgical resection was performed at least once in 85.7%. Tumor persistence was documented in 27% and was related to the size and invasiveness of the lesion (Fig. 1). In selected cases, radiotherapy proved to be effective in controlling or preventing tumor growth.

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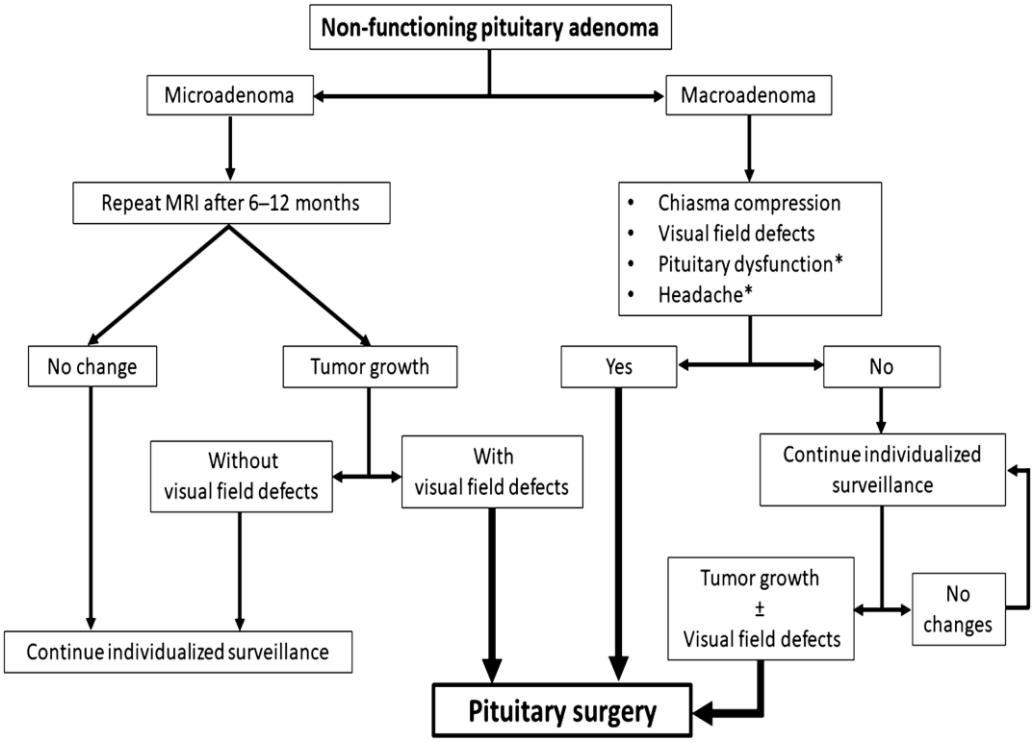

Figure 1: Indication for pituitary surgery in patients with non-functioning pituitary adenomas. Surgery is currently recommended in patients with adenomas abutting or compressing the chiasma with visual field deficits. In the absence of visual impairment, a conservative management may be considered.

DISCUSSION

A prospective study was performed by Chen et al (12) to evaluate the presentation, therapeutic management, and clinical outcome of nonfunctioning pituitary adenomas (NFPAs). In most of 385 consecutive patients, NFPAs were macro adenomas. The mean follow-up duration was 5.5 ±1.4 years. Presentation was dominated by headache, visual disturbance, and hypo pituitarism. Pituitary apoplexy (clinical and subclinical) was observed in 88 patients. Appropriate steroids replacement was given before surgery. Endoscope-assisted trans sphenoidal surgery (TSS) was performed and was well tolerated by all patients. At discharge, visual disturbances were improved in 215 (87.6%) patients who had complained of visual impairment preoperatively. The shorter the time from presentation of pituitary apoplexy to surgery, the better the outcome in visual function. Seventy two (18.7%) patients developed transient diabetes insipidus (DI) and 85 (22.1%) patients developed hypo natremia, but all these improved within six weeks. Hypo cortisolism was confirmed in 84 (21.8%) patients with an abnormal postoperative day 2 (POD2) 0800 serum cortisol level and in 122 (31.7%) patients with an abnormal POD6 0800 serum cortisol level. Hypothyroidism occurred in 135 (35.1%) patients. Steroids replacement was thus given immediately. Eight (2.1%) patients needed lifetime hormone substitution. No adrenal crisis occurred. Five (1.3%) patients died within six weeks. Residual tumors were confirmed in 79 patients (20.8%) by postoperative four-month enhanced MR imaging. Tumor recurrence or regrowth occurred in 56 patients (14.7%) during the follow-up period. These patients required repeat TSS or radiosurgery. The findings of this study support the use of TSS as a feasible initial treatment for NFPAs. With appropriate peri operative management of abnormal fluid, electrolyte, and endocrinological function, TSS was associated with minimum morbidity and was well tolerated by patients regardless of age. However, close screening of pituitary function and adequate neuroradiological follow-up should be performed after surgery for detection of tumor recurrence or re growth. The indications for repeat TSS and postoperative radiosurgery in residual or recurrent NFPAs should be better defined. Ntali et al (15) found in their study that NFA account for 14-54% of pituitary adenomas and have a prevalence of 7-41.3/100,000 population. Their standardized incidence rate is 0.65-2.34/100,000 and the peak occurence is from the fourth to the eighth decade. The clinical spectrum of NFPAs varies from being completely asymptomatic to causing significant hypothalamic/pituitary dysfunction and visual field compromise due to their large size. Most patients present with symptoms of mass effect, such as headaches, visual field defects, ophthalmoplegias, and hypopituitarism but also hyperprolactinaemia due to pituitary stalk deviation and less frequently pituitary apoplexy. Non-functioning pituitary incidentalomas are found on brain imaging performed for an unrelated reason. Diagnostic approach includes magnetic resonance imaging of the sellar region, laboratory evaluations, screening for hormone

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hypersecretion and for hypopituitarism, and a visual field examination if the lesion abuts the optic nerves or chiasm. Vargas et al (17) found that nonfunctioning pituitary adenomas (NFPAs) are the most common benign lesions of the pituitary gland.

CONCLUSION

Most patients present with symptoms of mass effect, such as headaches, visual field defects, ophthalmoplegia and hypopituitarism but also hyperprolactinaemia due to pituitary stalk deviation and less frequently pituitary apoplexy. The diagnosis and treatment of NFPA are complex and require a multidisciplinary approach. Treatment options for NFPAs include active surveillance, surgical resection, and radiotherapy. Pituitary surgery is currently recommended as first-line treatment in patients with visual impairment due to adenomas compressing the optic nerves or chiasma. Radiotherapy is reserved for large tumor remnants or tumor recurrence following one or more surgical attempts. Special emphasis should be laid on multimodal management to ascertain optimal long term tumor control with best hormonal outcome.

CONFLICT OF INTEREST- Nil

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