CONGRESS OF NEUROLOGICAL SURGEONS SYSTEMATIC REVIEW AND EVIDENCE-BASED GUIDELINE ON PRETREATMENT OPHTHALMOLOGY EVALUATION IN PATIENTS WITH SUSPECTED NONFUNCTIONING PITUITARY ADENOMAS

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ABSTRACT

Background: Nonfunctioning pituitary adenomas (NFPAs) are the most frequent pituitary tumors. Visual symptoms from NFPAs are common and include visual field defects, loss of central vision, and motility problems resulting in diplopia.

Objective: To create evidence-based guidelines in an attempt to formulate guidance for preoperative ophthalmologic evaluation of NFPA patients.

Methods: An extensive literature search was performed. Only clinical articles describing preoperative ophthalmologic evaluation of adult patients with NFPAs were included. To ascertain the class of evidence for the posttreatment follow-up, the authors used the Clinical Assessment evidence-based classification.

Results: Six studies met the inclusion criteria with respect to the questions regarding the preoperative ophthalmologic evaluation of NFPA patients. Based on the studies located through the search, the authors formulated evidence-based recommendations as they pertain to the necessity of ophthalmologic evaluation before surgical treatment.

Conclusions: Preoperative ophthalmologic evaluation is recommended. Such evaluation can provide prognostic factors for recovery and, when paired with postoperative evaluation, documents postoperative change. In addition to formal ophthalmologic examination, tests of value include automated static perimetry and optical coherence tomography (OCT). Older

patients and patients with longer duration (over 4 months) of vision loss should be counseled regarding the reduced chance of postoperative vision improvement.

RECOMMENDATIONS

Question

What is the role of ophthalmologic evaluation in pretreatment assessment of nonfunctioning adenoma patients?

Level III Recommendation

- Pretreatment evaluation of NFPA patients by an ophthalmologist is recommended. Ophthalmologic evaluation identifies patients with asymptomatic visual deficits due to the ophthalmologist's ability to quantitate psychophysical (acuity and visual fields), functional (quantitation of afferent pupillary defect and visual evoked potentials [VEP]), and anatomical (disc appearance and ocular coherence tomography [OCT]) assessment. Ophthalmologic evaluation may also provide prognostic factors for recovery and, when paired with postoperative evaluation, documents postoperative change.

Question

Are there ophthalmologic tests of particular value in the pretreatment assessment of nonfunctioning adenoma patients?

Level III Recommendations

- Automated static perimetry is recommended for early detection of visual field deficits, many of which the patient will be unaware of, in patients with nonfunctioning pituitary adenomas. Automated static perimetry, even with a standard III size test object, will often pick up subtle bitemporal visual field defects, less commonly homonymous defects, and, infrequently, arcuate defects characteristic of optic nerve pathology.
- Visual evoked potentials may be used to assess the optic nerves in nonfunctioning pituitary adenoma patients in a manner that may correlate with visual field deficits, but false positives and negatives may limit this testing to cases in which psychophysical areas, such as acuity and visual fields, cannot be assessed.

Question

Are there preoperative prognostic factors associated with the chances of postoperative vision improvement after nonfunctioning adenoma resection that can inform patients and their providers?

Level III Recommendations

- It is recommended that older patients and patients with longer duration (>4 months) of vision loss be counseled regarding the reduced chance of postoperative vision improvement.

- Formal ophthalmologic examination, looking for optic nerve atrophy or optical coherence tomography (OCT) to measure both retinal nerve fiber layer (RNFL) thickness and the presence of damage to the ganglion cell layer on algorithms that segment the macular cube, is recommended to assess a patient's chances of postoperative vision improvement.
- Although not yet standard of practice, anatomic assessment of the anterior visual pathways provided with the use of optical coherence tomography documents previous damage, showing evidence of nerve fiber bundle thinning and evidence of ganglion cell dropout with segmentation analysis.

INTRODUCTION

Visual impairment is a potentially devastating symptom from a nonfunctioning adenoma that can dramatically impair a patient's quality of life.[1,2] Nonfunctioning pituitary adenomas (NFPAs) have a high incidence of both optic atrophy and visual field defects.[3] In a 1983 study out of Montreal, nonfunctioning adenomas had 60% incidence of visual field defects.[4] These findings have been noted earlier by some groups[5] and confirmed by other contemporaneous studies.[6-9] Today, fortuitous discovery, usually secondary to imaging for other reasons (headache, head trauma, and unassociated complaints) has led to the more frequent diagnosis of "incidentalomas,"[10] rendering visual symptoms less prevalent in adenomas diagnosed by imaging but only slightly less prevalent in nonfunctioning adenomas undergoing surgery.

Potential visual symptoms from a nonfunctioning adenoma include visual field defects, loss of central vision, and motility problems resulting in diplopia. While visual acuity measurements to a large extent remained the same over the past 150 years, our ability to study visual fields has advanced tremendously, due not in small part to studies by Harvey Cushing (including a series of 7 papers on visual field assessment related to intracranial pathology). The advent of Goldmann perimetry in the 1940s permitted the first generally available tool for quantitative visual field assessment. More recently, the development of automated static perimetry has permitted more reproducible quantitative assessment of visual field impairment. It must be remembered, however, that measurement of acuity and visual fields remains psychophysical, and therefore results are only as good as the patient is able or willing to give.

Improvements in assessing the physiology of vision include improvements in quantitative visual evoked potential (VEP) and the early introduction of multifocal VEP. It is in the study of anatomy, however, that the last 20 years have seen a tremendous advance, with the advent of ocular coherence tomography (OCT) offering a more quantitative tool than reliance on funduscopic assessment of optic nerve atrophy. Funduscopic evaluation still plays a role when OCT is not available. OCT provides accurate reproducible assessment of nerve fiber layer thickness, and with new segmentation algorithms, the ability to measure residual ganglion cell layer within the retina as a measure of damage to the optic nerve and visual pathways. Many of these more recent techniques, including OCT and automated perimetry, have only had a limited track record in studying patients with nonfunctioning pituitary adenomas.

It is important to recognize that while psychophysics, physiology, and anatomy tend to parallel each other, there can be substantial disparities. This is none more true than in the case of

patients who have had pituitary adenomas that have affected the visual pathways, where there may be substantial recovery including normalization of visual fields, and yet the anatomy will not recover, with persistent optic atrophy and OCT changes. Therefore, it is unlikely that any of these studies will completely replace the other, and future work on assessment of the visual system in patients with pituitary tumors will need to include measures of all.

Here, the guidelines task force engaged in a multidisciplinary effort to establish recommendations related to preoperative assessment of vision in nonfunctioning adenoma patients. To do so, the authors performed a comprehensive review of the literature on visual symptoms from nonfunctioning adenomas, tools for evaluating vision in nonfunctioning adenoma patients, and prognostic factors for improvement.

METHODOLOGY

Process Overview

The evidence-based clinical practice guideline task force members and the Tumor Section of the Congress of Neurological Surgeons (CNS) and the American Association of Neurological Surgeons (AANS) conducted a systematic review of the literature relevant to the management of NFPAs. Additional details of the systematic review 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 (JGC). 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 task force 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 evidence-based clinical practice guideline taskforce members and the medical librarian using previously published search strategies to identify relevant studies (Appendix A).[11-18]

RESULTS

Study Selection

The searches resulted in 447 articles, of which a total of 96 were recalled for full-text review. Ninety studies were excluded following full-text review, and 6 studies met the inclusion criteria and are included as evidence to support this chapter. A flow chart summarizing study selection can be found in Figure 1.

The Role of Ophthalmologic Evaluation in Pretreatment Assessment of Patients with Nonfunctioning Pituitary Adenomas

In spite of the marked increase in the percentage of patients with pituitary adenomas that are asymptomatic (the result of the advent of imaging and a better understanding of the endocrine manifestations), a substantial number of patients with nonfunctioning macroadenomas still present with measurable visual disturbances.[3] Often, patients with obvious chiasmal compression may not be aware of visual loss, discovered only on quantitative ophthalmic assessment.[19] One Class III study retrospectively classified optic chiasm compression on MRI as: no contact (Grade 0), contact without deformity (Grade 1), compression with deformity but preservation of cisternal CSF (Grade 2), compression with deformity and loss of cisternal CSF (Grade 3), or compression with deformity, loss of cisternal CSF, and cerebral compression (Grade 4).[20] Of 11 patients with nonfunctioning adenomas and no visual symptoms, Goldman perimetry revealed 3 patients to have early temporal deficits, of which one had Grade 2 compression on MRI and two had Grade 3 compression on MRI.[20] A larger prospective study will be needed to determine whether Grade 1 patients can have field deficits on automated perimetry. This lack of awareness of deficits identified during testing is particularly prevalent in the elderly, with one study presenting Class III evidence retrospectively in which 64% of adenoma patients over age 65 had detectable visual deficits on detailed physical examination, even though only 39% complained of vision loss.[19] Similarly, another study presented Class III evidence that patients over age 60 were more likely to have a delay in adenoma diagnosis over 6 months, and that this delay is a negative predictive factor in improvement discussed below.[21] Patients with larger nonfunctioning adenomas tend to have more visual symptoms (Table 1).[22]

Patient-specific anatomy is another factor influencing which nonfunctioning adenoma patients are likely to present with vision loss, with one study of 98 adenomas presenting Class III evidence pointing out that the relative position of the chiasm may influence the incidence of visual field defects, with a decrease frequency of visual deficits occurring in patients with an anatomically prefixed optic chiasm.[23]

The Role of Ophthalmologic Tests in the Pretreatment Assessment of Nonfunctioning Adenoma Patients

While not always feasible, preoperative examination by an ophthalmologist has marked benefits for NFPA patients and their providers. An ophthalmologist's exam including measuring the best corrected acuity (requiring refraction and commenting on alternative causes of decreased acuity including cataracts and macular pathology) and quantitative psychophysics with automated static perimetry can be useful for identifying prognostic factors listed below by quantifying the degree of anatomic damage that exists before surgery.

Physiology studies, including VEP, are less studied. The use of VEP was reported in a Class III study from 1989 in which 34 patients with null cell adenomas and patient-reported visual symptoms underwent preoperative VEP.[24] All patients with a visual field deficit had VEP abnormalities, but 14 eyes in 10 patients with normal acuity had abnormal VEP. The laterality of the VEP abnormality correlated well with the radiographic laterality of tumor extension. These results have not been subsequently built upon, and the role for VEP remains extremely limited as compared to acuity measurements and perimetry (Table 1).

Patients with pituitary tumors can also present with complaints of double vision due to cavernous sinus compression of any of the 3 cranial nerves (III, IV, and VI) mediating eye mobility. The incidence of this is much less common than visual field defects, decreased acuity, and optic atrophy, with one Class III study reporting 1 of 29 nonfunctioning adenoma patients reporting diplopia and exhibiting a partial third nerve palsy and another patient reporting diplopia without any nerve palsies, felt to reflect hemifield slide in patients with field cuts where the disparate residual nasal hemifields cannot be aligned.[25] Recognition of cranial nerve involvement is usually based on pattern recognition. This can be done by looking at the 9 cardinal positions of gaze (straight, up, down, left, right, up right, up left, down right, and down left), or more quickly by the use of a red glass test or Maddox rod. The pattern of a sixth nerve palsy is an esodeviation increasing on ipsilateral gaze. A fourth nerve palsy produces an ipsilateral hyper deviation increasing on contralateral gaze and with ipsilateral head tilt. A third nerve palsy is marked by an exodeviation increasing on contralateral gaze with an ipsilateral hyper on down gaze and a contralateral hyper on up gaze (often with associated ipsilateral ptosis and mydriasis). These patterns can be rapidly identified with a Maddox rod and can be quantitated by the use of measurements with prisms in 9 cardinal positions or the use of a Hess or Lancaster screen. While these measurements can identify subtle abnormalities in cranial nerve function existing without diplopia in NFPA patients whose tumors invade or compress the cavernous sinus (instead of diplopia these patients might instead describe blurry vision when they look to one side), we were unable to cover evidence meeting inclusion criteria specifically supporting a role for Maddox rod, prism measurements, or the use of a Hess or Lancaster screen to evaluate oculomotor function in NFPA patients not complaining of diplopia.

The Role of Preoperative Prognostic Factors Related to Vision Improvement after Nonfunctioning Adenoma Resection that Can Inform Patients and Their Providers

One study presented Class III evidence that the absence of significant optic nerve atrophy on formal ophthalmologic examination may be a good prognostic sign for recovery, with 82% of patients exhibiting no atrophy showing postoperative visual field improvement compared to 67% of patients with unilateral optic nerve atrophy and 57% of patients with bilateral optic nerve

atrophy.[23] Another study presented Class III evidence in which patients with nonfunctioning adenomas were stratified into 3 age groups: 18 to 44 years (29 patients), 45 to 64 years (38 patients), and 65 years and older (38 patients). While visual field improvement did not vary across age groups, normalization did trend toward being more frequent in the younger group (58% vs 44% vs 41%), but that trend was not significant (P = .09).[26] Another study presented retrospective Class III evidence in which duration of vision loss interacted with age to reduce the probability of postoperative return to baseline vision (Table 1).[21]

Degree of optic atrophy as a prognostic factor has been analyzed more quantitatively by optical coherence tomography (OCT), a technique that measures retinal nerve fiber layer (RNFL) thickness. In one Class III study, of 17 nonfunctioning adenoma patients, among the eyes with a visual defect before treatment, the odds of complete recovery 3 months after surgery was multiplied by 1.29 for each 1-micron increase of mean RNFL (odds ratio [OR], 1.29; P = .037). This was independent from age and duration of symptoms, which carried their own prognostic value. Inferior RNFL was a particularly strong prognostic factor (OR, 6.31 per micron; P < .001).[27] These studies are limited and await further confirmation.

DISCUSSION

Limitations

This review of the literature revealed no Class I data concerning nonfunctioning pituitary adenomas and visual findings, although conducting a double blinded randomized control trial would be very difficult to undertake due to the strict criteria surrounding such a trial and the nature of the disease and variations in the time at which patients are diagnosed. The non-comparative case series we identified also lacked sufficient duration of follow-up[28] or sufficient rigorous quantitative assessment[3,7,9,22,29-47] to be considered Class II evidence based on the definitions we utilized. For example, many studies failed to report their method of assessing visual acuity, and even fewer emphasized the importance of best corrected acuity to avoid contamination with other visual reasons for decreased acuity. Often, visual function is said to return to "normal" without criteria.[47] Very few papers had all patients seen by an ophthalmologist, although this is likely a reflection of the challenges involved in making such arrangements. Many studies present cursory visual information while focusing on the safety of the reported treatment technique.[48] When mentioned, acuity improvement has been stated as "significant" with a one-line improvement in function.[49] Authors suggest the use of uncorrected visual acuity.[50]

Another challenge is finding a quantitative means of assessing extrafoveal (visual field) visual function. There is often no data on distinguishing homonymous from "quadrantic" defects.[47] Some studies have reported visual fields based initially on confrontation with quantitative data only on follow-up.[51] Other retrospective studies include patients with only confrontation or near vision data.[37] While most recent studies now utilize automated static perimetry, some still report Goldmann perimetry,[47] and even when using automated fields there is no universal agreement on the platform used and even less agreement on comparing visual fields. Some authors have come up with their own scoring system for perimetry.[52] Several studies report "normalization"[47]

or “complete resolution”[51] of visual fields without defining criteria. Some studies have suggested minimal changes in grey scale of automated perimetry to be significant.[53]

Conclusion

Maintenance of visual function remains critical to a patient’s health and well-being. As nonfunctioning pituitary adenomas frequently present with visual symptoms, it is imperative that neurosurgeons be aware of the symptoms and how they can be best quantitated and followed. The advent of more quantitative assessment, both of psychophysics and of anatomy, will likely influence thinking about these tumors in the future. Preoperative assessment of a nonfunctioning adenoma patient by a neuro-ophthalmologist provides important insight into patients previously felt to be asymptomatic and, when performed without delaying surgery, offers valuable objective insight into the exact nature of a patient’s visual deficit and prognostic insight into the chances of postoperative visual improvement. Models at some institutions recognize the importance of multidisciplinary assessment including ophthalmologic, endocrine, and radiographic studies to optimize care for all pituitary patients,[54] and future studies will be needed to validate the benefits of these models.

Future Research

It will be important to tie increasing quantitative assessment, both of the psychophysics and anatomy, to predictions regarding recovery and future recurrence. It may be possible in the future to present data suggesting likelihood of both improvement and later changes to our patients.

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FIGURES

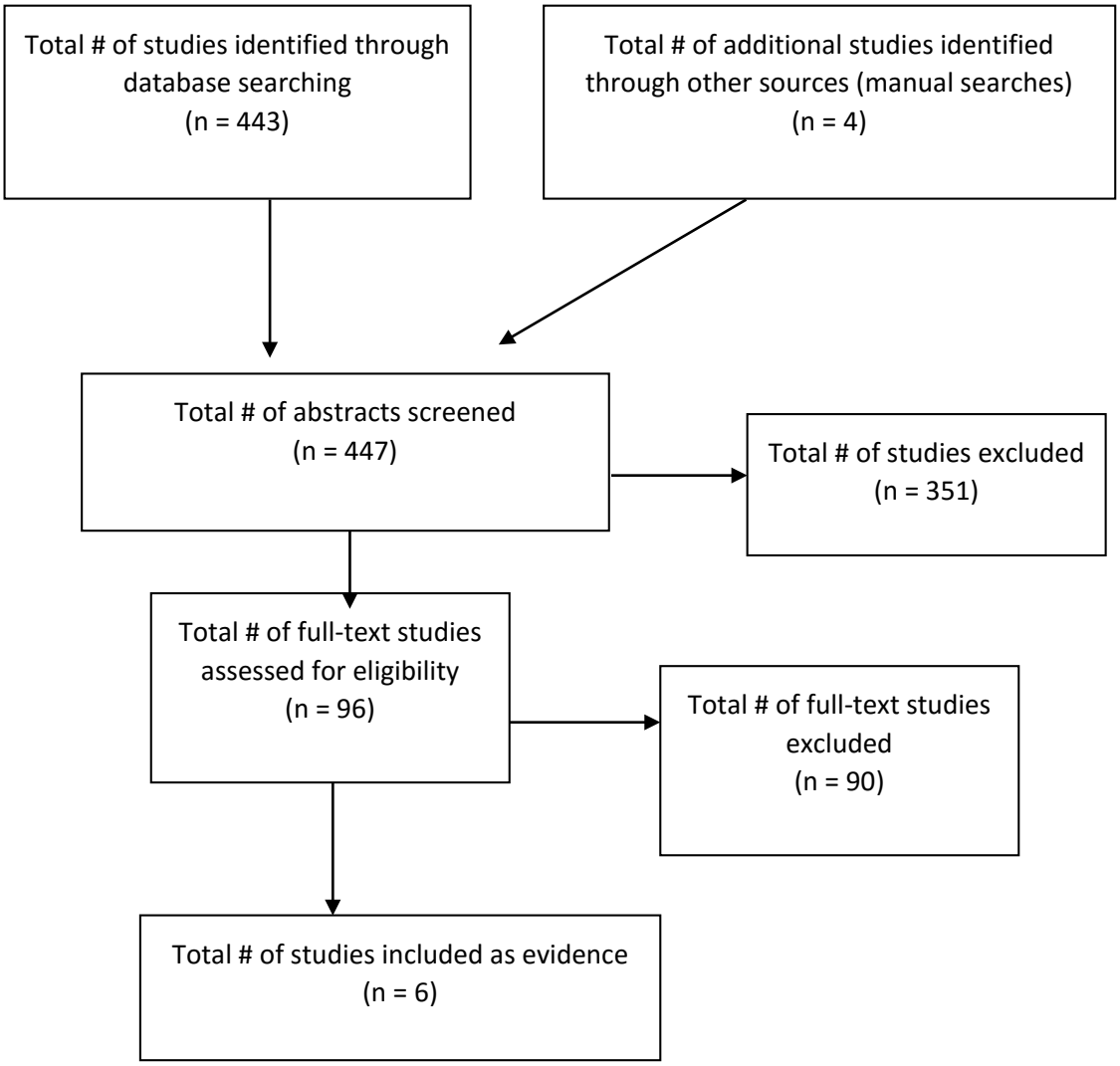

Figure 1: Article Flowchart

TABLES

Table 1 Evidence Table

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Fujimoto N, Saeki N, Miyauchi O, Adachi-Usami E (2002)[20]	Series of 15 patients with asymptomatic pituitary tumors (86% = 13/15 were NFPA) detected by MRI and 12 patients with visional symptoms from pituitary tumors (8/12 = NFPA). Vertical step, temporal depression, Goldmann perimetry, and automated perimetry used to evaluate patients.	Clinical Assessment / III	All patients with symptomatic NFPA had vertical step and temporal depression in the upper field. Of 11 patients with non-functioning adenomas and no visual symptoms, Goldman perimetry revealed 3 patients to have early temporal deficits, of whom 1 had Grade 2 compression on MRI and 2 had Grade 3 compression on MRI. Vertical step: 96% sensitivity; 100% specificity Temporal depression: 100% sensitivity; 98% specificity MRI demonstrated Grade 3 or Grade 4 compression in all symptomatic patients.

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Jahangiri A, Lamborn KR, Blevins L, Kunwar S, Aghi MK (2012)[21]	Retrospective prognostic study of 75 NFPA patients with symptoms of decreased visual acuity or diminished visual fields treated with endonasal microsurgical transsphenoidal resection. Post-op visual exams were conducted between 1.5 months and 6 months after surgery.	Prognostic / III	Postoperative Visual Improvement: Duration of symptoms and age of diagnosis were not statistically significant predictors of postoperative visual improvement. Postoperative Normalization of Vision: Duration of symptoms and age (categorical/non-continuous; 20-39 years vs 40-59 years vs 60-89 years) were statistically significant indicators of postoperative normalization of vision. Patients with normalization of vision following surgical resection had a significantly shorter duration of symptoms vs patients who did not return to baseline vision (3.5 months vs 12 months; *P* = .048)

Schmalisch K, Milian M, Schimitzek T, Lagreze WA, Honneger J (2012)[23]	A retrospective prognostic/diagnostic cohort study of 98 consecutively treated patients with MRI-confirmed NFPA were evaluated. Statistical analysis to determine potential correlational associations between the position of the tumor and the scoring system for determining chiasma syndrome was conducted. Additional analysis included receiver operating characteristic (ROC) curves to determine the sensitivities and specificities of the values of coronal and sagittal extension to detect chiasma syndrome. Computerized perimetry or Goldmann kinetic perimetry were used: "Visual field examination was performed with either. All patients studied with coronal and sagittal MRI." We classified the site of the optic chiasm in relation to the suprasellar adenoma and introduced 3 grades: anterior, superior, and posterior. "Classified visual field defects into 'unilateral concentric restriction, retinal nerve fiber layer, visual field defect, unilateral involvement of the temporal hemifield, anterior junctional syndrome, complete or incomplete bitemporal visual field defect, binasal visual field defect, posterior junctional scotoma (homonymous hemianopsia), homonymous visual field defect, and normal visual fields.'" Limited data.	Clinical Assessment / III	Seventy percent (69/98) of patients with NFPA had visual field defects; 81.2% (56/69) of patients with visual disturbances were bilateral; 10.1% (7/69) were unilateral temporal hemifield defects; 27.5% (19/69) of patients with visual field defects had bilateral optic atrophy, and 13.1% (9/69) had unilateral optic atrophy. Chiasm position (ie, anterior, superior, or posterior) was not a statistically significant indicator of visual disturbances. Suprasellar adenoma extension is a statistically significant indicator of a decline in visual acuity. The authors reported 82% of patients with pre-op chiasma syndrome without optic atrophy had vision improvements, compared to 67% of patients with preoperative atrophy in at least 1 eye, and only 57% of patients with bilateral optic atrophy showed improvement in visual fields. **Sensitivities and Specificities in Detecting Chiasma Syndrome:** Coronal View: 13 mm—84% sensitivity and 76% specificity **12 mm—87% sensitivity and 72% specificity** 11 mm—90% sensitivity and 66% specificity

			Sagittal View: 9 mm—84% sensitivity and 76% specificity **8 mm—87% sensitivity and 76% specificity** 7 mm—93% sensitivity and 62% specificity 12 mm coronal view and 8 mm sagittal view are the suggested cut-off values in detecting chiasma syndrome.

Holder GE, Bullock PR (1989)[24]	Retrospective case series of 34 patients with histological confirmed NFPAs and pre-treatment visual evoked potential (VEP) examination. Mean age of patients was 55.8 years (range 25-74 years). All patients had Topcon perimetry and some had Friedman perimetry. Color vision testing with Ishihara plates.	Clinical Assessment / III	Eighty-five percent of patients (29/34) presented with either visual failure or disturbance. Headache was a feature of 10/34 patients. Visual field defects were discovered incidentally. Twenty-four percent of patients (8/34) had been misdiagnosed prior to neurosurgical referral. Mean duration of visual symptoms prior to diagnosis was 16 months (range 1 week to 4 years). At the time of neurosurgical referral, 18% of patients (6/34) had 1 eye below 6/60 visual acuity (patient could only see at 6 meters what a "normal" sighted person should see at 60 meters), and one patient's vision had worsened to "no perception of light." Some patients suffered rapid deterioration in vision (without apoplexy) while under observation for several years. Severe defects in color vision were associated with loss of central visual field. Twenty-six percent of patients (9/34) "had an unequivocally normal fundal appearance in both eyes despite a mean duration of visual symptoms of 13 months."
Robenshtok E, Benbassat CA,	Retrospective observational cohort study of 105 NFPA patients treated with transsphenoidal surgery,	Therapeutic / III	No significant pre-treatment differences in visual symptoms/deficiencies and no significant post-treatment differences in regards to visual field

Author (Year)	Study Description	Classification Process/ Evidence Class	Conclusions
Hirsch D, et al (2014)[26]	transcranial surgery, radiation therapy, or observation. Outcomes were analyzed and reported according to 3 stratified age groups: 18-44 years; 45-64 years; ≥64 years.		nominalization, improvements, and/or deterioration in visual symptoms/defects.
Jacob M, Raverot G, Jouanneau E, et al (2009)[27]	Prospective cohort single-center study of 19 consecutive adenoma patients (17 NFPA) with compression of visual apparatus. Automated visual fields and OCT were performed before treatment and 2 weeks and 3 months after treatment.	Prognostic / III	Among the eyes with a visual field defect before treatment, the odds of complete recovery after 3 months from the initial VF defect were multiplied by 1.29 for each increase by 1 micron of mean RFNL derived from OCT (*P* = .037).

APPENDIX A

PubMed Search Strategy

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 (("Visual Field Tests"[Mesh] OR "Diagnostic Techniques, Ophthalmological"[Mesh] OR "visual fields" OR "visual field" OR ophthalmolog*[tiab] OR "Vision Disorders"[Mesh] OR (visual AND (deficit* OR impairment* OR disorder*))) OR ((OCT OR “optical coherence tomography”) OR (“Heidelberg retinal tomography” OR “Heidelberg retina tomography” OR "Heidelberg retinal tomograph” OR “Heidelberg retina tomograph” OR HRT) OR (PRNFLT OR (“retinal nerve fiber” AND “layer thickness”)) OR ((stratus OR cirrus) AND “spectral domain”) OR (octopus AND (900 OR perimeter OR perimetry)))
5. NOT Letter[pt] NOT Comment[pt]
   Limit to English, Humans, publication date to 10/01/2014

Cochrane Search Strategy

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)