Congress of Neurological Surgeons

GUIDELINES

CONGRESS OF NEUROLOGICAL SURGEONS SYSTEMATIC REVIEW AND EVIDENCE–BASED GUIDELINE FOR PRETREATMENT ENDOCRINE EVALUATION OF PATIENTS WITH NONFUNCTIONING PITUITARY ADENOMAS

Sponsored by

Congress of Neurological Surgeons (CNS) and the AANS/CNS Tumor Section

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Joint Guidelines Committee of the American Association of Neurological Surgeons (AANS) and the Congress of Neurological Surgeons (CNS)

Maria Fleseriu, MD[1], Mary E. Bodach, MLIS[2], Luis M. Tumialan MD[3], Vivien Bonert, MD[4], Nelson M. Oyesiku, MD, PhD[5], Chirag G. Patil, MD[6], Zachary Litvack, MD[7], Manish K. Aghi, MD, PhD[8*], Gabriel Zada, MD[9*]

[1] Departments of Medicine and Neurological Surgery, OHSU Northwest Pituitary Center, Oregon Health Science University, Portland, Oregon, USA
[2] Guidelines Department, Congress of Neurological Surgeons, Schaumburg, Illinois, USA
[3] Barrow Neurological Institute, Phoenix, Arizona, USA
[4] Pituitary Center, Cedars-Sinai Medical Center, Los Angeles, California, USA
[5] Department of Neurosurgery, Emory University, Atlanta, Georgia, USA
[6] Department of Neurosurgery, Cedars-Sinai Medical Center, Los Angeles, California, USA
[7] Department of Neurosurgery, George Washington University, Washington, DC, USA
[8] Department of Neurosurgery, University of California, San Francisco, San Francisco, California, USA
[9] Department of Neurosurgery, University of Southern California, Los Angeles, California, USA
* These authors contributed equally to this work.

Correspondence:

Gabriel Zada, MD
Department of Neurosurgery
University of Southern California
1200 N State St, Suite 3300
Los Angeles, CA 90033
E-mail: gzada@usc.edu

ABSTRACT

Background: Nonfunctioning pituitary adenomas (NFPAs) are among the most common pituitary lesions and may present with hypopituitarism and/or hyperprolactinemia.

Objective: To review the existing literature as it pertains to preoperative endocrine assessment in the workup for NFPAs.

Methods: A systematic review methodology was utilized to identify and screen articles assessing the role and results of preoperative laboratory assessment in patients with NFPAs. The prevalence of individual pituitary hormonal axis deficiencies was reviewed.

Results: Twenty-nine studies met inclusion criteria for analysis. No Class I evidence was available, and all studies met criteria for Class II evidence. Baseline serum laboratory assessment showed a prevalence of overall hypopituitarism in 37% to 85% of patients. The most common hormonal axis deficiency was growth hormone deficiency, prevalent in 61% to 100% of patients. The next most common deficit was hypogonadism, seen in 36% to 95% of patients. Adrenal insufficiency was diagnosed in 17% to 62% of patients. Finally, hypothyroidism was seen in 8% to 81% of patients. Hyperprolactinemia was seen in 25% to 65% of patients, with a mean level of 39 ng/mL and with a minority of patients exceeding a serum prolactin level of 200 ng/mL. No

evidence supporting routine biomarker testing (e.g., alpha-subunit or chromogranin A) or genetic testing in patients with sporadic NFPAs was available.

Conclusion: Despite a paucity of Class I evidence, multiple retrospective studies have demonstrated a high prevalence of hypopituitarism in patients with NFPAs. Routine endocrine analysis of all anterior pituitary axes to assess for hypopituitarism is recommended, with prolactin and IGF-1 evaluation also valuable to assess for hypersecretion states that might not be clinically suspected.

RECOMMENDATIONS

Question

Which endocrine axes should be checked preoperatively in NFPA patients?

Target Population

These recommendations apply to adult patients with recurrent or residual nonfunctioning pituitary adenomas (NFPAs).

Level II Recommendations

Routine endocrine evaluation of all anterior pituitary axes to assess for hypopituitarism is recommended because, beyond revealing a significant rate of deficits beyond the level of clinical suspicion for all pituitary axes, the cutoff values to initiate thyroid and adrenal replacement might be different in a patient with panhypopituitarism versus isolated deficiencies.

Routine prolactin testing is recommended in all patients with suspected NFPA to rule out hypersecretion that might not be clinically suspected.

Level III Recommendations

Routine insulin-like growth factor 1 (IGF-1) evaluation is recommended in all patients with suspected NFPA to rule out growth hormone (GH) hypersecretion that might not be clinically suspected.

Question

What is the role for preoperative hormone replacement in NFPA patients?

Target Population

These recommendations apply to adult patients with recurrent or residual nonfunctioning pituitary adenomas (NFPAs).

Level II Recommendation

Replacement for adrenal insufficiency and significant hypothyroidism is recommended in all patients preoperatively.

INTRODUCTION

Nonfunctioning pituitary adenomas (NFPAs) are among the most common pituitary adenomas and are defined by a lack of any functional hormonal products. They are often diagnosed because they cause local compression of the pituitary gland and optic chiasm, and may present clinically with signs and symptoms of hypopituitarism, visual loss, and headaches, among others. Many NFPAs are also diagnosed incidentally on CT or MR studies. The aim of this systematic review and evidence-based guideline is to highlight any prior studies assessing preoperative laboratory evaluation in patients with NFPAs. Although NFPAs are partially defined by a paucity of hormonal oversecretion (with the exception of hyperprolactinemia caused by the pituitary stalk effect), we aimed to review any pertinent results relating to the role of laboratory values, including a workup for hypopituitarism, assessment of hyperprolactinemia, and other diagnostic lab or genetic evaluations that have been assessed in NFPAs in prior research studies.

The medical literature was searched systematically to identify articles focusing on the role of the preoperative laboratory evaluation in NFPAs. Abstracts from the results of these searches were screened by multiple reviewers, and full-text articles from potentially significant articles were secondarily reviewed for application of inclusion and exclusion criteria. Outcomes studied included the particular laboratory value and results for the detection of each particular endocrinopathy.

METHODOLOGY

Process Overview

The evidence-based Clinical Practice Guideline Task Force members and the Tumor Section of the Congress of Neurological Surgeons and the American Association of Neurological Surgeons conducted a systematic review of the literature relevant to the management of nonfunctioning pituitary adenomas (NFPAs). Additional details of the systematic review and the methods the group used to create it are provided below and within the introduction and methodology chapter of the guideline.

Disclaimer of Liability

This clinical systematic review and evidence-based guideline was developed by a physician volunteer task force as an educational tool that reflects the current state of knowledge at the time of completion. The presentations are designed to provide an accurate review of the subject matter covered. This guideline is disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in its development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a physician should be sought. The

recommendations contained in this guideline may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in this guideline must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

Potential Conflicts of Interest

All NFPA Guideline Task Force members were required to disclose all potential COIs prior to beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Committee. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination and participation on the task force. The CNS Guidelines Committee and Guideline Task Force Chair may approve nominations of task force members with possible conflicts and restrict the writing, reviewing, and/or voting privileges of that person to topics that are unrelated to the possible COIs.

Literature Search

The guideline task force members collaborated with a medical librarian to search for articles published from January 1, 1966, to October 1, 2014. Two electronic databases were searched, PubMed and The Cochrane Central Register of Controlled Trials. Strategies for searching electronic databases were constructed by the guideline taskforce members and the medical librarian using previously published search strategies to identify relevant studies (Appendix A).[1-8]

RESULTS

Twenty-nine articles met the criteria for inclusion and were included as evidence to support the conclusions in this chapter (Table 1). A flow chart summarizing study selection can be found in Figure 1. No Class I evidence was available to support the role of specific diagnostic laboratory evaluation in the work-up and diagnosis of NFPAs. Several Class II studies were identified to support the role of specific laboratory tests in the work-up of NFPAs.

Laboratory Assessment of Serum Prolactin in Patients with NFPAs

In the work-up of patients with pituitary adenomas, the serum prolactin level is perhaps the most important laboratory level that dictates a given patient's treatment course. The ability to distinguish between a prolactinoma (for which medical therapy represents first-line therapy in most patients) and an NFPA with hyperprolactinemia caused by the pituitary stalk effect (a surgically treated disease for most patients) is a critical one and depends on the size of the tumor and the level of clinical suspicion. According to our systematic literature review, no Class I evidence was available to support a given threshold of serum prolactin that can be used to distinguish these 2 subtypes of pituitary adenomas. However, multiple retrospective and several prospective studies reported their findings pertaining to laboratory assessment of serum prolactin in NFPA patients. Results from these studies indicate that the incidence of hyperprolactinemia in patients with histologically verified NFPAs is 25%-65% (1848 patients)[9-18] (Table 2).

In a large study involving 721 patients with NFPAs by Nomikos et al, preoperative hyperprolactinemia was noted in 25.3% of patients.[16] Behan et al performed a retrospective analysis in 250 patients with NFPAs, reporting baseline hyperprolactinemia in 44.8% of patients.[10] Karavitaki et al published their findings from a retrospective analysis of 226 patients with NFPAs.[15] The authors found hyperprolactinemia in 38.5% of patients. The median prolactin level in the entire group was 18 ng/mL (range 0.8-73.6 ng/mL). A serum prolactin level of <94.3 ng/mL was seen in 98.7% of patients. Of the 3 subjects with a serum prolactin >94.3 ng/mL, 2 were on estrogen treatment. The authors concluded that patients with a prolactin >94.3 ng/mL almost never have NFPAs.[15] In a study by Fatemi et al involving 223 patients with NFPAs, the prevalence of hyperprolactinemia caused by pituitary stalk effect was 54%.[14]

Comtois et al studied serum prolactin levels in 126 patients with NFPAs and identified baseline hyperprolactinemia in 65% of patients, with a mean level of 39 ng/mL.[11] In a retrospective analysis of 104 patients with NFPAs by Cury et al, the prevalence of preoperative hyperprolactinemia was 38.5%.[12] In a study by Drange et al involving 99 NFPA patients, 47% were found to have laboratory evidence of hyperprolactinemia.[13] Tjeerdsma et al studied baseline endocrine function in 40 patients with NFPAs and reported baseline hyperprolactinemia in 50% of patients.[17] In their study, hyperprolactinemia was associated with additional anterior pituitary axis deficiencies. In another study by Tominaga et al involving 33 NFPA patients, baseline hyperprolactinemia was evident in 42% of patients.[18] Arafah et al reported results from a prospective study involving 26 patients with NFPAs and noted that mild hyperprolactinemia (PRL of 29-53 ng/mL) was seen in 46% of patients.[9]

In another large retrospective study by Gsponer et al[19], the authors sought to determine a threshold of prolactin that could reliably differentiate between NFPAs and prolactinomas. They found that a basal prolactin level above 85 ng/mL in the absence of renal failure or any prolactin-enhancing drugs, and a prolactin increment less than 30% following thyrotropin-releasing hormone (TRH), reliably ruled out pituitary stalk effect from an NFPA.

In 2010, Hong et al published results from a retrospective analysis in 117 patients with prolactinomas as well as NFPAs.[20] NFPAs were associated with older age, extrasellar extension, and a prolactin level <100 ng/mL, while prolactin levels above 250 ng/mL were exclusively associated with prolactinomas and never represented stalk effect from NFPAs, a more stringent cutoff than used in the studies above and felt to represent a diagnostic criteria for prolactinoma with acceptably low false positive rates. Furthermore, GH deficiency was more common in patients with NFPAs than those with prolactinomas. The authors concluded that preoperative serum prolactin levels <100 ng/mL and the presence of a hypofunctioning GH axis were predictive of NFPAs.

Endocrine Axis Testing and the Prevalence of Hypopituitarism

Multiple retrospective studies and a handful of prospective observational studies have assessed baseline function of multiple anterior pituitary axes in patients with NFPAs. The overall prevalence of partial hypopituitarism in patients with NFPAs ranged from 37%-85%[13,14,16,21-23] (1240 patients) (Table 3). On the other hand, panhypopituitarism was much less frequent and was evident in 6%-29% of patients.[24,25] Of the involved endocrine axes, the most commonly affected pituitary axis was the growth hormone (GH) axis, with 61%-100% of patients showing laboratory evidence of GH deficiency[9,12,17,25-28] (903 patients) (Table 4). Central hypogonadism

was the next most commonly affected axis and was noted in 36%-96% of patients[9,11-13,16,17,24-26,28-30] (1911 patients) (Table 5). Adrenal insufficiency was the following most commonly involved axis, noted in 17%-62% of patients[9,11,12,16,24,25,27-30] (1486 patients) (Table 6). Finally, 8%-81% of 1911 assessed patients in these studies[9,11,12,16,17,24-30] (Table 7) exhibited central hypothyroidism. Central hypothyroidism is defined as inappropriately low serum TSH in the presence of low-normal serum T4 and T3 concentrations. Central hypothyroidism is typically confirmed by the thyrotropin releasing hormone stimulation test, in which serum TSH is measured serially post-TRH at 20 and 60 minutes, with a normal response defined as the 20-minute TSH value being higher than the 60-minute TSH value. A flat response is seen in pituitary disease, and delayed response, with the 60-minute value higher than the 20-minute value, is seen in hypothalamic disease. Diabetes insipidus was a very uncommon finding, reported to occur in 7% of patients with NFPAs at the time of clinical presentation.[28]

In the largest observational study included, Nomikos et al[16] reported on 721 patients with NFPAs who had full preoperative endocrine data available. Of these patients, over 85% had evidence of preoperative hypopituitarism. Patients had evidence of secondary adrenal insufficiency (31%), hypogonadism (76.6%), and hypothyroidism (19.1%). In another large prospective observational study by Chen et al,[26] baseline hypopituitarism was analyzed in 385 patients with NFPAs. Baseline hypothyroidism was noted in 35.8% of patients, hypogonadism in 41%, hypoprolactinemia in 17.9%, and GH deficiency in 61%. In 2008, Fatemi et al reported results from a retrospective analysis of 223 patients with NFPAs who underwent transsphenoidal surgical resection.[14] Preoperative hormonal dysfunction was diagnosed in 194 patients (84%). In a retrospective analysis including 155 patients with NFPAs, Wichers-Rother et al determined baseline GH deficiency in 85% of patients, hypogonadism in 55% of patients, hypothyroidism in 30% of patients, and adrenal insufficiency in 31% of patients.[27]

In another retrospective study looking at baseline hypopituitarism in 126 patients with NFPAs by Comtois et al,[11] hypogonadism was seen in 75% of patients, adrenal insufficiency in 36%, and hypothyroidism in 18%. A retrospective study by Berkmann et al included 114 patients with NFPAs.[21] The authors reported preoperative hypopituitarism in 83 patients (72.8%). Dekkers et al published a retrospective analysis of 109 consecutive patients with NFPAs.[25] They reported GH deficiency in 77% of patients, hypogonadism in 75%, adrenal insufficiency in 53%, hypothyroidism in 43%, and panhypopituitarism in 29% of patients. Cury et al systematically studied preoperative endocrine levels in 104 patients with NFPAs.[12] They found GH deficiency in 81.4% of patients, hypogonadism in 63.3%, adrenal hypofunction in 59.5%, and hypothyroidism in 20.4%. Ebersold et al reported results following retrospective analysis of 100 patients with NFPAs and examined baseline endocrine function.[29] They reported hypogonadism in 36% of patients, hypothyroidism in 32% of patients, and adrenal insufficiency in 17% of patients. Similarly, in a large retrospective registration study by Drange et al including 99 patients with NFPAs,[13] hypopituitarism was evident in 44% of patients, with the gonadal axis affected in 93% of these patients. Colao et al published their findings in 84 patients with NFPAs who were assessed retrospectively.[28] They reported baseline GH deficiency in 65% of patients, hypogonadism in 56%, hypoadrenalism in 23%, hypothyroidism in 8%, and diabetes insipidus in 7% of patients. Webb et al published their findings from a retrospective study including 56 NFPAs. Of these patients, 52% had some element of preoperative hypopituitarism.[22] Tjeerdsma et al reported baseline endocrine function in 40 patients with NFPAs.[17] They reported a prevalence of GH deficiency in 865 of patients, hypogonadism in 66.5%, and hypothyroidism in 67% of NFPA patients. In a smaller retrospective study by Marazuela et al,[24] 35 patients with

NFPAs were analyzed for preoperative pituitary dysfunction. The authors reported baseline hypogonadism in 69% of patients, adrenal insufficiency in 20%, hypothyroidism in 23%, and panhypopituitarism in 6% of patients.

In a retrospective study published in 2007, Del Monte et al reported results from routine preoperative laboratory assessment in 27 patients with NFPAs.[23] They identified global anterior hypopituitarism in 33% of patients and partial hypopituitarism in 37% of patients. Greenman et al studied baseline hormonal function in 26 patients with NFPAs.[30] The authors reported baseline hypogonadism in 78% of patients, adrenal insufficiency in 43%, and hypothyroidism in 23% of patients. In a prospective study by Arafah et al that examined preoperative serum endocrine function in 26 patients with NFPAs, the authors reported GH deficiency in 100% of patients, hypogonadism in 96% of patients, hypothyroidism in 81% of patients, and adrenal insufficiency in 62% of patients.[9]

A study by Vierhapper et al in 1998 assessed the extent of growth hormone deficiency in 33 patients with NFPAs and evidence of hypopituitarism in at least 1 other hormonal axis.[31] Following GHRH-stimulation testing, patients with NFPAs had lower levels of GH than control subjects. The authors concluded that although GH stimulation tests are superior to other biochemical tests for GH deficiency, they are still an inadequate method to reliably diagnose GH deficiency in an individual patient and should be considered only in patients with other types of hypopituitarism exhibiting symptoms of GH deficiency.[31] In a prospective study by Beentjes et al,[32] 34 patients with NFPAs were prospectively evaluated with a peak GH to insulin tolerance test (ITT) and GHRH in relation to prolactin levels. In patients with hyperprolactinemia, an insufficient GH peak was demonstrated via ITT in 16 patients (47%) and GHRH stimulation in 7 patients (21%). Peak GH to ITT was lower in 24 patients with other hormonal axis deficiencies. The authors concluded that ITT and GHRH tests cannot be used interchangeably in diagnosing GH deficiency in patients with NFPAs.[32]

Assessment of Other Hormonal Oversecretion and Endocrine Biomarkers in NFPAs

A retrospective observational study of transsphenoidal pituitary surgery included 37 patients with NFPAs.[33] Of these patients, 19 (45.9%) showed subsequent positivity for GH immunostaining despite a lack of clinical suspicion for acromegaly. Three of these patients (8.1%) had slightly elevated IGF-1 levels. This led the authors to conclude that preoperative laboratory assessment for NFPAs should include an IGF-1 level.

Laboratory assessment of gonadotropes and the alpha-subunit have also been made in patients with NFPAs, both at baseline and following TRH administration, recognizing that this process is different between men and women, between pre- and postmenopausal women, and between women have had a hysterectomy. Although many NFPAs exhibit positive immunochemistry for LH and/or FSH (over 90% in some series),[34] only a minority (<10%) show actual evidence of hypergonadism. Popovic et al assessed the in vivo responses of LH, FSH, and alpha-subunit to TRH in 23 patients with NFPAs.[34] They found that a bolus dose of TRH increased levels of FSH, LH, or alpha-subunit in 23 of 24 patients with NFPAs. In a similar study by Chanson et al,[35] 26 patients with NFPAs underwent LH-beta measurement following TRH stimulation. LH-beta hypersecretion was detected in 7 of 26 patients (26%), with concomitant elevations of FSH and/or alpha-subunit in an additional 3 patients. The authors concluded that assessment of LH-beta following TRH stimulation is rarely helpful for determining the gonadotropic nature of

NFPAs.[35] In another retrospective analysis in which TRH and LHRH was administered for provocative testing in the baseline setting,[18] Tominaga et al showed GH deficiency in 97% of patients, LH deficiency in 52%, hypoadrenalism in 48%, FSH deficiency in 42%, hypothyroidism in 19%, and hypoprolactinemia in 6.5% of patients.

Although not widely used, chromogranin A (CGA) has also been assessed as a potential biomarker for NFPAs. In a prospective case-control study by Gussi et al,[36] 3 of 27 patients with NFPAs had elevations of serum CGA at 576, 143, and 241 ng/mL, respectively. As the authors acknowledge, the low prevalence of CGA elevations in the NFPA population makes its utility as a sensitive biomarker less reliable.

Genetic Testing in Patients with NFPAs

In 2012, Cazabat et al published their results from a prospective single-center observational study in which 113 patients with presumed sporadic NFPAs underwent genetic screening for germline mutations in the *AIP* gene.[37] Of the 113 patients, only 1 patient (0.9%) had evidence of an *AIP* mutation.

DISCUSSION

A systematic literature review of studies performing baseline assessments of endocrine function in patients with NFPAs identified 29 research articles that evaluated the entire spectrum of anterior pituitary function. Although no Class I evidence was available, sufficient Class II evidence exists to support routine endocrine analysis of anterior pituitary hormones in patients with suspected NFPAs. The overall prevalence of hypopituitarism was 37%-85%, with deficiency in the GH axis being the most frequent hormonal axis deficiency, with a prevalence of 61-100%. The next most common finding was hypogonadism, which was prevalent in 36%-95% of NFPA patients. Adrenal insufficiency was identified in 17%-62% of patients, followed by hypothyroidism in 8%-81% of patients. Clinical evidence of hyperprolactinemia thought to be secondary to pituitary stalk effect was prevalent in 25%-65% of patients. Taken together, there is sufficient data to suggest routine endocrine axis testing of all anterior pituitary hormones in patients with newly diagnosed pituitary adenomas and clinical suspicion of NFPAs.

Although the prevalence of the overall and individual endocrine axis deficiency is apparent from the compiled data, no evidence-based recommendations can be provided to support any particular methods of working up a particular hormonal axis deficiency beyond routine laboratory screening. A random prolactin value, diluted in patients with large tumors to eliminate possible hook effect, should be sufficient for diagnosis. Multiple tests (including low-dose Cortrosyn stimulation test, high-dose Cortrosyn stimulation test, or insulin tolerance test) for cortisol stimulation testing have been used to diagnose adrenal insufficiency in patients with NFPAs, with indications for these tests limited to use as follow-up tests in patients with a fasting morning serum cortisol suggesting that their basal cortisol level is low enough to warrant further evaluation for central adrenal insufficiency. However, due to study design and absence of comparative data, we cannot assess sensitivity and specificity of each test.

The biochemical evaluation of central hypothyroidism and central hypogonadism seems more straightforward in these studies, the large majority making the diagnosis using free T4 and TSH,

respectively, estradiol or testosterone, and FSH and LH. Additional stimulation testing with TRH was shown to be of limited benefit in the workup of NFPA patients. The evaluation for GH deficiency has also been done by using different stimulation tests in function of availability of stimulation agents and/or timeline of each study.

The potential for suspected NFPAs to in actuality be functional tumors causing acromegaly or Cushing's disease without apparent clinical manifestations is a reality. The study by Pawlikowski et al revealed an elevated IGF-1 in 8.1% of patients with presumed NFPAs and immunopositivity for GH in 45.9% of their series,[33] calling these tumors "silent somatotropinomas." No studies performing exhaustive work-ups for hypercortisolemia in patients with presumed NFPAs without clinical evidence of Cushing's syndrome were identified; thus, biochemical routine evaluation to exclude the presence of hypercortisolemia in the absence of clinical suspicion cannot be recommended based on the available data at this time. Additionally, insufficient evidence was available to support the routine testing of any clinical biomarkers in patients with NFPAs, including the alpha-subunit and chromogranin A. Similarly, routine genetic testing in patients with NFPAs without any familial history was deemed to be low yield and is not routinely recommended.

Limitations and Future Research

The current study is limited by its systematic review methodology, which is inherently susceptible to various sources of bias, including publication, selection, and information bias. Similarly, the recommendations made are based on Class II or III evidence, without any prospective randomized controlled trial data available to truly compare efficacy of the treatment modalities in question. Recommendations for checking all pituitary axes preoperatively are based on the interactions between different hormonal axes that influence decisions about replacing thyroid and cortisol hormone,[38] which come from the general literature on hypopituitarism rather than adenomas specifically. And recommendations for preoperative thyroid and cortisol hormone replacement arise from studies in which slow awakening from anesthesia was reported in patients with these deficiencies undergoing non-pituitary surgeries,[39] as well as studies of perioperative stress dose steroids (intraoperative and postoperative) summarized in other articles in this set of guidelines as well as in guidelines from other societies,[40] from which it is reasonable to conclude about the risks of not replacing these particular hormones but not something one could safely choose to investigate in adenoma patients specifically. Nevertheless, the results of this review highlight the existing evidence available to guide a focused endocrine workup in patients with newly diagnosed pituitary adenomas without clinical evidence of hormonal hypersecretion disorders such as Cushing's disease and acromegaly.

CONCLUSION

Baseline laboratory analysis in patients with NFPAs is an important aspect of preoperative assessment and overall comprehensive care. The prevalence of overall hypopituitarism in patients with NFPAs is high, with GH deficiency and hypogonadism being the most commonly affected axes, followed by adrenal insufficiency and hypothyroidism. Routine endocrine axis

testing of all anterior pituitary hormones in patients with newly diagnosed pituitary adenomas and clinical suspicion of NFPAs is recommended.

Assessment of baseline prolactin is imperative to rule out a prolactinoma, with hyperprolactinemia secondary to stalk effect occurring in 38.7% of NFPA patients. Assessment of preoperative IGF-1 Levels is also recommended to rule out acromegaly or clinically silent GH secreting tumors. No clinical evidence is available to support the measurement of any biomarkers pertaining to NFPAs, such as alpha-subunit or chromogranin A. There is also little evidence for now to support the role of routine genetic testing in patients with sporadic NFPAs.

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Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

FIGURES

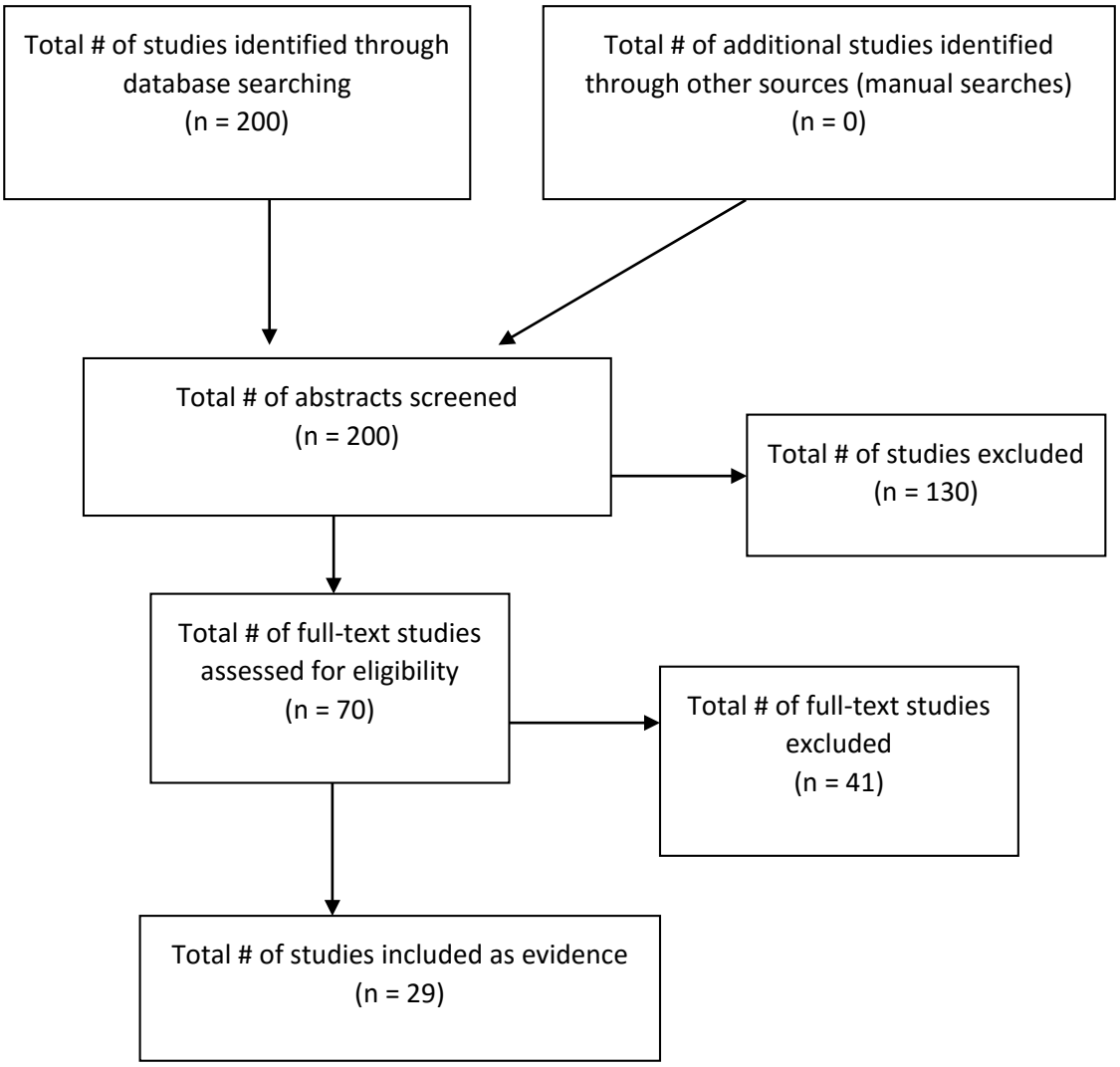

Figure 1 Article Flowchart

TABLES

Table 1: Evidence Table

Author (Year)	Description of Study	Classification Process / Evidence Class	Conclusions
Cazabat L, Bouligand J, Salenave S, Bernier M, Gaillard S, Parker F, Young J, Guiochon-Mantel A, Chanson P (2012)[37]	Prospective, single-center study. The entire coding sequence of the AIP gene was screened for germline mutations in 113 patients with non-functioning pituitary adenomas. A subgroup of patients was screened for large deletions or duplications of the AIP and MEN1 genes by multiplex ligation-dependent probe amplification.	Diagnostic / II	AIP mutations were detected in one of 113 patients with nonfunctioning adenomas (0.9%). This large prospective cohort study confirms the very low prevalence of germline AIP mutations in patients with apparently sporadic pituitary adenomas.
Pawlikowski M, Kuta J, Fuss-Chmielewska J, Winczyk K (2012)[33]	A retrospective observational study at a single institution. Fifty-six patients with pituitary adenomas who underwent TSS were included in the study. Thirty-seven patients before the surgery with clinically nonfunctioning pituitary adenomas (CNFPAs) were diagnosed.	Diagnostic / III	Among the pituitary tumors diagnosed before the surgery as clinically nonfunctioning, 45.9% showed GH immunopositivity. The authors concluded that GH immunopositivity occurs in nearly half of “clinically” nonfunctioning pituitary adenomas, and they recommend that IGF-1 determination in blood before the surgery and immunohistochemical examination of adenoma for GH after the surgery should be performed as standard in all patients suffering from pituitary tumors irrespective of the presence or absence of acromegaly symptoms.

Author (Year)	Description of Study	Classification Process / Evidence Class	Conclusions
Hong JW, Lee MK, Kim SH, Lee EJ, et al (2010)[20]	Retrospective study to evaluate characteristics that discriminate prolactinoma from non-functioning pituitary macroadenoma with hyperprolactinemia. We included 117 patients with hyperprolactinemic pituitary macroadenomas. Patients were divided into 3 groups: prolactinoma that responded to dopamine agonist (DA) treatment (PRDA); prolactinoma requiring surgical treatment (PRS); and non-functioning pituitary adenoma with hyperprolactinemia (NFPAH).	Diagnostic / II	Old-age low serum prolactin levels and extrasellar extension were associated with NFPAH. Most patients with NFPAH had serum prolactin levels less than 100 ng/ml. GH deficiency was more common in patients with NFPAH compared with patients with PRS and PRDA, without difference of tumor size. Galactorrhea and amenorrhea were less frequent in patients with NFPAH than in patients with PRS and PRDA. In conclusion, old age, extrasellar tumor extension with relatively low prolactin levels, visual defect, and GH deficiency were considered suggestive of non-functioning pituitary adenoma.
Cury ML, Fernandes JC, Machado HR, Elias LL, Moreira AC, Castro M (2009)[12]	Retrospective study of a Southeast Brazilian experience of NFPA in which 104 patients were evaluated by the same team of endocrinologists and neurosurgeon. Patients underwent biochemical evaluation radiological studies and visual field assessment.	Diagnostic / II	Hypopituitarism and neuro-ophthalmological defects were observed in 89%. The authors also observed GH deficiency (81.4%), hypogonadism (63.3%), adrenal hypofunction (59.5%), hypothyroidism (20.4%), and high (38.5%) and low (16.7%) prolactin levels. Preoperative imaging classified 93% of the tumors as macroadenomas. Their data confirmed elevated prevalence of mass effect and hypopituitarism in patients harboring NFPA.

Author (Year)	Description of Study	Classification Process / Evidence Class	Conclusions
Fatemi N, Dusick JR, Mattozo C, McArthur DL, Cohan P, Boscardin J, Wang C, Swerdloff RS, Kelly DF (2008)[14]	Retrospective analysis of 223 patients with NFPAs out of 444 total with pituitary adenomas that underwent transsphenoidal resection over an 8-year period at a single institution. Those with previous sellar radiotherapy were excluded.	Diagnostic / II	Of 231 patients with endocrine-inactive adenomas, 194 (84%) had preoperative hormonal dysfunction, including 120 (54%) with "stalk compression" hyperprolactinemia.
Del Monte P, Foppiani L, Ruelle A, Andrioli G, Bandelloni R, Quilici P, Prete C, Palummeri E, Marugo A, Bernasconi D (2007)[23]	Retrospective study to evaluate multiple features, including the clinical presentation characteristics of non-functioning pituitary macroadenomas (NFPM) in elderly patients. Twenty-seven patients (65-81 years; 13 males and 14 females) with NFPM (20-45 mm in diameter) were studied.	Clinical Assessment / II	Endocrinological evaluation on diagnosis showed global anterior hypopituitarism in 33% and partial hypopituitarism in 37% of patients.

Author (Year)	Description of Study	Classification Process / Evidence Class	Conclusions
Gussi IL, Young J, Baudin E, Bidart JM, Chanson P (2003)[36]	Prospective case-control study to assess the sensitivity of CgA measurement in sporadic pituitary adenomas. Serum CgA was measured using a solid-phase 2-site immunoradiometric assay based on monoclonal antibodies that bind to 2 distinct contiguous epitopes within the 145-245 region of CgA	Diagnostic / II	Twenty-seven patients (12 men [64.2 +/- 11.8 years]), including 7 premenopausal women (38.4 +/- 5.7 years), and 8 postmenopausal women (67.7 +/- 10.3 years)] with NFPA. Mean basal CgA concentration in 14 normal subjects was 80.2 ng/ml (SD: 31.7; range 19-124). A cut-off value for normal range was thus set at 125 ng/ml. Three out of 27 subjects with NFPA (11%) had elevated basal CgA levels (576, 143, and 241 ng/ml, respectively). Serum levels of CgA were not influenced by TRH in any of the NFPA subjects (including those 3 with increased basal levels). The authors concluded that CgA serum levels measurement are not a helpful marker for the clinical management of functioning and nonfunctioning pituitary adenomas.

Author (Year)	Description of Study	Classification Process / Evidence Class	Conclusions
Drange MR, Fram NR, Herman-Bonert V, Melmed S (2000)[13]	Retrospective registration of 371 patients (99 clinically nonfunctioning tumors [CNFTs]) with radiological, biochemical, and clinical evidence of pituitary tumors was performed. Analysis of this primarily specialist-referred population revealed a female predominance among CNFT (60%).	Diagnostic / II	Males had a significantly greater frequency of macroadenomas than females for CNFTs (92% vs 68%). Concurrent hyperprolactinemia was present in CNFT (47%).
Gsponer J, De Tribolet N, Deruaz JP, Janzer R, Uske A, Mirimanoff RO, Reymond MJ, Rey F, Temler E, Gaillard RC, Gomez F (1999)[19]	Retrospective study on 353 consecutive patients with the presumptive diagnosis of pituitary tumor investigated from January 1984 through December 1997 at University Hospital, Lausanne, Switzerland. Nonsecreting adenomas (NSAs) were the most frequent pituitary tumors (40%).	Diagnostic / II	For the differential diagnosis of hyperprolactinemia basal prolactin (PRL) levels above 85 micrograms/L in the absence of renal failure and PRL-enhancing drugs and a PRL increment of less than 30% after thyrotropin-releasing hormone (TRH) accurately ruled out functional hyperprolactinemia due to NSA.

Popovic V, Damjanovic S (1998)[34]	Paradoxical response of luteinizing hormone (LH,) follicle-stimulating hormone (FSH), and alpha-subunits (alpha-SU) to thyrotropin-releasing hormone (TRH) have previously been reported. This study assessed the in vivo responses of LH, FSH, and alpha-SU to TRH in 34 patients with clinically nonfunctioning pituitary tumors (NFT).	Diagnostic / II	Twenty-three clinically NFT were postoperatively analyzed by immunocytochemistry, and 21 stained positive for beta-FSH and/or beta-LH. Two patients with NFT had elevated basal circulating levels of FSH (41.5 IU/L) and thus were characterized as FSH-secreting adenomas. TRH in these patients increased LH from basal 1.6 IU/L to 32.6 IU/L. In other patients with NFT, circulating levels of glycoprotein peptides were not elevated. TRH induced significant rise of LH in 8 (23.5%), FSH in 5 (14.7%), and alpha-SU in 10 (29.4%) patients with NFT. Thus, a bolus dose of TRH elicited a notable increment in FSH, LH, or alpha-SU in 23 of 34 patients with NFT. The authors confirmed that most NFTs are capable of synthesizing gonadotropin hormones and subunits (beta-FSH, beta-LH) and that most patients responded by either FSH, LH, or alpha-SU secretion after TRH, independent of basal hormone levels.

Author (Year)	Description of Study	Classification Process / Evidence Class	Conclusions
Vierhapper H (1998)[31]	The study included 33 patients with non-functioning pituitary macroadenomas prior to transsphenoidal adenomectomy. This study was conducted to evaluate whether stimulated concentrations of growth hormone (GH) are of practical use in establishing the diagnosis of acquired GH deficiency.	Prognostic / II	Patients with pituitary macroadenomas who needed substitution therapy for at least 1 additional pituitary hormone presented with lower ($P < .05$) GHRH-stimulated GH secretion (3.2 +/- 4.3 ng/ml) than the remaining patients with pituitary tumors (7.2 +/- 6.6 mg/ml).

Author (Year)	Description of Study	Classification Process / Evidence Class	Conclusions
Chanson P, Pantel J, Young J, Couzinet B, Bidart JM, Schaison G (1997)[35]	Prospective study in normal subjects and 26 patients with NFPA to assess if the paradoxical free LH beta response to TRH may be a useful clinical tool for determining the gonadotropic nature of NFPA. The authors used a very specific and sensitive immunoradiometric assay (IRMA) for free LH beta measurement and another specific IRMA to check the absence of free CG beta.	Diagnostic / II	In patients with NFPA, LH beta hypersecretion was found basally and/or after stimulation with TRH in 3 of 16 men, 3 of 5 premenopausal women, and 1 of 5 postmenopausal women; ie, 7 of 26 patients (26%). In 3 of these 7 cases, alpha-subunit and/or FSH levels were also increased. The LH beta measurement was thus truly informative on the gonadotropic nature of NFPA in only 4 out of 26 cases (15%). Basal plasma levels of LH beta were undetectable in normal men and premenopausal women in the early follicular phase. In contrast, normal postmenopausal women had increased basal plasma, LH beta parallel to dimeric LH, and alpha-subunit levels. In healthy subjects, stimulation with GnRH elicited an increase in LH beta, while TRH was ineffective. The authors concluded that, using a very sensitive and specific IRMA, free LH beta measurement is rarely helpful for determining the gonadotropic nature of NFPA.

Author (Year)	Description of Study	Classification Process / Evidence Class	Conclusions
Beentjes JA, Tjeerdsma G, Sluiter WJ, Dullaart RP (1996)[32]	Prospective study on 34 patients (20 females and 14 males [median age 52 (23-77) years]) with untreated non-functioning pituitary macroadenomas evaluated preoperatively in a university hospital setting. The analysis included the peak GH to ITT and to 100 micrograms GHRH in relation to an elevated PRL level (>200 mIU/l for males and >600 mIU/l for females) as an indication of hypothalamic-pituitary dysregulation as well as in relation to other anterior pituitary hormone deficiencies. A peak GH <5 micrograms/l in either test indicated GH deficiency.	Diagnostic / II	In the whole group, the median peak GH to GHRH (3.6 [0.9-26.3] micrograms/l) was higher than to ITT (1.6 [0.2-7.8] micrograms/l; *P* < .001). This difference was seen only in 19 patients with concomitant hyperprolactinaemia (*P* < .001). When hyperprolactinaemia was present, an insufficient GH peak was demonstrated by ITT in 16 cases and by GHRH stimulation in 7 cases (*P* < .01). Peak GH to ITT was lower in 24 patients with, compared to 10 patients without, other hormonal deficiencies (1.4 [0.2-5.6] vs 3.0 [1.0-7.8] micrograms/l; *P* < .02) but was not related to elevated PRL. In contrast, GHRH-stimulated GH was higher in hyperprolactinaemic than in normoprolactinaemic patients (5.9 [1.6-26.3] vs 2.9 [0.9-5.4] micrograms/l; *P* < .001) and was not related to the presence of other pituitary hormone deficiencies. Basal GH was positively correlated with PRL (R(s) = 0.36; *P* < .05). The authors concluded that ITT and GHRH tests cannot be used interchangeably in diagnosing GH deficiency in patients with non-functioning pituitary macroadenoma and hyperprolactinaemia and that hyperprolactinaemia may be associated with a diminished somatostatin tone, leading to a higher basal and GHRH-stimulated GH without having an effect on peak GH to ITT.

Author (Year)	Description of Study	Classification Process / Evidence Class	Conclusions
Tjeerdsma (1996)[17]	Prospective case series of 40 consecutively enrolled patients with NFPAs and reported baseline hyperprolactinemia in 50% of patients. Hyperprolactinemia was defined as serum prolactin .200 mIU/I and .600 mIU/I in women.	Diagnostic / II	Hyperprolactinemia was associated with additional anterior pituitary axis deficiencies.
Greenman et al (1995)[30]	A prospective case series of 26 patients with NFPAs were studied.	Diagnostic / II	Authors reported baseline hypogonadism in 78% of patients, adrenal insufficiency in 43%, and hypothyroidism in 23% of patients. Impaired adrenal function was documented in 9 of 21 patients. Before surgery, more than 1 pituitary hormone axis was involved in 56% of patients. After surgery, 35% of patients had more than 1 pituitary hormone axis impaired after surgery. Postoperatively, the authors reported hypogonadism in 46% of patients, adrenal insufficiency in 50%, and hypothyroidism in 12%.
Berkmann et al (2012)[21]	A retrospective observational study at a single institution in Switzerland. A total of 182 patients who underwent surgical intervention for pituitary lesions were included. One hundred fourteen of 182 patients (63%) had NFPAs.	Clinical Assessment / II	Of 114 patients with NFPAs, 83 presented with preoperative hypopituitarism.

Author (Year)	Description of Study	Classification Process / Evidence Class	Conclusions
Chen et al (2011)[26]	A prospective observational study of 385 patients with NFPAs who underwent surgical intervention for resection of tumor. Mean follow-up was 5.5+/-1.4 years. Hypopituitarism at baseline was analyzed.	Clinical Assessment / II	In 385 patients analyzed before and after endoscope-assisted transsphenoidal resection of tumor, preoperative hypopituitarism was noted as follows: hypothyroidism 35.8%, hypogonadism 41%, hypoprolactinemia 17.9%, GH deficiency 61%.
Nomikos et al (2004)[16]	Retrospective study on 822 patients who underwent primary surgery in a single center: 721 cases had complete set of endocrinological data.	Clinical Assessment / II	Preoperative hypopituitarism found in 561 (85%) and 53 (86.3%) of the patients belonging to the transsphenoidal and the transcranial groups, respectively: 163 (31%) of the patients had secondary adrenal deficiency, 463 (76.6%) had hypogonadism, and 105 (19.1%) were hypothyroid. Preoperatively, prolactin levels were mildly elevated in 167 patients (25.3%).
Marazuela M, Astigarraga B, Vicente A, Estrada J, Cuerda C, García-Uría J, Lucas T (1994)[24]	Retrospective study in 35 patients with non-functioning pituitary adenomas studied before and after transsphenoidal surgery in a single center.	Clinical Assessment / II	Preoperatively, 24 patients (69%) had abnormal pituitary function, 24 (69%) had hypogonadism, 7 (20%) adrenal insufficiency, 8 (23%) hypothyroidism, and 2 (6%) panhypopituitarism.

Author (Year)	Description of Study	Classification Process / Evidence Class	Conclusions
Karavitaki et al (2006)[15]	Retrospective analysis of 226 patients with histological proven NFAs. Median age 55 years (18-88), 65% men, 41 patients on medications that can influence prolactin levels.	Diagnostic / II	Hyperprolactinaemia was found in 38.5% (87/226) of the patients. The median serum PRL values in the total group were 386 mU/l (range 16-3257) (males: median 299 mU/l, range 16-1560; females: median 572 mU/l, range 20-3257) and, in those not taking drugs capable of increasing serum PRL, 363 mU/l (range 16-2565) (males: median 299 mU/l, range 16-1560; females: median 572 mU/l, range 20-2565). Serum PRL <2000 mU/l was found in 98.7% (223/226) of the total group and in 99.5% (184/185) of those not taking drugs. Among the 3 subjects with serum PRL >2000 mU/l, 2 were on estrogen treatment. The authors concluded that a serum PRL >2000 mU/l is almost never encountered in nonfunctioning pituitary macroadenomas.

Author (Year)	Description of Study	Classification Process / Evidence Class	Conclusions
Webb et al (1999)[22]	Retrospective analysis of 234 patients with pituitary adenomas (56 NFA) treated with transsphenoidal resection. Preoperative anterior pituitary function was evaluated: PRL, free T4, TSH, cortisol, ACTH or ACTH stimulation test, GH stimulation after ITT. Hypogonadism was defined by low testosterone, low LH and FSH in men, inappropriately low FSH and LH in postmenopausal women, or low estradiol with low/low normal LH and FSH in premenopausal women with menstrual abnormalities.	Clinical Assessment / II	Of 56 patients with NFPAs, 52% had some element of hypopituitarism preoperatively.
Comtois R, Beauregard H, Somma M, Serri O, Aris-Jilwan N, Hardy J (1991)[11]	Retrospective study on 126 patients who underwent transsphenoidal surgery for primary treatment of NFA in a single center from 1962 to 1987. Data on preoperative hormonal work-up was collected. There were 73 male and 53 female patients (mean age, 50 +/- 12 years).	Clinical Assessment / II	Endocrine evaluation revealed the presence of hypogonadism in 75% (87 of 115), adrenal insufficiency in 36% (46 of 126), and hypothyroidism in 18% (21 of 122). Plasma prolactin was increased in 65% (56 of 86) with a mean level of 39 +/- 14 micrograms/l (normal, 3 to 20 micrograms/l).

Author (Year)	Description of Study	Classification Process / Evidence Class	Conclusions
Arafah et al (1986)[9]	Prospective study of 26 patients with large nonfunctioning pituitary adenomas before and 2-3 months after transsphenoidal adenomectomy. Basal serum PRL, GH, TSH, LH, FSH, and ACTH levels were measured, and dynamic studies of their secretion were also analyzed.	Clinical Assessment / II	Preoperatively, GH deficiency was found in all 26 patients (100%), hypogonadism in 25 patients (96%), hypothyroidism in 21 patients (81%), and adrenal insufficiency in 16 patients (62%). Serum PRL levels were low (1.5-4 ng/ml) in 5 patients, normal (5-20 ng/ml) in 9 patients, and mildly elevated (21-53 ng/ml) in the remaining 12 patients.
Colao A, Cerbone G, Cappabianca P, Ferone D, Alfieri A, Di Salle F, Faggiano A, Merola B, de Divitiis E, Lombardi G (1998)[28]	Retrospective study in 84 patients with clinical nonfunctioning pituitary adenomas (NFPA) subjected to 1-10 years of follow-up. Hormonal evaluation was done before and after surgery.	Clinical Assessment / II	At diagnosis, deficiency of GH, TSH, ACTH, FSH, LH, and ADH was documented in 55, 7, 19, 47, and 6 patients, respectively.

Author (Year)	Description of Study	Classification Process / Evidence Class	Conclusions
Dekkers OM, Pereira AM, Roelfsema F, Voormolen JH, Neelis KJ, Schroijen MA, Smit JW, Romijn JA (2006)[25]	Retrospective follow-up study of 109 consecutive patients (age 56 +/- 13 years) operated for NFMA between 1992 and 2004.	Clinical Assessment / II	Preoperatively, 77% of patients had GH deficiency, 75% hypogonadism, 53% adrenal insufficiency, 43% hypothyroidism; overall, 29% patients had panhypopituitarism.
Tominaga A, Uozumi T, Arita K, Kurisu K, Yano T, Hirohata T (1995)[18]	Retrospective study of 33 patients whose anterior pituitary function was evaluated by provocative tests such as insulin induced hypoglycemia, thyrotropin releasing hormone administration test, and luteinizing hormone releasing hormone administration test.	Clinical Assessment / II	Preoperative endocrinological evaluation showed impaired secretion of GH in 30 out of 31 patients (97%), LH in 16 patients (52%), ACTH in 15 patients (48%), FSH in 13 patients (42%), TSH in 6 patients (19%), and PRL in two patients (6.5%). Hyperprolactinemia was found in 13 patients (42%).

Author (Year)	Description of Study	Classification Process / Evidence Class	Conclusions
Wichers-Rother et al (2004)[27]	Retrospective analysis of 155 patients with NFPA to evaluate anterior pituitary function before and after transsphenoidal and/or transcranial surgery. Thirty patients harbored a macroadenoma, 109 underwent transsphenoidal surgery (group 1), and 21 underwent transcranial surgery (group 2). Twenty-five patients presented a microadenoma (transsphenoidal surgery, group 3). Endocrine studies included basal serum levels and dynamic testing of anterior pituitary partial function.	Clinical Assessment / II	Preoperatively, in group 1, 2, and 3, GH deficiency was found in 85%, 90%, and 80%; gonadal dysfunction in 61%, 57%, and 24%; adrenal insufficiency in 31%, 38%, and 28%; and hypothyroidism in 32%, 38%, and 12%.
Ebersold MJ, Quast LM, Laws ER Jr, Scheithauer B, Randall RV (1986)[29]	One hundred patients who had undergone a transsphenoidal procedure in a single center.	Clinical Assessment / II	36% hypogoandism, 17% adrenal insufficiency, 32% hypothyroidism.

Author (Year)	Description of Study	Classification Process / Evidence Class	Conclusions
Behan LA, O'Sullivan EP, Glynn N, Woods C, Crowley RK, Tun TK, Smith D, Thompson CJ, Agha A (2013)[10]	Retrospective study. Clinical, biochemical, histopathological, and radiological data were recorded and analyzed in 250 subjects with NFPA.	Diagnostic / II	Of 250 patients, 44.8% were hyperprolactinemic at presentation, and out of these patients, 73.2% had PRL <1000 mIU/l and 24.1% had PRL between 1000 and 1999 mIU/l. 55.3% of patients with hyperprolactinemia were female. 2.7% (3 females, 2 of them pregnant) had PRL >2000 mIU/l, 94.3 ng/ml). No male subjects and no subjects with an intrasellar macroadenoma had serum PRL >1000 mIU/l (47.2 ng/ml). Forty-three subjects taking medications known to raise PRL did not have overall higher PRL levels.

Table 2. Prevalence of hyperprolactinemia in patients with NFPAs.

Author (Year)	n	Hyperprolactinemia (%)
Nomikos (2004)[16]	721	25.3
Behan (2013)[10]	250	44.8
Karavitaki (2006)[15]	226	38.5
Fatemi (2008)[14]	223	54
Comtois (1991)[11]	126	65
Cury (2009)[12]	104	38.5
Drange (2000)[13]	99	47
Tjeerdsma (1996)[17]	40	50
Tominaga (1995)[18]	33	42
Arafah (1986)[9]	26	46
TOTAL	1848	Range: 25%-65%

Table 3. Prevalence of overall hypopituitarism in patients with NFPAs.

Author (Year)	n	Hypopituitarism
Nomikos (2004)[16]	721	85
Fatemi (2008)[14]	223	84
Berkmann (2012)[21]	114	72.8
Drange (2000)[13]	99	44
Webb (1999)[22]	56	52
Del Monte (2007)[23]	27	37
TOTAL	1240	Range: 37%-85%

Table 4. Prevalence of GH deficiency in patients with NFPAs.

Author (Year)	n	GH deficiency
Chen (2011)[26]	385	61
Wichers-Rother (2004)[27]	155	85
Dekkers (2006)[25]	109	77
Cury (2009)[12]	104	81.4
Colao (1998)[28]	84	65
Tjeerdsma (1996)[17]	40	86
Arafah (1986)[9]	26	100
TOTAL	903	Range: 61%-100%

Table 5. Prevalence of hypogonadism in patients with NFPAs.

Author (Year)	n	Hypogonadism
Nomikos (2004)[16]	721	76.6
Chen (2011)[26]	385	41
Wichers-Rother (2004)[27]	155	55
Comtois (1991)[11]	126	75
Dekkers (2006)[25]	109	75
Cury (2009)[12]	104	63.3
Ebersold (1986)[29]	100	36
Colao (1998)[28]	84	56
Tjeerdsma (1996)[17]	40	66.5
Marazuela (1994)[24]	35	69
Arafah (1986)[9]	26	96
Greenman (1995)[30]	26	78
TOTAL	1911	Range: 36%-96%

Table 6. Prevalence of adrenal insufficiency in patients with NFPAs.

Author (Year)	n	Adrenal Insufficiency
Nomikos (2004)[16]	721	31
Wichers-Rother (2004)[27]	155	31
Comtois (1991)[11]	126	36
Dekkers (2006)[25]	109	53
Cury (2009)[12]	104	59.5
Ebersold (1986)[29]	100	17
Colao (1998)[28]	84	23
Marazuela (1994)[24]	35	20
Arafah (1986)[9]	26	62
Greenman (1995)[30]	26	43
TOTAL	1486	Range: 17%-62%

Table 7 Prevalence of hypothyroidism in patients with NFPAs.

Author (Year)	n	Hypothyroidism
Nomikos (2004)[16]	721	19.1
Chen (2011)[26]	385	35.8
Wichers-Rother (2004)[27]	155	30
Comtois (1991)[11]	126	18
Dekkers (2006)[25]	109	43
Cury (2009)[12]	104	20.4
Ebersold (1986)[29]	100	32
Colao (1998)[28]	84	8
Tjeerdsma (1996)[17]	40	67
Marazuela (1994)[24]	35	23
Arafah (1986)[9]	26	81
Greenman (1995)[30]	26	23
TOTAL	1911	Range: 8%-81%

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APPENDIX A

Search Strategies

Cochrane

1. MeSH descriptor Pituitary Neoplasms
2. MeSH descriptor Adenoma
3. 1 and 2
4. ((pituitary OR hypophyse* OR sellar) NEAR/4 (microadenoma* OR adenoma* OR macroadenoma* OR incidentaloma* or chromophobe*)):ti,ab,kw
5. 3 or 4 and (asymptomatic* OR nonfunction* OR non-function* OR nonsecret* OR non-secret* OR inactive OR null OR inert OR silent)

PubMed

1. (("Pituitary Neoplasms"[Majr] AND Adenoma[Mesh]) OR "Adenoma, Chromophobe"[Majr] OR "Sella Turcica"[Majr])
2. (microadenoma* OR adenoma* OR macroadenoma* OR incidentaloma* OR chromophobe*[Title/Abstract]) AND (pituitary OR hypophyse* OR sellar[Title/Abstract])
3. (1 OR 2) AND (asymptomatic* OR nonfunction* OR non-function* OR nonsecret* OR non-secret* OR inactive OR null OR inert OR silent)
4. 3 AND "Hyperpituitarism"[Mesh] OR "Hypopituitarism"[Mesh] OR ("stalk effect" OR "disconnection hyperprolactinemia")
5. 4 AND "Diagnostic techniques, endocrine"[Mesh] OR diagnosis[tiab] OR (endocrine AND (function OR functioning OR status))
6. NOT Comment[pt] NOT Letter[pt]

Limits: English, Humans, publication date 1966 to 10/1/2014