Transnasal transsphenoidal pituitary surgery in a large tertiary hospital, a retrospective study.

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Running title: Belgian retrospective pituitary tumor study

Abstract

OBJECTIVES

Pituitary adenomas, although being small tumors, can have quite an impact on patients' lives causing hormonal and visual disturbances, for which surgery must be performed. As a large peripheral hospital with specialists in pituitary surgery, an assessment of the efficacy and safety of transnasal transsphenoidal pituitary surgery was made.

METHODS

A retrospective analysis of neurosurgical reports as well as pre- and postoperative imaging was made to evaluate the presenting symptoms, tumoral variables, peri-operative morbidity, and long-term outcome.

RESULTS

This cohort included 105 patients who were operated for pituitary adenomas over a 9-year period, with a slight male predominance. Adenomas had a mean maximum diameter of almost 25mm, with one-third of tumors presenting with a Knosp-grade 3 or 4. As expected, most patients presented with either visual (32.4%) or hormonal (40.0%) disturbances. After surgery, 85.3% had complete resolution of visual deficits, and 97.1% had normalisation of hormonal hypersecretion. Postoperative hormonal insufficiency requiring substitution was observed in 43.1% and was significantly more frequent in males and in non-functioning pituitary adenomas. Postoperative cerebrospinal fluid leakage was observed in 2.9%, and merely one patient developed meningitis. Tumor recurrence was significantly more frequent in patients with partial resection as compared to complete resection (25.6% vs 7.9%).

CONCLUSION

This study demonstrates that transnasal transsphenoidal pituitary surgery can be performed safely and effectively in a large non-university hospital, improving visual and/or hormonal disturbances as

well as providing long-term tumor control. Patients with larger adenomas are at an increased risk to develop postoperative hypopituitarism.

Keywords

complications; hypopituitarism; outcome; pituitary adenoma; transsphenoidal surgery

Abbreviations

ACTH	adrenocorticotropic hormone
CSF	cerebrospinal fluid
DI	diabetes insipidus
ELD	external lumbar drain
GH	growth hormone
NFA	non-functioning pituitary adenoma
PA	pituitary adenoma
PRL	prolactin
TSH	thyroid stimulating hormone
TSS	transsphenoidal surgery

Introduction

Pituitary adenoma (PA) are mostly benign tumors originating from adenohypophyseal cells. They represent one of the most common intracranial tumors and are detected in 15-22.5% of the population according to autopsy reports and MRI-scans for other purposes [1-3]. PA often remain small and asymptomatic, as clinically relevant PA have a lower prevalence of approximately 0.1% [2].

PA can be divided regarding their size into micro- (<10mm) and macro-adenoma (>10mm), as well as secreting and non-secreting PA [2]. Presenting symptoms can be due to hormonal dysregulation or mass effect on the cranial nerves surrounding the cavernous sinus, leading to visual disturbances. A less frequent presentation is pituitary apoplexy (2-12%), where patients may present with sudden headache, visual and/or hormonal disturbances caused by an acute volume increase of a pre-existing PA due to a hemorrhage or necrosis [4].

In this study, a consecutive cohort of 105 patients operated for PA were retrospectively analysed regarding clinical presentation, surgery, complications, and outcome.

Material and methods

1. Study population

This study was approved by the ethical committee of Ziekenhuis Oost Limburg (ZOL) in Genk, Belgium.

A retrospective analysis was performed on patients operated for PA in a single centre (ZOL) from January 1st 2010 until December 31st 2018. The year 2010 was chosen as this was the first full year of endoscopic pituitary surgeries. The patient cohort was obtained through a query in the operation logs. Cases were excluded if follow-up took place at another centre, or if pathology didn't reveal a PA, after which 105 individual patients remained for analysis. Patients were seen pre- and postoperatively by a neurosurgeon and an endocrinologist, as well as an ophthalmologist if visual problems were apparent during clinical examination. Imaging through MRI-scans was performed preoperatively, 3 months and

1 year postoperatively, followed by yearly scanning in most cases and more frequently in selected cases (Image 1).

2. Variables

Demographic variables included patient gender and age. Tumor variables covered tumor pathology, maximum tumor diameter, as well as suprasellar extension and Knosp-grading. Clinical variables were classified with presenting symptoms (apoplexy, visual deficits, hormonal imbalance, cranial neuropathy), postoperative symptoms (visual deficits, hormonal status), complications (hemorrhage, cerebrospinal fluid (CSF) leakage, meningitis) and oncological outcome. Extent of resection (partial/complete) was determined on an MRI-scan after 3 months. Recurrence was defined as tumoral regrowth in case of NFA and renewed hormonal hypersecretion in secreting PA. Visual deficits were evaluated with a Goldmann- or automated perimetry.

Patients presenting with hormonal imbalances were divided into hormonal hypersecretion and clinically significant hypopituitarism. A hormonal workup was performed by measuring basal hormonal production with secondary testing as needed. The hormonal status one year postoperatively was used as the final benchmark. Hypopituitarism was noted when there was a shortage of one or more hormones for which substitution therapy was required. Primary hypothyroidism was excluded as hormonal insufficiency if patients only required L-thyroxine supplementation. Panhypopituitarism was noted when supplementation of at least 4 different hormones was necessary.

3. Transsphenoidal surgery

A bi-nostril endoscopic endonasal approach was used to perform the TSS, using a 2- or 3-handed technique. A classic procedure is performed by making a wide sphenoidotomy followed by tumor removal with a wide array of curettes until visual confirmation of a complete resection is obtained or the arachnoid membrane of the sellar diaphragm settles in. The sellar cavity is filled with either

autologous adipose tissue or covered with Tisseel. In case of an apparent CSF-leak, the decision is made to place an external lumbar drain (ELD) and/or to perform a quadriceps muscle/fascia lata plasty/Tachosyl coverage or a combination depending on surgeon's preference. The ELD is left in place for 5-7 days, draining approximately 10 milliliters CSF per hour. Postoperative nasal hemorrhages were addressed by re-look surgery to obtain hemostasis whenever nasal packing was insufficient.

4. Statistical analysis

Continuous data were presented as mean, median, or frequency. Frequency distribution was used for categorical variables. Study variables were analysed with a two-tailed Fisher's exact test for dichotomous variables and one-way ANOVA or Kruskal-Wallis ANOVA by ranks for dichotomous and continuous data. Results with a P-value of <0.05 were deemed significant. Statistical analysis was performed using GraphPad Prism 8.4.1 and Statistica 13.

Results

1. Demographics and tumor characteristics

A total of 105 patients were analysed in this retrospective series. There was slight male predominance, accounting for 56.2% of patients. A median age of 59 years was observed (range 18-84y) (Table 1). Patients with secreting PA were significantly younger compared to those with a NFA (median age 42 vs 64 years; $p<0.0001$).

While there was no difference in the distribution of micro- and macro-adenomas in both genders ($p=0.134$), female patients did present significantly more with secreting PA (61.8% vs 38.2%; $p=0.012$). The average size of PA was 24.7mm, and 7.6% were micro-adenomas. There were 97 macro-adenomas (92.4%) with 87.6% having suprasellar extension and 35.2% with extension into the cavernous sinus (Knosp grade 3 and 4) (Table 1 and Figure 1).

2. Clinical presentation

Most presenting symptoms were visual deficits in 34 cases (32.4% of the entire population), followed by hormonal hypersecretion in 34 cases (32.4%), hormonal shortage in 8 cases (7.6%), cranial nerve deficits in 8 cases (7.6%) and 17 patients (16.2%) with pituitary apoplexy (Table 2). Visual field deficits consisted of bitemporal heteronymous hemianopia in 85.3%, bilateral quadrantanopia in 8.8%, central visual loss or hemianopia in 5.8%. Thirty-four patients had hormonal hypersecretion with an excess of prolactin (PRL; 32.3%), growth hormone (GH; 32.3%), adrenocorticotropic hormone (ACTH; 32.3%) or thyroid stimulating hormone (TSH; 2.9%). Cranial nerve deficits (n=8) encompassed the oculomotor nerve (62.5%), the abducens nerve (12.5%), or both nerves (25.0%) (Table 2).

All patients with a micro-adenoma (n=8) underwent surgery due to hypersecretion, including 7 with Cushing's disease and one with acromegaly. All 17 patients with apoplexy had macro-adenomas, including 4 with a cranial neuropathy, 2 with a visual field deficit, 3 with hormonal imbalances, and 5 with a combination of symptoms. Three patients with apoplexy only experienced an acute headache.

3. Complications

Analysis of peri-operative complications revealed 3 cases (2.9%) of postoperative nasal haemorrhage that required reoperation as nasal packing had not resolved the problem.

Intra-operative CSF-leakage was observed in 18 patients (17.1%). Postoperative CSF leakage was observed in 3 patients (2.9%), including one CSF leak that had not been detected intraoperatively. One patient developed postoperative meningitis, which was recognised early and treated with antibiotics, resulting in a rapid and complete recovery.

When comparing peri-operative CSF-leakage between different age group, no significant differences were observed (20.0% of 18-40y, 17.1% of 41-60y, and 9.1% of >61 years old; p=0.652). Gender-analysis did reveal that women had significantly more intraoperative CSF-leaks (26.1% vs 10.2%; p=0.039). Patients with apoplexy (5.6% vs 19.3%; p=0.294) or cavernous sinus invasion (18.5% vs 7.7%; p=0.459) did not have significantly more CSF-leaks. No difference was observed comparing leakage-

rates between micro- and macro-adenomas (12.5% vs 17.5%; p>0.999) or in adenomas with supra- versus infra-sellar extension (3.3% vs 0.0%; p>0.999), individual size-analysis between PA with diameters <25mm versus ≥25mm did reveal more CSF-leaks (9.4% vs 25.0%; p=0.041) in the latter group.

4. Outcome

4.1 Visual and other cranial nerve deficits

One patient died from non-related causes and 2 patients were lost to follow-up, 102 patients remained for the outcome analysis. Thirty-four patients experienced preoperative visual field deficits that completely resolved in 29 (85.3%) and partially resolved in 4 (11.8%) cases. Similar results were observed for preoperative cranial neuropathies that completely resolved in 7 patients (87.5%) and partially resolved in one patient (12.5%). No new cranial neuropathies or visual problems were observed postoperatively.

4.2 Hormonal balance

In the entire series (n=102), one patient recovered from preoperative hormonal insufficiency and another patient recovered from diabetes insipidus (DI). Preoperatively, 34 patients (33.3%) (Table 3) had hormonal hypersecretion, of which all except one (97.1%) obtained normalization. Fifty-three patients (52.0%) maintained a normal hormonal balance. Three patients (2.9%) maintained their preoperative hormonal deficit. Thirty-seven patients (36.3%) developed new hormonal insufficiencies, of which 4 patients had panhypopituitarism and 11 patients developed DI combined with other hormonal insufficiencies. Four patients (3.9%) developed isolated DI and three patients (2.9%) required additional hormonal supplementation after surgery.

We found that younger patients developed significantly more DI when comparing <45 and >65 years (p=0.007). Patients with NFA were significantly more prone to develop postoperative hypopituitarism as compared to patients with secreting tumors (51.5% vs 23.5%; p=0.010). Furthermore, men

developed significantly more postoperative hormonal insufficiency compared to women (56.1% vs 22.2%; p= 0.0006).

4.3 Oncological outcome

During the study period, recurrence was observed in 15 patients (14.7%) with an average time to recurrence of 33.3 months (range 6-86 months). Seven recurrences were observed in secreting adenomas (3 ACTH-, 1 GH-, 2 PRL-, and 1 TSH-secreting). No significant difference in average time to recurrence was observed between secreting and non-secreting adenomas (26.9m vs 39.0m; p=0.280) and invasive adenomas did not result in more recurrences (p= 0.686).

Postoperative MRI-scans revealed a partial resection in 39 patients (38.2%), these patients had significantly more recurrences compared to complete resections (25.6% vs 7.9%; p=0.021). Complete resection did not result in more hormonal imbalances as compared to incomplete resection (41.0% vs 54.0%; p=0.227).

Discussion

This study was performed to retrospectively evaluate the safety and efficacy of transnasal transsphenoidal surgery for different types of PA in a single large peripheral centre (where the technique was introduced in 2010).

1. Demographics

We noted a slight male predominance, which is atypical considering the female predominance in other studies on PA. A study in another part of Belgium, as well as in Malta, demonstrated a female to male ratio of 2:1 [1,5]. An 8-fold higher frequency of prolactinomas was noted in females compared to males in Banbury (UK), [6]. The rather low amount of prolactinomas included in this cohort (10.8%) is probably due to our conservative surgical approach to prolactinomas, most of which are treated with non-surgically, which may explain our slight male predominance. However, there were significantly more secreting PA in the female group as compared to men, in conjunction with findings in a

population study in Northern Finland [7]. The median age in our cohort was 59 years, which is considerably higher than in the epidemiological studies, which registered a mean age of 32-44 years old. This is likely due to an abundance of NFA, and the observed significant difference in median age between secreting PA and NFA (42 vs 64 years, $p < 0.0001$).

2. Clinical presentation

One-third of the population experienced preoperative visual field deficits, followed closely by presentation with hormonal hypersecretion, conform a study in New Zealand that prospectively evaluated presenting symptoms in PA [8]. Postoperative visual field recovery occurs in 3 stages: early fast recovery (minutes - days), early slow recovery (weeks - months), and late recovery (months - years). Most improvement is observed in the early fast phase, followed by the early slow phase, with recovery after 4 months being rather unlikely [9]. This study reveals that 85.3% of patients experience a full visual recovery, with the remaining 14.7% showing improved visual fields 1 year postoperatively. A meta-analysis by Thotakura et al demonstrated that care should be taken to operate in a timely fashion as patients with a shorter history of visual symptoms (<1 year) have been shown to have significantly better visual outcomes [10].

Cranial nerve deficits (mostly oculomotor nerve deficits) were observed as a presenting symptom in 8 patients (7.6%), most of which (n=5, 62.5%) had apoplexy. Postoperatively, there was normalization of cranial nerve function in 87.5%, without any new cranial nerve deficits. New cranial nerve deficits following TSS occur in 0-5.3% of patients in recent literature [11-13].

In this cohort, the number of patients suffering from preoperative hypopituitarism was quite low (6.9%), in contrast to other studies mentioning an incidence as high as 39-70% [14-16]. This might be due to the exclusion of primary hypothyroidism as hormonal insufficiency (patients only taking L-thyroxine preoperatively), as well as the expedient timing for surgery after a new diagnosis of PA. Because of this short interval, starting new medication for mild hormonal deficits will often be done when there is a residual deficit after surgery rather than preoperatively. Finally, the low percentage

may also result from our inclusion criteria, as only clinically relevant hormonal shortages (those requiring hormonal supplementation rather than being at the lower limit of normal) were marked as an insufficiency. In this regard, another retrospective analysis found that only 50% of patients with NFA experience symptoms of hypopituitarism preoperatively [14].

Surgery completely restored hormonal deficits in one out of 7 patients in this study. Correction of a preoperative hormonal deficit is rather rare, even after successful resection of the tumor [17]. A correction of the preoperative hormonal deficit may be obtained in 3-40% of surgeries [14,18].

All except one patient with a secreting adenoma obtained normalization of the hypersecreted hormone after surgery (n=33, 97.1%), indicating satisfactory results may be obtained even for secreting adenomas (often deemed as challenging cases) in large tertiary hospitals. Of note, success rates vary widely among different studies (range 32% to 73%) [16,17].

3. Complications

The most frequently mentioned risks associated with PA resection include postoperative CSF-leakage and damage to healthy pituitary tissue resulting in transient or permanent hypopituitarism and/or DI [19].

Postoperative CSF-leakage is a major cause of morbidity following endonasal transsphenoidal pituitary surgery, with the risk for developing meningitis and the need for reoperation to repair the CSF-fistula. The reported incidence of postoperative CSF-leakage varies from 1.3-13% [20-23]. Our study reports a rate of 2.9%, with only one patient experiencing meningitis cured by prompt treatment. Our peri-operative CSF leakage rate was 17.1%, and patients were usually treated with a combination of meticulous reconstruction and an ELD.

Risk factors for postoperative CSF-leakage include surgery for ACTH-producing adenomas, intra-operative CSF-leakage, and an elevated body mass index [21,24]. Our study revealed a significantly increased risk for postoperative CSF-leakage in females and for adenomas ≥25mm in size. Zwagerman

[25] evaluated placement of an ELD following endoscopic endonasal skull base surgery in a randomized controlled trial and observed a significant improvement in postoperative CSF-leakage in patients with an ELD (8.2%) as compared to a control group (21.2%). Another study revealed a significantly decreased risk for postoperative CSF-leakage meningitis in patients with an ELD as compared to those without (1.4% vs 13.6%) [26]. However, using state-of-the-art endonasal technique may not only reduce the incidence but also improve our ability to recognize and to effectively reconstruct an eventual intraoperative CSF leak as compared to the original transseptal technique.

The incidence of postoperative hypopituitarism varies from 5.5 to 36% among different studies [14-16,27,28]. We observed the need for new hormonal supplementation after surgery in 43.1% of patients. This is likely due to a lower incidence of preoperative hormonal insufficiency in this study (as explained above). A recent review revealed that the hypothalamic-pituitary-adrenal axis is more susceptible to damage with resulting low ACTH levels and a diminished stress response after surgery [14]. Not surprisingly, both pre- and postoperatively, hydrocortisone is the most frequently supplemented hormone in this cohort. Furthermore, gender (male) and NFA were identified as predictors for postoperative hormonal impairment, as observed in other studies [29]. While tumor size is also believed to be a risk factor [16,30], no significant difference was observed in the frequency of postoperative hormonal impairment when comparing tumors <25mm and ≥25mm.

DI is a frequent side-effect following pituitary surgery and may be transient or permanent. Permanent DI is caused by damage to hypothalamus or proximal infundibulum [31] and has a variable incidence in the literature (1.9% to 10.1%) [15,32,33], compared to 14.7% (n=15) in this cohort. Intra-operative CSF-leakage and younger age are inconsistently described as risk factors for development of DI [34]. While younger age does indeed seem to be a risk factor when comparing <45 and >65 years old (p=0.007). As also observed by Boling [35], intra-operative CSF-leakage did not significantly correlate with an increased incidence of permanent DI (p=0.135) in this cohort.

4. Oncological outcome

Partial resection was observed in 38.2% of patients, in line with 33% as reported by Lee [36]. This number is quite high and may be explained by the number of large NFA in this cohort. Extent of resection is a known risk factor for recurrence [36] as confirmed in patients with partial resection (25.6% vs 7.9%; p=0.021) in this cohort.

Fifteen patients (14.7%) had a tumor recurrence with an average time of 33 months. More precisely, 7 patients (20.6%) with a secreting adenoma and 8 patients (11.9%) with an NFA recurred. Recent reports estimate the incidence of recurrence around 15-20% (<2 years after surgery), although this may be an underestimation, especially in NFA, as recurrent tumors may only become symptomatic due to mass effect when they have grown quite large, taking much longer to be discovered, while emphasizing the importance of scheduled long-term follow-up [36,37].

Conclusion

This retrospective study evaluates 105 patients who underwent TSS to remove a PA in a single Belgian centre. The study reveals the well-known spectrum of NFA and secreting adenomas, with a relative shortage of (micro)prolactinomas as compared to epidemiological studies. As such, the cohort mainly consists of macro-adenomas. This analysis reveals that visual and other cranial neuropathies tend to be, at least partially, restored after tumor resection, without causing any new deficit except for hormonal insufficiency. Postoperatively, new hormonal supplementation was necessary in 39% of patients due to inherently larger tumors of non-secreting nature and a relatively high threshold to start hormonal substitution preoperatively for hormones in the low normal range (except for cortisol). Complications were few with merely 2.9% experiencing postoperative CSF-leakage. Not surprisingly, this study revealed a higher recurrence rate in patients with partial as compared to complete resection. While TSS yields excellent results regarding visual and hormonal outcome, patients with larger adenomas should be counselled they are at an increased risk to develop postoperative hypopituitarism, while performing a more cautious partial resection comes with an increased risk of recurrence. In conclusion, transnasal transsphenoidal pituitary surgery can be considered a safe

operation with good results both clinically and oncologically in a tertiary hospital with specialised surgeons.

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Declaration of interest

The authors declare no potential conflict of interest.

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