Factors associated with delay to pituitary adenoma diagnosis in patients with visual loss

Clinical article

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Object. The duration of visual symptoms associated with a nonfunctioning pituitary adenoma (NFA) is a predictive factor for chances of visual improvement. The authors investigated factors associated with increased duration of visual symptoms in patients with NFAs.

Methods. The authors retrospectively reviewed NFAs resected at their institution between 2004 and 2010 for duration of visual symptoms, postoperative improvement, and associated factors.

Results. Seventy-five patients underwent NFA resection with a median visual symptom duration of 6.5 months (range 1 week–15 years). A multivariate logistic regression showed that duration of symptoms (p = 0.04), but not age at surgery (p = 0.2), predicted postoperative normalization of vision. Univariable nonparametric analyses investigating age at symptom onset, sex, race, insurance type, ophthalmological conditions, income, marital status, emergency department admission, language, and medical provider found that age was the only variable significantly prolonging symptom duration (p = 0.04), a finding confirmed by a multivariate regression analysis. Patients 20–39, 40–59, and 60–79 years old had median durations of symptoms of 4, 7, and 9 months, respectively. Seven older patients had symptoms attributed to preexisting ophthalmological conditions for a median of 18 months before NFA diagnosis. Among age and race subgroups, the largest difference in median symptom duration was between white patients in the 60–79-year age range (duration of 5 months) and nonwhite patients in the 60–79-year age range (duration of 24 months) (p = 0.04).

Conclusions. The authors found that older age was associated with delayed NFA diagnosis in visually impaired patients. Contributing factors were the attributing of visual symptoms from NFAs to other ophthalmological conditions in these patients, and delayed presentation in elderly nonwhite patients. These findings highlight challenges associated with timely NFA diagnosis in visually impaired patients, a key factor for chances of improvement.

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Key Words • pituitary adenoma • vision • symptoms • duration • elderly • pituitary surgery

Pituitary adenomas are extremely common, with a prevalence reported as high as 16.7% or 1 in 6 people in autopsy studies and studies of healthy volunteers undergoing MR imaging.9 The age-adjusted incidence of patients diagnosed with a pituitary adenoma reported by the Central Brain Tumor Registry of the United States (CBTRUS) is 0.9 per 100,000 person-years.19 Visual symptoms have been reported to be the most common presenting complaint for symptomatic nonfunctioning adenomas (NFAs)5,18 and, due to the gradual onset of these symptoms, it may take months, or even years, before a patient seeks medical care or before the diagnosis of NFA is made. A previous study confirmed a linear correlation between duration of visual symptoms and irreparable visual loss; therefore, it is critical for patients to seek care without delay once visual abnormalities develop.5 Because the delay in NFA diagnosis strongly predicts a higher risk of permanent visual loss, identifying factors associated with the delay in NFA diagnosis, which could either be due to delayed presentation to a medical provider or inability of the medical provider to make the correct diagnosis in a timely fashion, is of the utmost importance.

It is well documented that delay in diagnosis can lead to higher morbidity and mortality in a wide variety of diseases, and factors associated with the delay to diagnosis have been evaluated in diseases other than pituitary adenomas12,13 and could serve as a template to guide the study of factors associated with the delay in NFA diagnosis. In a study evaluating lymph node involvement of

Abbreviation used in this paper: NFA = nonfunctioning pituitary adenoma.

This article contains some figures that are displayed in color online but in black and white in the print edition.
breast cancer patients, advanced age was noted to be the most important factor causing a delay in diagnosis of elderly patients. Numerous studies have also found old age to be among the leading causes of delay in seeking treatment for patients with acute coronary syndrome. In terms of other visual disorders in which late diagnosis could be associated with permanent visual impairment like that seen with delayed NFA diagnosis, a retrospective study of glaucoma found that older age, female sex, and nonwhite race were associated with increased delay to glaucoma diagnosis.

In regard to pituitary adenomas, one study demonstrated reduced visual improvement after resection in elderly patients compared with younger patients, but that study did not investigate the duration of visual symptoms in these patients. We hypothesized, based on the findings in other diseases of older age being associated with a delay in diagnosis, that older age would be associated with an increased duration of visual symptoms before NFA diagnosis. To investigate this hypothesis and to identify other factors associated with delay from onset of visual symptoms to NFA diagnosis, an investigation that has yet to be conducted in the literature to date, we retrospectively reviewed NFA cases in patients with visual symptoms of specified duration that were resected at our institution during a 6-year interval.

Methods

Study Design and Population

We retrospectively reviewed the records of 75 patients with NFAs that were diagnosed when the patients presented with symptoms of decreased visual acuity or diminished visual fields (not ophthalmoplegias from cranial neuropathies) for which the patient or a family member specified a clear duration of symptoms. All patients had their visual deficit confirmed by the neurosurgeon during a preoperative physical examination. Eighteen patients were evaluated by an ophthalmologist preoperatively, and in all cases the neurosurgeon identified the same visual deficit as the ophthalmologist. Patients then underwent endonasal microsurgical transsphenoidal resection of the NFA at our institution between October 2004 and January 2010 within 1–29 days of their first MR imaging examination that showed the adenoma. Operations were performed by 2 surgeons (S.K. [69 cases] and M.K.A. [6 cases]). Inclusion criteria also included a pathology report consistent with pituitary adenoma that stained negative for adrenocorticotropic hormone, growth hormone, or prolactin. Cases in which presentation or surgical pathology was consistent with pituitary apoplexy were excluded. Postoperative visual assessment was documented by the neurosurgeon between 6 weeks and 6 months after surgery in all but 10 patients, with 18 patients undergoing postoperative evaluation by an ophthalmologist, whose evaluation results concurred with those of the neurosurgeon. This study was approved by the University of California, San Francisco Committee on Human Research (approval number H60736–34012–02).

Parameters Assessed

Age at the time of visual symptom onset and age at the time of surgery were treated as continuous variables. Tumor size was recorded as the average of 3 dimensions (anteroposterior, left to right, and superoinferior) for all cases as determined on preoperative MR images. Time in months from onset of visual field loss or diminished visual acuity until NFA diagnosis was recorded from the medical record. Records were also reviewed for ophthalmology evaluations and the presence of an ophthalmological diagnosis. Preoperative and postoperative visual assessments were obtained from records, with the latter recorded as normalization or improvement if the patient and provider concurred. Patient-specific continuous variables that were recorded and studied for correlation with duration of visual symptoms, visual improvement, or visual normalization included age at visual symptom onset, age at the time of surgery, and the median household income associated with the patient’s zip code of primary residence as derived from the census (http://factfinder.census.gov/servlet/ACSSAFFFacts) website. Noncontinuous variables considered were 1) insurance carrier (Medicare, Medicaid, uninsured, private insurer nonmanaged care, or private insurer managed care, with group size ranging from 5 to 26); 2) primary language (English, Spanish, or other); 3) race (as reported by the patient: white, Asian, Hispanic, black, or other, with group size ranging from 5 to 29); 4) marital status (married or unmarried at the time of surgery); 5) the nature of the primary medical provider (none, medical doctor, doctor of osteopathy, nurse practitioner, or physician's assistant); 6) employment status; and 7) whether the patient presented to the emergency department or was referred as an outpatient to the neurosurgery clinic.

Statistical Analysis

The Spearman correlation coefficient (for continuous variables) and the Kruskal-Wallis test (for discrete variables) were used to assess association with duration of symptoms. Those variables with p < 0.1 were included in a multivariate model. The Student t-test was used for parametric comparisons between variables. The Fisher exact test was used to compare proportions. Multivariate logistic regression was used to evaluate the impact of the log (base 10) of duration of visual symptoms and age at diagnosis on visual improvement or visual normalization, while multivariate general regression was used to evaluate the impact of age at symptom onset, race, and other ophthalmological diagnoses on the log (base 10) of duration of visual symptoms. All 2-way interaction terms were included to assess whether any pairs of these predictor variables interacted, but they did not, allowing the multivariate logistic regression to be used without concern for confounding interactions. Because a few patients had extremely long durations of symptoms, the logarithm of duration was used to prevent the few cases from being overweighted in the analysis for all parametric analyses. Analyses were performed utilizing SPSS Statistics version 17.0 software (SPSS, Inc.). The p values are 2-tailed, with p values < 0.05 considered statistically significant.
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Results

Patient Population

A total of 75 patients (46 males, 29 females; 29 white, 46 nonwhite) presented with visual field loss or diminished visual acuity for a median duration of 6.5 months (range 1 week–15 years). The visual deficits were bitemporal hemianopia in 30 patients, were difficult to definitively define in 19 patients, were uniaural in 12 patients, and involved a quadrantopia in one eye combined with a quadrantopia or hemianopia in the other eye in 8 patients. Data were missing for the remaining 6 patients. The mean age at diagnosis was 55 years (range 22–82 years). Preoperative MR images revealed the mean tumor diameter to be 2.7 cm (range 0.9–6.1 cm). Forty-six patients (61%) presented with other symptoms in addition to their visual symptoms. Ten patients presented through the emergency department with a median duration of visual symptoms of 4 months (range 1 week–15 years) including 2 patients with no insurance with visual symptoms for 6.5 and 9 months, while the other 65 patients presented through the neurosurgery clinic. Ten patients with a mean age of 72 years (range 56–88 years) had other ophthalmological diagnoses (7 with cataracts, 3 with diabetic retinopathy, and 2 with glaucoma) and presented with visual field loss or diminished visual acuity for a median of 18 months before being diagnosed with their NFA, with records showing that 7 of these 10 patients underwent evaluation by an ophthalmologist for 9 months to 10 years under the presumption that their symptoms were attributable to their preexisting ophthalmological condition.

Impact of Duration of Visual Symptoms on Chances of Improvement in Vision or Return to Baseline Vision

Of the 65 patients who underwent postoperative visual examination at least 6 weeks after surgery, 50 (77%) experienced some postoperative visual improvement, while 24 (37%) experienced postoperative resolution of all visual deficits attributable to the tumor. We used multivariate logistic regression to analyze the relationship between 2 variables, age at diagnosis and duration of visual symptoms, with postoperative improvement or normalization of vision. After confirming no interaction between age at diagnosis and the logarithm of duration of visual symptoms (p = 0.14), we found that, while neither age at diagnosis nor duration of symptoms proved predictive of postoperative visual improvement (p = 0.6 for each variable), duration of symptoms (p = 0.04) but not age at diagnosis (p = 0.2) proved predictive of postoperative return to baseline vision.

Nineteen (58%) of 33 patients with visual symptoms present for 6 months or fewer reported return to baseline vision postoperatively that could be confirmed on physical examination, which is more than the 5 (16%) of 32 patients with visual symptoms present for longer than 6 months who experienced postoperative return to baseline vision (p = 0.007). This trend persisted when dividing the patients into 3 nearly equally sized groups: those with symptoms for 4 months or fewer (67% return to baseline vision), those with symptoms for 4–12 months (40% return to baseline vision), and those with symptoms for 12 or more months (18% return to baseline vision) (p = 0.02). Patients who had return to baseline vision had a shorter duration of symptoms (median 3.5 months) than patients who did not have return to baseline vision (median duration 12 months) (p = 0.048) (Fig. 1). In dividing patients into 3 groups based on decade of life at the time of surgery (patients in their 20s and 30s; those in their 40s and 50s; and those in their 60s, 70s, and 80s) and then further dividing each of these 3 groups into 2 subgroups (those with visual symptoms for longer than 6 months and those with symptoms for 6 or fewer months, with the 6-month cutoff chosen because it was the median duration of symptoms for the entire group), we found that the decline in the rate of return to visual baseline after surgery as a function of duration of visual symptoms in each of the 3 age subgroups went from not statistically significant in patients 20–39 years old at the time of surgery (67% return to baseline vision with symptoms present for 6 or fewer months vs 50% return to baseline vision with symptoms present for longer than 6 months, p = 0.5) to significant in patients 40–59 years old at the time of surgery (54% return to baseline vision with symptoms present for 6 or fewer months vs 11% return to baseline vision with symptoms present for longer than 6 months, p = 0.046) to even more significant in patients 60–89 years old at the time of surgery (56% return to baseline vision with symptoms present for 6 or fewer months vs 6% return to baseline vision with symptoms present for longer than 6 months, p = 0.007) (Fig. 2). In other words, the age-related decline in rate of recovery to baseline vision was steeper in the groups with symptoms for over 6 months (from 50% in the youngest group down to 11% in the middle-aged group and 6% in the oldest group) than it was in the groups with symptoms for 6 or fewer months (from 67% in the youngest group down to 56% in the oldest group) (Fig. 2).

![Figure 1](https://example.com/figure1.png)

**Fig. 1.** Difference in duration of symptoms in patients with or without postoperative normalization of vision. Box and whisker plot illustrating the minimum (lower whisker), 25th percentile (lower edge of box), median (line in the box), 75th percentile (upper edge of box), and maximum (upper whisker) duration of visual symptoms in months (on a logarithmic scale on the y axis) in patients without and with postoperative normalization of vision. Patients who had return to baseline vision had a shorter duration of symptoms than patients who did not have return to baseline vision (p = 0.048). n = number of patients.
Factors Predicting Longer Duration of Visual Symptoms

We assessed the impact of 10 variables (age at symptom onset, sex, race, insurance, presence of other ophthalmological conditions, median annual household income of the patient’s zip code, marital status, presenting through emergency department versus clinic, primary language spoken, and primary medical provider) on pre-operative duration of visual symptoms (Table 1). Older patient age was the only variable that exerted a statistically significant (p = 0.04) tendency to prolong duration of symptoms. Nonwhite race and presence of any ophthalmological diagnosis were also estimated to result in prolonging the duration of symptoms, but the differences were not quite statistically significant (p = 0.07). We then determined whether these 3 variables (age at symptom onset, race, and the presence of any ophthalmological diagnosis) with potential effects on duration of symptoms based on univariate analyses exerted effects on duration of symptoms in a multivariate regression. We first confirmed that all 2-way interactions between pairs of these 3 predictors were not statistically significant (p = 0.9 for all 3 paired interactions). We then found that, in a multivariate regression analysis, age at symptom onset continued to exert a statistically significant effect on the logarithm of duration of visual symptoms (p = 0.03), while nonwhite race and the presence of any ophthalmological diagnosis exerted effects that were not quite statistically significant (p = 0.09 for each). We then found that, in a multivariate regression analysis, age at symptom onset continued to exert a statistically significant effect on the logarithm of duration of visual symptoms (p = 0.03), while nonwhite race and the presence of any ophthalmological diagnosis exerted effects that were not quite statistically significant (p = 0.09 for each). Patients 20–39 years old at the time of visual symptom onset had a median duration of symptoms of 4 months, those 40–59 years old at the time of visual symptom onset had a median duration of symptoms of 7 months, and those 60–79 years old at the time of presentation had a median duration of symptoms of 9 months (p = 0.04) (Fig. 3).
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Fig. 3. Duration of visual symptoms as a function of patient’s age at symptom onset. Box and whisker plot illustrating the minimum (lower whisker), 25th percentile (lower edge of box), median (line in the box), 75th percentile (upper edge of box), and maximum (upper whisker) duration of visual symptoms in months (on a logarithmic scale on the y axis) in 3 age groups spanning 2 decades per age group (20–39 years, 40–59 years, and 60–79 years). There was a trend toward an increased duration of visual symptoms from the lower to the upper age group (p = 0.04).

into age subgroups and by race, the only statistically significant difference in duration of symptoms was between white patients in their 60s and 70s (median duration of symptoms 24 months) and nonwhite patients in their 60s and 70s (median duration of symptoms 24 months) (p = 0.04) (Fig. 4).

Discussion

In this report, we summarize the clinical and socioeconomic characteristics of patients who presented with visual symptoms to our institution within the last 6 years, which led to the diagnosis and resection of an NFA. The relationship between the duration of visual symptoms and the extent of improvement in vision following resection of an NFA has been described in the literature, with shorter durations exhibiting superior visual improvement following surgical therapy, a finding confirmed in our report. Thus, it is imperative to advance our understanding of the underlying factors causing delay in NFA diagnosis in patients with visual symptoms to improve the visual outcomes after neurosurgical resection of NFAs. Our comprehensive analysis of the factors that have a significant impact on the duration of visual symptoms, which had not been established prior to this report, revealed that older age was associated with an increased duration of visual symptoms before NFA diagnosis, a potential explanation for why older patients with visual symptoms were less likely to improve after NFA resection in a previous series.

Our data show that older patients who seek medical care and undergo resection of an NFA within the first 6 months of noticing visual changes benefit from the surgery in a very comparable manner as younger patients in their 20s and 30s. Elderly patients with visual symptoms lasting longer than 6 months, however, exhibit much less improvement in their vision following resection than younger patients, underscoring that early diagnosis is particularly important in the elderly. Unfortunately, we found that the elderly had a greater tendency to be diagnosed with NFAs later in the course of their visual symptoms than younger patients.

There are 3 potential factors that could contribute to the increased delay in NFA diagnosis in elderly patients with visual symptoms: 1) acceptance by patients of declining vision as a natural result of the aging process; 2) other ophthalmological conditions confounding the diagnosis; and 3) a particular delay in diagnosis in nonwhite elderly patients.

Regarding the first factor, a number of studies have been conducted to assess the attitude of elderly patients in regard to their physical symptoms. They show that these patients often consider mild symptoms as a normal condition of the aging process. In particular, it has been shown that elderly patients accept declining vision as a natural part of the aging process, which leads these patients to not seek attention for cataracts, glaucoma, and diabetic retinopathy, an attitude that could also prevent these patients from seeking medical evaluation for visual symptoms resulting from an NFA. It is important to raise awareness of NFAs as a treatable cause of vision loss among the elderly and their care providers. Pituitary surgery has been demonstrated to be quite safe in the elderly with only slightly greater morbidity than in younger patients. In addition, we found that the rate of visual improvement in NFAs diagnosed within 6 months of onset of visual symptoms in the elderly in our series was 6%, nearly 10-fold lower than if diagnosis took longer than 6 months from onset of symptoms and better than the rates of visual improvement when age-related eye diseases are treated in the elderly.
Regarding the second factor, patients who seek care for visual symptoms usually report to an optometrist or an ophthalmologist for their first line of treatment. While drastic changes in vision in young patients can cause an ophthalmologist to suspect pituitary adenoma or at least obtain a brain MR imaging study, the high prevalence of ocular diseases in the elderly population may cause the provider to overlook the diagnosis of a pituitary tumor as the etiology for visual symptoms in this group of patients. It has been reported that 1 in 3 persons older than 65 years of age suffers from a vision-reducing ocular disease. The most common eye diseases in these patients include glaucoma, age-related macular degeneration, diabetic retinopathy, and cataracts. With pituitary adenoma falling lower in the differential diagnosis of visual deficits in elderly patients, it is not uncommon for the first diagnosis to be made as one of the age-related eye diseases, and for the medical provider to embark on a prolonged course of working up and treating one of these diseases before recognizing the failure of the patient's condition to improve and obtaining a brain MR imaging study. Indeed, a number of patients in our study underwent cataract surgery without any improvement in their vision and were later worked up for a pituitary tumor. This delay in diagnosis can prolong the duration of visual symptoms beyond the 6-month threshold beyond which elderly patients faced particularly poor chances of return to baseline vision after pituitary surgery. Our study suggests that all medical providers, particularly optometrists and ophthalmologists, should be more aware of the possibility of pituitary adenoma as a possible cause of visual symptoms in the elderly, and suggest that they should rule out this possible etiology with a brain MR imaging study in parallel with diagnosing and treating any age-related eye diseases in the elderly. Failure to do so will increase the chance of permanent vision loss.

Regarding the third factor that we found contributed to the age-related increase in duration of visual symptoms prior to NFA diagnosis (that is, race), we found that nonwhite elderly patients had a particularly long delay in time from onset of visual symptoms to diagnosis. Potential explanations for this finding could include the increased incidence of other ophthalmological conditions such as glaucoma in nonwhite patients, although our patients with other ophthalmological conditions were 60% white; the decreased health literacy found in elderly nonwhite patients delaying their recognition of visual symptoms and the need to seek care for them; or the perception that age-related visual decline is a natural part of the aging process may be more engrained in nonwhite elderly patients. There are several limitations of this study. The first limitation is the retrospective nature of the study, particularly when relying on chart review for visual examination findings and information about duration of symptoms. The second limitation is the lack of quantified visual field assessment done by an ophthalmologist. The third limitation is the small number of patients in relation to the number of variables analyzed, which was unfortunately necessary because we could only include patients in whom thorough documentation of a visual examination existed but could increase the risk of false-positive results.

This study reemphasizes the correlation between duration of visual symptoms and the impact of resection of the adenoma in restoring vision. Our analysis shows that the only statistically significant factor linked to a prolonged duration of visual symptoms was age. We also found that resection of an NFA in the elderly can be almost as beneficial in restoring vision as it is in younger patients as long as the duration of symptoms is less than 6 months. When the duration of symptoms surpasses 6 months, the elderly are far less likely than younger patients to have their vision restored after resection of an NFA. Future studies are clearly warranted to confirm our findings and could be implemented through a prospective design involving collaboration with an ophthalmologist to pinpoint the magnitude and duration of visual symptoms as accurately as possible. Should such studies confirm our findings, it will be important to increase the awareness among patients and clinicians of pituitary adenomas as a treatable cause of visual impairment in the elderly that need to be recognized in a timely fashion to maximize the chances of visual recovery.

Conclusions

We found that older age was associated with delayed diagnosis with endocrine inactive pituitary adenoma in visually impaired patients. Factors contributing to the delay in adenoma diagnosis were the attributing of visual symptoms to other ophthalmological conditions in these patients, and delayed presentation in elderly nonwhite patients. These findings highlight challenges associated with timely pituitary adenoma diagnosis in visually impaired patients, a key factor in the chances of visual improvement in these patients.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Aghi. Acquisition of data: Jahangiri. Analysis and interpretation of data: Aghi, Lamborn. Drafting the article: Jahangiri. Critically revising the article: Aghi, Lamborn, Blevins, Kunwar. Statistical analysis: Aghi, Lamborn. Study supervision: Aghi.

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