

Clinically Non-Functioning Pituitary Tumours (CNFPTs)

The Diagnostic Pathway (11-2K-234)

Common presenting symptoms:

Pituitary adenomas are benign neoplasms of the pituitary gland. Clinically non-functioning adenomas are characterized by the absence of clinical and biochemical evidence of pituitary hormonal overproduction.

Clinically non-functioning pituitary **microadenomas** are confined to the sella turcica and usually do not cause any signs or symptoms. They are often discovered incidentally during radiological imaging for other indications.

The clinical signs and symptoms of clinically non-functioning **macroadenomas** are determined merely by mass effects of the tumour. The main complaints are visual field defects with or without decreased visual acuity, effects of hypopituitarism and occasionally headaches. Other presenting symptoms are rarely apoplexy, cranial nerve deficits, and optic nerve atrophy. Typically, macroadenomas cause a bitemporal visual field defect, which is explained by the anatomy of the visual pathways in the optic chiasm. In addition to pituitary deficiencies, non-functioning macroadenomas can be accompanied by mild/moderate hyperprolactinaemia secondary to pituitary stalk interruption syndrome.

Clinical assessment:

In the majority of patients presenting with non-functioning macroadenomas, pituitary insufficiency is present to some degree. GH deficiency is present in about 85% and gonadal deficiency in about 75% of all patients, whereas corticotroph (38%) and thyrotroph deficiencies (32%) are present to a lesser degree. Therefore, the endocrine evaluation of all patients with macroadenomas should include appropriate assessment of hormonal pituitary function.

Because the diagnosis of clinically non-functioning pituitary adenomas is made by exclusion of hormone overproduction, the evaluation of the medical history and the physical examination should include a search for signs and symptoms of hormonally active pituitary adenomas, like acromegaly, and Cushing's disease. Careful evaluation of the pituitary function is indicated to exclude overproduction of one or more pituitary hormones.

Radiological assessment:

All patients with a suspected pituitary adenoma should have a MRI scan as per current WCFT imaging protocol for pituitary tumours which includes the following sequences:

- T2 axial brain images
- T1 sagittal and coronal images of pituitary
- Post gadolinium T1 sagittal and coronal images of pituitary

Differential Diagnosis: Adenomas account for more than 90% of intrasellar tumours. The most common other intrasellar tumours are Rathke's cleft cysts, craniopharyngiomas, metastatic carcinomas, chordomas and meningiomas.

Ophthalmological assessment:

In patients with macroadenomas where optic apparatus involvement is seen on imaging, formal visual field testing should be performed.

All new diagnoses of CNFPTs to be put through the Regional Pituitary MDT

The Treatment Pathway (11-2K-235)

Surgery:

Main **aims for treatment** of patients with clinically non-functioning macroadenomas are the preservation or restoration of visual function and adequate long-term tumour control. Because recovery from pituitary dysfunction is not likely to happen in many patients, the aim of transsphenoidal surgery should be improvement and protection of visual function, rather than improvement of pituitary function.

Transsphenoidal surgery is the treatment of choice in patients with visual field defects because this is the only treatment modality leading to immediate decompression of the optic nerve. Visual recovery can already be demonstrated within the first days after surgery. Improvement of visual function can continue even until 1 yr after surgical treatment, at least in some patients. Because there is a significant correlation between the severity of visual loss before surgery and persisting visual field defects after treatment, the delay of surgery should not unnecessarily be prolonged.

The optimal treatment strategy in patients with a clinically non-functioning macroadenoma and normal visual fields is a challenge. For patients without compression of the optic nerve, treatment decisions should be individualized and consider age, proximity of the tumour to the chiasm, pituitary function, fertility status, and preferences of the patients.

Conservative approach:

- Assessments of pituitary endocrine function at regular intervals (every 6-12 months) are recommended because the remaining pituitary function can be compromised by growth of the macroadenoma
- An MRI should be repeated within 1 year
- Radiological assessment by MRI is recommended with yearly intervals, which may be extended to two yearly intervals in the absence of progression of the macroadenoma
- The interval for visual field assessment depends upon the distance between the pituitary adenoma and the optic chiasm.

Main **disadvantages** of a conservative approach:

- possibility of the development of visual field defects
- apoplexy
- hypopituitarism

From observational studies it has been shown that growth will be observed in approximately 50% of patients with a non-functioning macroadenoma during a follow-up period of about 5 years. The 'watch and wait' policy seems reasonable for microadenomas but is probably not a safe approach for all macroadenomas, which appear to have a significant growth potential; in these cases, given the lack of established medical treatment, the decision for surgical intervention should balance the presence of significant comorbidities and the anaesthetic/peri-operative risks at presentation against the probability of tumour enlargement and its consequences, as well as the possible loss of advantages associated with early operation.

Radiotherapy:

A number of retrospective studies have assessed recurrence rates of clinically nonfunctioning pituitary macroadenomas after transsphenoidal surgery.

In studies on patients without postoperative radiotherapy, regrowth rates ranged between 6 and 46%. Even after prophylactic postoperative radiotherapy, regrowth was observed in 0–36%, underscoring the fact that radiotherapy does not prevent tumour regrowth in all patients.

The average duration of follow-up in all series is limited to only 7.4 yr after surgery. Prolongation of this duration of follow-up will most likely result in a higher rate of recurrence or regrowth than appreciated by the currently available data.

Overall, the available data would suggest a benefit of postoperative radiotherapy with respect to long-term tumour control. Studies with a randomized comparison between surgery with and surgery without postoperative radiotherapy are lacking. A study comparing two hospitals with different treatment strategies with respect to postoperative radiotherapy establishes the positive effect of postoperative radiotherapy on tumour recurrence.

The main limitation to the use of radiation therapy is safety. Hypopituitarism is observed in over 50% of patients receiving radiation therapy after 5–10 years. However, if hypopituitarism is already present in a patient, this is less of an issue. There is also a small risk of vision defects and radiation induced optic neuropathy. Conventional radiotherapy may carry a risk of second tumours or cerebrovascular events due to radiation vasculopathy.

The Follow Up Pathway (11-2K-236)

To minimise duplication of clinic appointments and MRI scans the following is proposed:

- A joint neurosurgery / neuro-endocrinology clinic appointment is desirable – this minimises clinic appointments and avoids duplication of follow-up imaging and follow up pituitary function testing
- MRI is the modality of choice for follow up and should be performed as per current WCFT imaging protocol for pituitary tumours
- Once tumour growth control has been established following the appropriate treatment modalities, follow-up could be transferred and / or shared with the patient's local hospital-based Endocrinology team
- Referral back to the joint neurosurgery / neuro-endocrinology clinic and the regional Pituitary MDT can take place at any time during the follow-up pathway when evidence of tumour regrowth become evident

Radiological follow up:

- Postoperative MRI 3–4 months after surgery to establish a baseline for future follow-up
- A second postoperative MRI should be performed about 1 yr after initial treatment.
- Subsequent intervals of MRI scanning after surgery depends on individual characteristics such as the volume of the residual tumour, the distance between the residual tumour and the optic chiasm, the administration of post-operative radiotherapy and clinical judgement
- It is important to compare sequential MRIs with the first postoperative MRI because the increase in tumour volume might be too small to detect on subsequent MRI
- Tumour re-growth is not prevented by radiotherapy in all cases, careful radiological follow-up is also necessary after radiotherapy
- In some studies a more aggressive behaviour of ACTH-positive non-functioning macroadenomas was suggested, ACTH positivity may be a determinant for the frequency of postoperative MRI

Pituitary function:

- Pituitary function (dynamic testing) should be assessed 3 months after surgery
- Because the growth of non-operated adenomas as well as the re-growth of operated adenomas can be accompanied by new pituitary deficiencies, hormonal evaluation every 6-12 months is also recommended in these patients without panhypopituitarism
- After radiation therapy, repeated assessment of pituitary function over the years is needed because hypopituitarism can take 10 or more years to develop

Ophthalmological follow-up:

- Ophthalmological assessment within several weeks after surgery
- Subsequent assessments after 1 and 2 years, to estimate the final effect of surgical treatment on visual function. These data serve as baseline values for potential effects of tumour recurrence during the long-term follow-up.
- The role of visual assessment for detection of tumour growth is limited. Although visual assessment is a specific tool, its use is limited due to the low negative predictive value for tumour recurrence, especially in patients with a relative large distance between pituitary tumour and optic chiasm.

REFERENCES

