Usefulness of critical flicker fusion frequency measurement and its laterality for evaluating compressive optic neuropathy due to pituitary neuroendocrine tumors

Akira Taguchi (akira.taguch.0929@gmail.com)
Hiroshima University
Yasuyuki Kinoshita
Hiroshima University
Kana Tokumo
Hiroshima University
Atsushi Tominaga
Hiroshima Prefectural Hospital
Yoshiaki Kiuchi
Hiroshima University
Fumiyuki Yamasaki
Hiroshima University
Nobutaka Horie
Hiroshima University

Research Article

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Abstract

Objective

Critical flicker fusion frequency (CFF) is a short but sensitive method for evaluating optic nerve function. We measured CFF in patients with pituitary neuroendocrine tumors (Pit-NETs) to assess its usefulness.

Methods

Data from 184 patients with nonfunctioning Pit-NETs, who had been treated with transsphenoidal surgery and had no medical history of eye diseases, was used in this retrospective study. Visual acuity decline (VAD) was defined as > 0.10 reduction in logMAR visual acuity and CFF decline (CFD) was defined as CFF value < 35 Hz. Visual field defect (VFD) was evaluated by automated perimetry on a Humphrey visual field analyzer. Potential association between abnormal test results and tumor height from the suprasellar were analyzed.

Results

Contact between the optic nerve or chiasma and the tumor was present and absent in 161 and 23 patients, respectively. In patients showing contact, the difference in CFF between the left and right eyes was larger ($p = 0.0008$), and the optimal cut-off value using the receiver operating characteristic curve was 3 Hz. Therefore, ≥ 3 Hz was considered positive for CFF laterality (CFL), the most prevalent condition. Tumor height was lower in patients with CFL positivity compared to those with VAD or VFD ($p < 0.01$). The prevalence of test abnormalities was the highest for small tumors compared to those of other tests.

Conclusion

Changes in CFL permit early detection of Pit-NETs. Our results indicate that CFF laterality can be seen in the early stages of compressive optic neuropathy due to Pit-NET.

Introduction

Pituitary neuroendocrine tumors (Pit-NETs) are common intracranial tumors that are categorized as either nonfunctioning or functioning Pit-NETs. Nonfunctioning Pit-NETs account for 14–54% of all Pit-NETs and can present with headache and visual function deficits due to a mass effect [14]. Specifically, visual field defects are caused by compression of the optic chiasm by the pituitary tumor and typically present as bitemporal hemianopsia. However, depending on the position of the chiasma and/or pattern of compression of the chiasma by the pituitary tumors, some patients may show other symptoms such as unilateral visual field defects or loss of the lower part of the visual field [14], while other patients may be

unaware of their visual field loss [15]. Importantly, in routine clinical practice, the detection of optic neuropathy due to unknown pituitary tumors may be delayed in patients with cataracts or glaucoma because of characteristic visual acuity decline and field defects in these patients. Optic neuropathy due to compression is an essential indication for surgery in patients with pituitary tumors; however, the current standard definition of compressive optic neuropathy, which is based on visual acuity decline or visual field defects, is insufficient for detecting compressive optic neuropathy in the early stages. Therefore, specific tests for identifying optic neuropathy in the early stages are desirable.

Critical flicker fusion frequency (CFF), a sensitive method for assessing temporal vision, is defined as the frequency at which flickering light is perceived as continuous. CFF is a well-known method for evaluating optic neuropathies, such as optic neuritis and ischemic neuropathy [22], because CFF decline is seen prior to visual acuity decline in optic neuritis. Moreover, in clinical settings, CFF evaluation has the advantage of not being affected by the presence of cataract or glaucoma during the early stages [4].

Therefore, we hypothesized that, compared to standard assessment methods, CFF measurements are more sensitive for detecting compressive optic neuropathy caused by pituitary tumors during the early stages. To comprehensively assess compressive optic neuropathy, we choose patients with nonfunctioning Pit-NETs, and the purpose of this study was to determine the clinical value of CFF measurement in patients with nonfunctioning Pit-NETs. We also evaluated the laterality of CFF in patients with nonfunctioning Pit-NETs because the laterality of visual acuity decline and/or visual field defect is sometimes seen in these patients.

Materials And Methods

This retrospective study was approved by the institutional review board (E-2022), and the requirement for written informed consent was waived due to the anonymous nature of the data used.

Patients

Between 2008 and 2021, 268 patients with nonfunctioning Pit-NETs had undergone initial transsphenoidal surgery at our institution. Among them, we excluded patients with cataract or those with a history of cataract surgery (n = 33, 12.3%), glaucoma (n = 20, 7.5%) and/or other ophthalmic diseases (n = 12, 4.5%) on preoperative ophthalmic examination, and those who were not evaluated via detailed preoperative ophthalmic examination (n = 37, 13.8%). Therefore, we retrieved final data from 184 patients and analyzed their information on age, sex, medical history, tumor volume, radiographical findings, and ophthalmological evaluations from medical records. Patients with cerebrospinal fluid space between tumor and optic chiasm on magnetic resonance imaging (MRI) were classified into the non-affected group (n = 23, 12.5%), and those who were concerned regarding some influence on visual function caused by the mass effect of the tumor were classified into the affected group (n = 161, 87.5%).

Radiological assessment

All patients underwent 3T-MRI and head computed tomography within 1 month prior to surgery for assessment of tumor volume and shape. Tumor volume (cm^3) was calculated as Width × Height × Depth/2. Tumors in which a cyst component accounted for more than 50% of the tumor volume were defined as cystic tumors while others were defined as solid tumors. Definition of tumor height is depicted in figure 1. A line (line 1) was drawn parallel to the sphenoidal planum from the height of the exit of the optic canal. Next, a line was drawn perpendicular to line 1 from the site where the optic chiasm was most compressed (point A), and the length (mm) from point A to the intersection (arrow) was defined as tumor height at the suprasellar section (tumor height). Furthermore, patients in the affected were classified into four groups according to tumor height as small (<5.5 mm), mild (5.5–9.5 mm), moderate (9.5–13.5 mm), or large (>13.5 mm). Lateral tumor growth into the cavernous sinus was categorized according to the Knosp classification [12].

Ophthalmic evaluation

All patients underwent ophthalmic evaluation within 1 month prior to surgery. CFF was measured using an instrument developed at the Kinki University (R E medical, Inc.: normal range is defined as ≥ 35 Hz), measurements were obtained thrice for each eye, and the average value was used for each eye. CFF of <35 Hz was defined as CFF decline. The difference in CFF of the left and right eyes was compared between the affected and non-affected groups and a difference of ≥3Hz in CFF was defined as positive for CFF laterality (CFL). Therefore, a patient who had CFF decline and/or was CFL positivity was categorized as having a CFF abnormality.

The best-corrected visual acuity (BCVA) was converted to logMAR notation and visual acuity decline was defined based on the International Council of Ophthalmology visual standard as logMAR visual acuity higher than 0.10 (decimal notation BCVA of <0.8) [9]. Visual field assessment was performed by automated perimetry on a Humphrey visual field analyzer (HVFA), and visual field defect was defined based on the presence or absence of visual field abnormalities that were identified using the method reported by Fujimoto et al [6]. The worse value between the left and the right eyes was used when analyzing the relationship among patient characteristics, tumor properties, and visual function.

Visual acuity examination took approximately 10 min, CFF approximately 5 min, and HVFA approximately 30 min, respectively for both eyes.

Surgical procedures

Transsphenoidal surgery was performed through one nostril as an endoscopic procedure and has been described in detail previously [11]. For this study, Tumors in which ≥90% of the entire or suprasellar component could be resected by aspiration and curettage were defined as soft tumors.

Statistical analyses

The Shapiro–Wilk test was used to assess normality of data and continuous variables are expressed as median [interquartile range]. Categorical variables are represented as frequency (%). Skewed continuous variables were compared using the Kruskal–Wallis test, and categorical variables were compared using the Fisher's exact test. A *p*-value of <0.05 (two-tailed) was deemed significant. Receiver operating characteristic (ROC) curves were generated to determine the sensitivity and specificity of various cut-off values in the affected and non-affected groups, for the CFF and difference in CFL, respectively. A logistic regression model was used to calculate the adjusted odds ratios (ORs) with 95% confidence intervals (CIs) to identify factors related to CFL. All statistical analyses were performed using JMP® version 16 (SAS Institute Inc., Cary, NC, USA).

Results

Validity of definition of CFF laterality

Table 1 presents the characteristics of the non-affected and affected groups. There was no significant difference in patient background. Moreover, the affected group had more patients with abnormal visual function and larger tumors than the non-affected group. Furthermore, the difference between the left and right sides of the CFF was larger ($p = 0.0008$) and more number of patients had a difference of ≥3 Hz in the affected group than in the non-affected group ($p < 0.0001$).

The relationship between the mass effect on chiasma and the CFF or the difference of CFL was determined using the ROC curve. In the present study, at the cut-off CFF of 35.0 Hz (lower normal limit for an instrument developed at the Kinki University), an extremely high sensitivity was found (i.e., 95.7% sensitivity, 37.9% specificity, AUC = 0.77154, data not shown). Conversely, the optimal cut-off value of the difference in CFL was 3 Hz, and a slightly lower sensitivity but a higher specificity than CFF decline was found (i.e., 91.3% sensitivity, 52.8% specificity, AUC = 0.71118, Figure 2). Therefore, the combination of these two parameters (CFF abnormality) led to a high diagnostic accuracy to detect the mass effect on the optic chiasm.

Therefore, we have added positivity for CFL as one of the abnormal visual functions, such as visual acuity decline, visual field defect, and CFF decline, in the present study.

Characteristics of patients with abnormal visual function in the affected group

Table 2 lists the characteristics of patients with visual acuity decline, visual field defect, CFF decline, and CFL positivity. Visual acuity decline was seen in 24.7% of the patients, visual field defect in 47.1%, and CFF decline in 37.7%. CFL positivity was observed in 52.2% of the patients and was most sensitive to the presence of compressive Pit-NETs. Median tumor volume was lowest in CFL positive patients compared to those with visual acuity decline or visual field defect. Figure 3 compares median tumor height (95% CI) in patients with visual acuity decline, visual field defect, CFF decline, and CFL positivity. Tumor height was significantly lower in CFL positive patients compared to those with visual acuity decline ($p = 0.0009$) or visual field defect ($p = 0.0076$).

CFF decline and CFF laterality in the affected group

Assessment of the relationship between tumor volume and CFF showed that CFF decreased as the tumor volume increased (R^2 = 0.1729, p < 0.0001; CFF = −0.7526 × tumor height + 40.51). Similarly, we found that CFF decreased as tumor height increased (R^2 = 0.4358, p < 0.0001, CFF = −1.5950 × tumor height + 51.82). The correlation coefficient for tumor height was greater than that for tumor volume, indicating that tumor height at the suprasellar section is more correlated with the CFF values than tumor volume.

We also evaluated the relationship between tumor height and the difference value between CFF values for the left and the right eye (laterality value), and found that this difference value increased with tumor height (R^2 = 0.1734, p < 0.0001; laterality value = 0.6643 × tumor height −0.0410). On the other hand, as the tumor height increases, the CFF in both eyes tends to decrease and the CFF laterality value in some patients tends to decrease. Therefore, the correlation coefficient with tumor height was higher in the CFF value than in the CFF laterality value.

CFF abnormality

Table 3 lists the characteristics of patients with and without CFF abnormality. There were no significant differences in age, sex, and the prevalence of diabetes mellitus. Compared to those without CFF abnormality, both Median logMAR visual acuity and median tumor height were significantly higher in patients with CFF abnormality (p < 0.0001 for both). The ratio of Knops 0–2 was comparable (p = 1.0000), and the prevalence of cystic tumors tended to be lower in patients with CFF abnormality (6.3% vs. 15.4%, p = 0.0656).

Table 4 shows the results of logistic regression analysis of factors associated with CFF abnormality, and only tumor height (OR = 1.21, 95% CI: 1.11–1.33, p < 0.0001) displayed a strong association.

Abnormal test findings classified by tumor height

Figure 4 shows the prevalence of each abnormal test finding classified according to tumor height. Neither visual acuity decline nor CFF decline were seen at tumor height of <3.5 mm, but their prevalence rose with increasing height. CFF decline was more prevalent than visual acuity decline at almost all tumor height values analyzed. Further, among the three preoperative tests, the prevalence of CFF decline was equivalent to that of visual field defect at a tumor height of 9.4 mm or below, and visual field defect showed the highest prevalence at a tumor height of >9.5 mm.

CFL positivity showed a relatively high prevalence even at low tumor height; specifically, at a height of 5.5–7.4 mm, visual acuity decline was found in only 1 patient (4.0%), while CFF decline was found in 4 patients (16.0%), visual field defect in 5 patients (20.0%), and CFL positivity was seen in 11 patients (44.0%). Moreover, above a tumor height of >9.5 mm, CFL positivity was found in more than 50% of the patients.

We evaluated the clinical value of CFF abnormality by classifying tumors into four groups based on tumor height and comparing values between visual acuity decline and visual field defect (Figure 5). The prevalence of abnormal results was highest for CFF abnormality in the small and middle groups, suggesting a higher sensitivity of CFF measurements toward small Pit-NETs compared to other preoperative assessments. Nevertheless, patients with no abnormalities in any of the assessments were higher in the small group (n = 20, 57.1%) compared to the middle group (n = 23, 52.3%) or the moderate group (n = 10, 23.8%); all patients in the large group showed abnormal results in the preoperative tests.

Discussion

Here, we retrospectively assessed the prevalence of abnormal preoperative results in patients with Pit-NET and show that CFF laterality of ≥3 Hz was superior to other abnormal results in detecting early-stage Pit-NET. As CFL had a relatively high prevalence even among patients with low tumor height, CFL may be useful for detection even in the early stages of tumor growth. On the contrary, in patients with tumor height greater, the difference in CFF values between left and right eyes tended to be smaller; hence, we propose that abnormal CFF be defined as either CFL of ≥3 Hz or as CFF of <35 Hz. These criteria can comprehensively detect any changes in CFF, i.e., CFF abnormality, and enable early detection of Pit-NETs.

CFF and visual acuity

The optic nerve is composed of myelinated nerve fibers, which are the axons of the retinal ganglion cells, along with interstitial glial cells (oligodendrocytes, neuron glial 2 cells, astrocytes, and microglia) and the fibrovascular septa of the pia mater [21]. Optic neuritis is an inflammatory demyelinating disorder of the optic nerve that may also be associated with multiple sclerosis [19]. Conversely, nonarteritic anterior ischemic optic neuropathy (NAION), which cases damage to the entire optic nerve fiver, shows both CFF and visual acuity decline from the early stage [22]. A study that compared optic neuritis with NAION, i.e., demyelinating versus ischemic optic neuropathies, reported that CFF declined despite preserved central visual acuity in optic neuritis [22].

The cause of visual dysfunction in the patient cohort of this study was compression of the optic chiasma and/or nerve by the Pit-NETs, which led to decreased nerve conduction and demyelination, and consequent progressive visual dysfunction [3R]. Yamaguchi et al have reported that poor arterial supply to optic nerve at the distal intracranial and intracanalicular regions, and bending of the optic nerve at the entrance to the optic canal by pituitary tumor, cause ischemic neuropathy and regional ischemia, respectively, and result in visual disturbance [20]. This difference may be one of the reasons why a decrease in CFF is seen prior to visual acuity decline.

Visual acuity evaluation is common and simple; however, as shown in this study, the prevalence of abnormal visual acuity in Pit-NETs is low and insufficient for the early detection of pituitary tumors. In contrast, large Pit-NETs (macroadenoma) compress the optic chiasm and the pituitary stalk, and reduce portal circulation, causing visual and pituitary dysfunction [5]. Furthermore, it has been reported that when the tumor volume exceeded 10.5 ml, no patients with postoperative resolution of their hormone

deficiency were observed [2], and while 40% of pituitary incidentalomas grow, 20% become symptomatic [1]. Thus, early diagnosis and surgical resection before excessive tumor growth are important, and abnormal CFF is superior to visual dysfunction for detecting small tumors. Moreover, as CFF can help identify subclinical visual abnormalities, it can facilitate decision making on the suitability of surgical resection or follow-up for a pituitary incidentaloma that is in contact with the optic chiasma.

CFF and visual field defects

There is no doubt that a visual field examination is useful and important for diagnosing compressive optic neuropathy due to pituitary tumors. Fujimoto et al have described an analysis method using The Humphrey Field Analyzer threshold program (central 30-2) that has high sensitivity and specificity [6]. However, many conditions other than Pit-NETs also cause visual field defect, such as cataract, glaucoma, and retinal diseases. Gerges et al have reported that preoperative cataract was diagnosed in 16.8%–18.8% of patients with pituitary tumor and that 12.5% of all patients with a pituitary tumor had undergone cataract surgery prior to the diagnosis of pituitary tumor [7]. In contrast, CFF is unlikely to be affected by nonoptic neuropathic conditions such as cataract and early glaucoma [4]. As nonfunctioning Pit-NETs are often found in the middle-aged, especially after 60 years of age when patients are more likely to be diagnosed with glaucoma and cataracts [17], CFF measurement may be useful for differentiating among multiple eye conditions, apart from enabling early detection of Pit-NETs.

CFF laterality for the early detection of pituitary adenomas

In a study of 115 patients with Pit-NET who underwent testing by HVFA, only one patient had complete bitemporal hemianopsia while 42.6% had bitemporal or mixed visual field defect [13]. As such variations in bitemporal hemianopsia occur based on the pattern of optic nerve compression by the pituitary tumor [16]; these are categorized as asymmetry rather than laterality. Conversely, CFF can be quantified, and normally, there is almost no difference between the left and right eyes. Interestingly, in the present study, despite the presence of a small tumor, the prevalence of CFL positivity was higher than that of either visual acuity decline or visual field defect, and the prevalence of CFF abnormality was higher than that of visual acuity decline and field defect when tumor size was 5.5–9.5 mm. Therefore, the use of CFF abnormality may enable Pit-NETs detection before it increases in size and causes hypopituitarism, and may, thereby, contribute to a reduction in sequelae.

Finally, HVFA typically takes about 30 min, and conducting it requires time and effort from the patient as well. On the contrary, CFF measurement is short and simple as it takes only about 5 minutes. Therefore, in terms of patient burden, CFF measurement may be superior to HVFA.

Limitations

The above notwithstanding, this study has a few limitations. First, we excluded patients with cataract or glaucoma; therefore, the ability of CFF to diagnose Pit-NETs in these patients is unclear. Nevertheless, we excluded these patients to clearly define the purpose of this study. Second, visual acuity examination was

a one-time assessment and the results may have been affected by false positives and/or loss of reproducibility due to physical and mental conditions [18] [8] [10]. There are many other types of CFF measuring instruments, and each measuring instrument has a different normal range [22]. Regarding the difference between the left and right sides of the CFF, it is necessary to further examine whether the abnormal difference in other devices is noted in the present study. Nonetheless, we would like to emphasize that CFF measurement is a useful evaluation tool with clearly defined outcomes, and that it may be superior to visual acuity examination as the latter is associated with patient-related uncertainties.

Conclusion

In patients with compression optic neuropathy due to Pit-NETs, CFF measurement may be more sensitive than visual acuity examination for early-stage detection, and we show for the first time that compressive optic neuropathy due to Pit-NETs shows CFF laterality in the early stages. Thus, testing for CFF laterality can facilitate detection of small tumors in the early stages and represents a more sensitive evaluation method than HVFA, depending on the type of tumor.

Declarations

Ethics approval

This study was conducted retrospectively, utilized data obtained for clinical purposes, and was approved by the ethics committee of Hiroshima University Hospital (E-2022, 18 May 2020).

As patient data in this study are completely anonymized, any identification of individuals is difficult. Pertinent research content is available in the homepage of our institution.

Human and Animal Ethics

Not applicable.

Consent for publication

Not applicable.

Availability of supporting data

Not applicable.

Competing interests

All authors declare that they have no conflict of interest.

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Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Akira Taguchi, Yasuyuki Kinoshita, Kana Tokumo, and Fumiyuki Yamasaki. The first draft of the manuscript was written by Akira Taguchi, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Corresponding author: Akira Taguchi, MD

Department of Neurosurgery, Graduate School of Biomedical and Health Sciences, Hiroshima University

1-2-3, Kasumi, Minamiku, Hiroshima, 734-8551, Japan

Tel/Fax: +81822575227/+81822575229

E-mail: akira.taguch.0929@gmail.com

ORCID of Akira Taguchi: 0000-0002-2450-5674

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Tables

Table 1
Comparison between characteristics of the non-affected and affected patients

		Non-affected		Affected		*p*-value
Number of patients		23		161		
Sex, female/male		11/12		76/85		1.0000
Age, years, median	(IQR)	57	(46–62)	57	(46–69)	0.3736
DM	(%)	1	(4.4%)	16	(9.9%)	0.7000
logMAR visual acuity, median	(IQR)	−0.08	(− 0.18– −0.08)	0	(− 0.08– 0.10)	0.0046
Visual acuity decline	(%)	0	(0%)	39	(24.2%)	0.0049
CFF, median	(IQR)	46.0	(41.0–50.0)	39.3	(27.9–45.0)	< 0.0001
CFF decline	(%)	1	(4.4%)	61	(37.9%))	0.0007
Visual field defect	(%)	0	(0%)	74	(47.4%)	< 0.0001
Difference value of CFL, Hz	(IQR)	1	(0.3–2.0)	3	(1–10.7)	0.0008
CFL ≧ 3 Hz	(%)	2	(8.7%)	84	(52.2%)	< 0.0001
Knosp 0–2	(%)	15	(65.2%)	108	(67.1%)	1.0000
Soft tumor	(%)	18	(78.3%)	133	(83.1%)	0.5615
Tumor volume, cm^3, median	(IQR)	2.1	(1.0–4.9)	4.7	(2.4–8.8)	0.0025

CFF, critical flicker fusion frequency; CFL, laterality of CFF; DM, diabetes mellitus; IQR, interquartile range

Table 2
Characteristics of the patients with abnormal findings in visual function tests

		logMAR VA > 0.10		Visual field defect		CFF < 35 Hz		CFL ≥ 3Hz	
Number of patients		39		74		61		84	
Sex, female/male		19/20		36/38		35/26		38/46	
Age, years, median	(IQR)	55	(42–71)	57	(45–68)	57	(46–69)	55	(44–69)
DM, n = 16	(%)	5	(12.8%)	6	(8.1%)	5	(8.2%)	8	(9.5%)
logMAR VA, median	(IQR)	0.30	(0.22–1.22)	0.10	(0.00–0.30)	0.15	(0.00–0.40)	0.05	(−0.08–0.30)
CFF, Hz, median	(IQR)	22.1	(29.3–12.3)	27.4	(35.7–17.8)	22.5	(30.0–15.7)	30.0	(40.9–20.2)
Tumor volume, cm^3, median	(IQR)	9.4	(5.3–13.3)	7.1	(4.5–11.4)	7.2	(4.8–12.0)	6.2	(3.5–11.2)
Tumor height, mm, median	(IQR)	13.8	(12.0–17.4)	13.5	(10.7–16.6)	13.5	(10.4–16.8)	11.3	(7.4–14.5)
Knosp 0–2, n = 108	(%)	27	(69.2%)	47	(63.5%)	35	(57.4%)	55	(65.5%)
Cystic tumor, n = 16	(%)	5	(12.8%)	7	(9.5%)	4	(6.6%)	4	(4.8%)

CFF: critical flicker fusion frequency, CFL: laterality of CFF, DM: diabetes mellitus, VA: visual acuity, IQR: inter quartile range

Table 3
Comparison of characteristics in patients with and without CFF abnormality

CFF		Abnormal		Normal		*p*-value
Number of patients		96		65		
Sex, female/male		45/51		31/34		1.0000
Age, years, median	(IQR)	56	(45–69)	60	(48–68)	0.6716
DM	(%)	9	(9.4%)	7	(10.8%)	0.7933
logMAR VA, median	(IQR)	0.05	(− 0.08–0.30)	−0.08	(− 0.08–0.00)	< 0.0001
CFF, Hz, median	(IQR)	30.5	(39.9–20.8)	44.0	(47.5–40.5)	< 0.0001
Tumor volume, cm^3, median	(IQR)	6.0	(3.5–0.7)	2.7	(1.8–5.0)	< 0.0001
Tumor height, mm, median	(IQR)	11.7	(7.5–15.2)	7.2	(5.3–10.0)	< 0.0001
Knosp 0–2	(%)	32	(33.3%)	21	(32.3%)	1.0000
Cystic tumor	(%)	6	(6.3%)	10	(15.4%)	0.0656
CFF: critical fusion flicker frequency, DM: diabetes mellitus, VA: visual acuity, IQR: inter quartile range						

Table 4
Results of multivariate logistic regression analysis of factors related to CFF abnormality

	Wald χ^2	OR	95%CI	*p*-value
Age, years	0.03	1.00	0.97–1.03	0.8523
Sex, male	0.28	1.21	0.59–2.49	0.5998
Diabetes mellitus	0.02	1.09	0.33–3.63	0.8839
Tumor height, mm	19.19	1.21	1.11–1.33	< 0.0001
Knosp 0–2	0.12	1.14	0.53–2.43	0.7324
Cystic tumor	3.46	0.31	0.09–1.02	0.0627
CFF: critical fusion flicker frequency, CI: confidence interval, OR: odds ratio.				

Figures

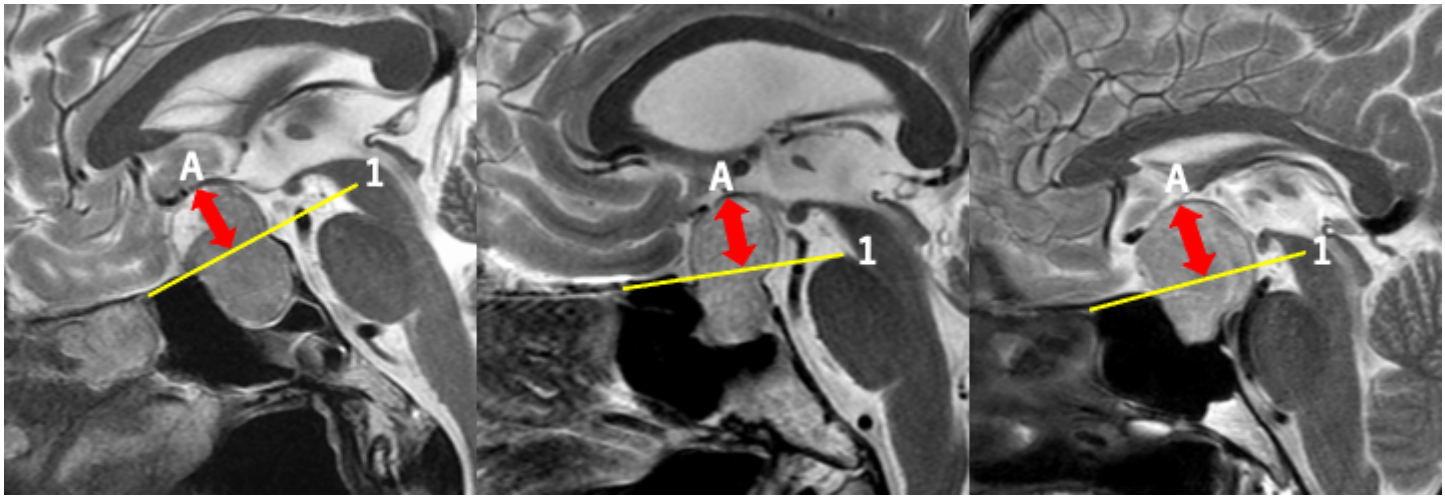

Figure 1

Definition of tumor height. A line (line 1) was drawn parallel to the sphenoidal planum from the height of the exit of the optic canal. A line was drawn perpendicular to line 1 from the site where the optic chiasm was most compressed (point A), and the length (mm) from point A to the intersection (arrow) was defined as tumor height at the suprasellar section (tumor height)

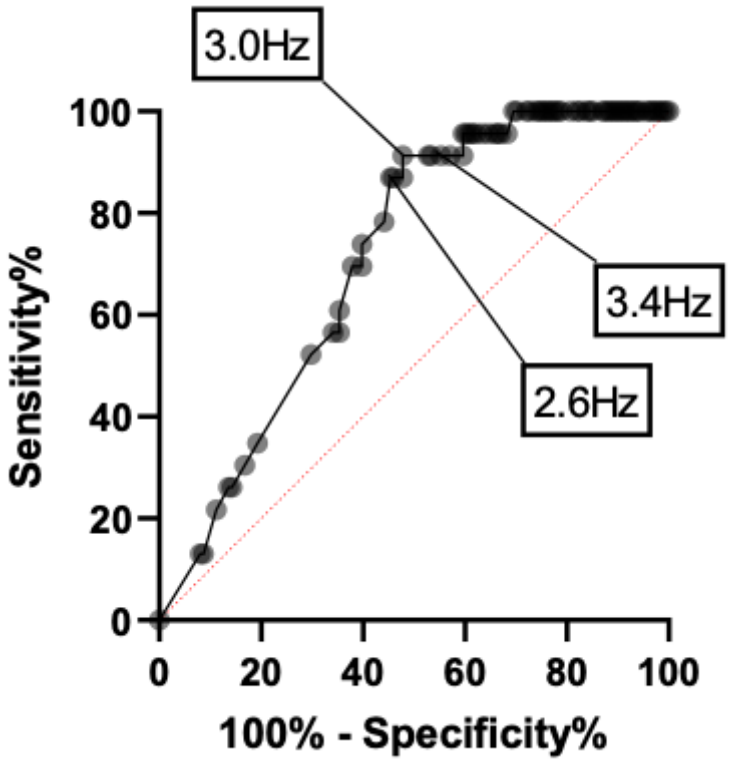

Figure 2

The optimal cut-off value of the difference in CFL was calculated by receiver operating characteristic curves, and we obtained the optimal relation between sensitivity (91.3%) and specificity (52.8%) at a cut-off value of 3 Hz. When reducing the cut-off value to 2.6 Hz, we achieved a sensitivity of 87.0% and a

specificity of 54.0%, pointing a slight increase in specificity but decrease in the sensitivity. The application of a cut-off value of 3.4 Hz would lead to a loss of specificity (i.e., 91.3% sensitivity and 46.6% specificity).

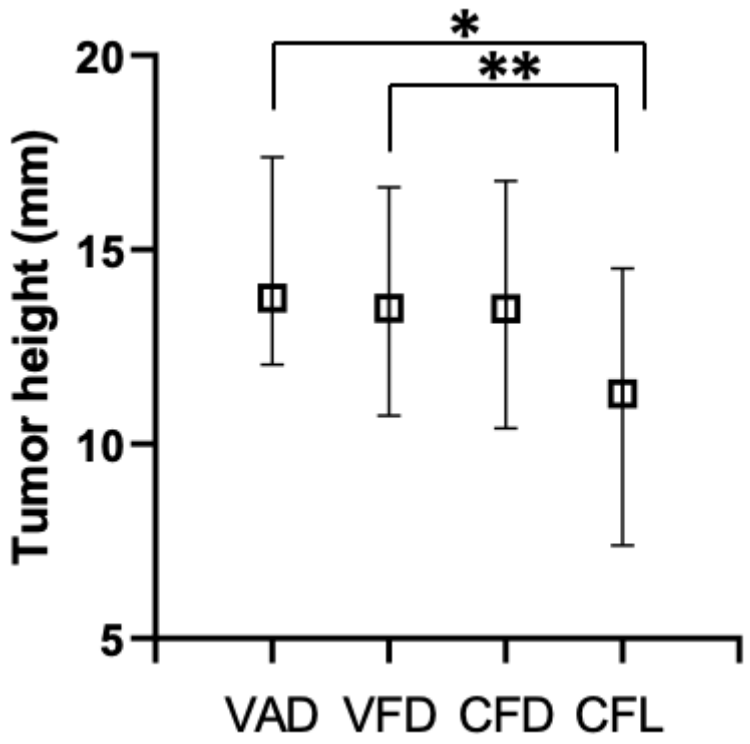

Figure 3

Median tumor height (95% confident intervals) in visual acuity decline (VAD), visual field defect (VFD), critical flicker fusion frequency (CFF) decline, and CFF laterality (CFL) groups. Tumor height was significantly different higher in VAD compared to CFL (*, $P = 0.0009$). Similarly, tumor height was significantly higher in VFD compared to CFL (**, $P = 0.0076$)

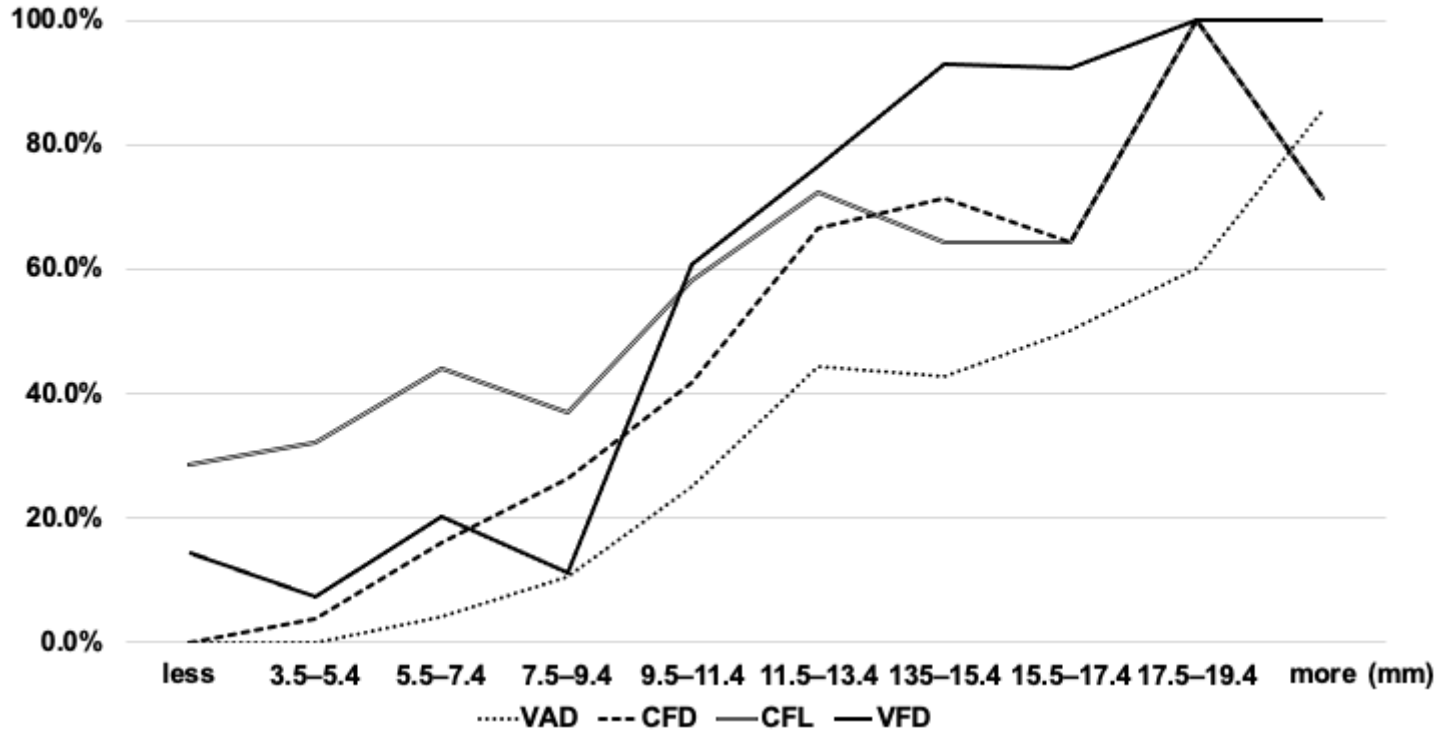

Figure 4

The prevalence of abnormal results in each preoperative evaluation, categorized according to tumor height. At tumor height <3.5 mm, the prevalence of both visual acuity decline (VAD) and critical flicker fusion frequency (CFF) decline was 0%, but as the height increased, their prevalence also expanded. CFF decline showed a higher prevalence than VAD at almost all tumor heights analyzed. Among the three testing methods used, the prevalence of visual field defect (VFD) was the highest at a tumor height of >9.5 mm, but was equivalent to that of CFF decline at a tumor height of 9.4 mm or below. On the other hand, CFL positivity showed a relatively high prevalence even at low tumor height. Specifically, at a height of 5.5–7.4 mm, VAD was found in one patient (4.0%), CFF decline in 4 patients (16.0%), VFD in 5 patients (20.0%), while CFL positivity was found in 11 patients (44.0%). Moreover, at tumor height >9.5 mm, CFL positivity was found in more than 50% of the patients

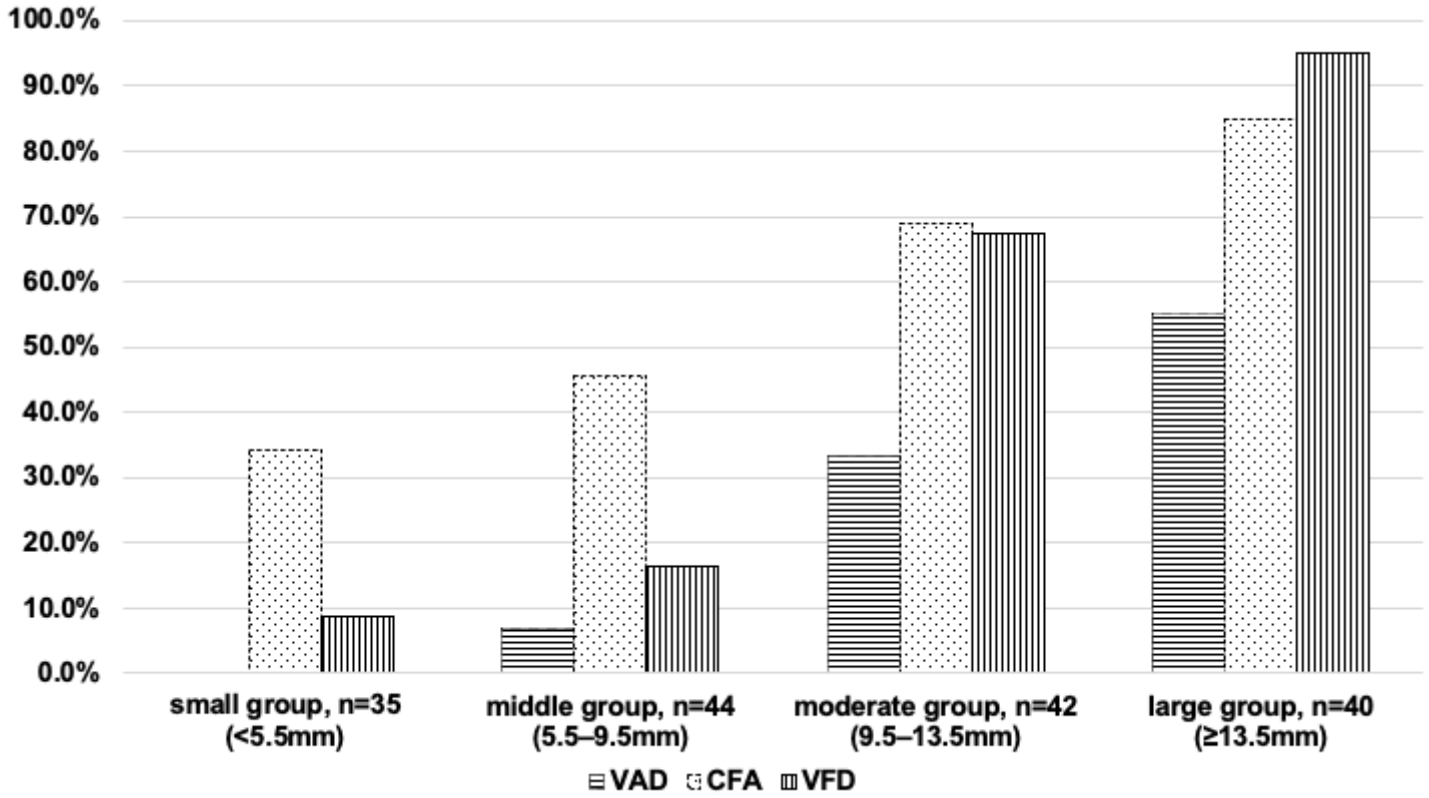

Figure 5

The prevalence of VAD, VFD, and CFF abnormality, classified as four groups based on tumor height. The prevalence of VAD, VFD, and CFF abnormality in the small group was 0.0%, 8.8%, and 34.3%, respectively. Their prevalence in the middle group was 6.8% for VAD, 16.3% for VFD, and 45.5% for CFF abnormality. Cognate values in the moderate group were 33.3% for VAD, 67.5% for VFD, and 69.0% for CFF abnormality, while they were 55.0% for VAD, 94.9% for VFD, and 85.0% for CFF abnormality, in the large group. Patients with no abnormalities in any of the tests comprised 57.1% (n = 20) of the patients in the small group, 52.3% (n = 23) of the patients in the middle group, and 23.8% (n = 10) in the moderate group. There were no such patients in the large group