Original Article
Yonsei Med J 2026 Feb;67(2):135-144
https://doi.org/10.3349/ymj.2025.0089
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Clinical and Neuroimaging Findings in Patients with Atypical Visual Field Defects

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Purpose: To investigate the clinical presentations and neuroimaging findings of patients with atypical visual field defects (VFDs)
Materials and Methods: This retrospective cross-sectional study included 159 patients who underwent brain magnetic resonance imaging for evaluation of atypical VFDs between 2013 and 2022. Clinical characteristics were compared based on neuroimaging results, and logistic regression was performed to identify independent risk factors for significant findings.
Results: Twenty-nine patients (18.2%) exhibited significant findings responsible for their atypical VFDs, most commonly intracranial tumors and cerebrovascular accidents. Older age [odds ratio (OR) 1.049, 95% confidence interval (CI) 1.018–1.081, p=0.002], symptom of decreased visual acuity (OR 5.790, 95% CI 2.361–14.195, p<0.001), incomplete homonymous hemianopsia (OR 15.167, 95% CI 3.096–74.300, p=0.001), absence of peripapillary atrophy (PPA) (OR 0.353, 95% CI 0.136–0.919, p=0.033) and rapidly progressive VFDs (OR 4.385, 95% CI 1.266–15.189, p=0.020) were independently associated with significant findings. Subgroup analysis based on the presence of glaucoma revealed that, among glaucoma patients, incomplete homonymous hemianopsia (p=0.001) and absence of PPA (p=0.016) were more prevalent among those with significant neuroimaging results. Among non-glaucoma patients, those with significant findings had greater pattern standard deviation (p=0.003) and more frequent rapidly progressive VFDs (p=0.041).
Conclusion: Atypical VFDs may indicate lesions along the visual pathway. Neuroimaging is recommended for patients with atypical VFDs, particularly those of older age or presenting with decreased visual acuity, rapid progression or incomplete homonymous hemianopsia.

Key Words: Visual field defect, neuroimaging, glaucoma, optic neuropathy

INTRODUCTION

Glaucoma is the most common optic neuropathy, but non-glaucomatous optic neuropathies, such as compressive, ischemic, or hereditary optic neuropathy, should not be missed during diagnostic work-ups due to their clinical significance. Differential diagnosis of optic neuropathies remains challenging in clinical situations. Even expert clinicians have encountered challenges in differentiating non-glaucomatous optic neuropathies from glaucoma.[1,2]

Along with this diagnostic process, a visual field test is essential to assess the function of the optic nerve and visual pathway, and is crucial to differentiate between optic neuropathies. However, the results of the visual field tests are inherently subjective and may be difficult to interpret with diagnostic certainty. Atypical visual field defects (VFDs) prompt further investigation to determine their underlying etiology. Several cases have reported that an abnormal VFD leads to misdiagnosis of glaucoma.[3-7] Also, the overlap of glaucoma and other optic neuropathies complicates the diagnosis.[8]

In cases where clinical and functional tests yield inconclusive results, including atypical VFDs, clinicians should consider neuroimaging to differentiate the underlying causes of optic neuropathy. Although previous studies have shown variable yields of neuroimaging in diagnosing glaucoma,[9-12] clinicians

Received: April 25, 2025 **Revised:** August 18, 2025
Accepted: August 26, 2025 **Published online:** December 8, 2025
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•The authors have no potential conflicts of interest to disclose.

may be hesitant to use routine neuroimaging due to concerns about low diagnostic yield.[12] However, undetected intracranial lesions may result in serious consequences if not appropriately managed. Therefore, many efforts have been made to discriminate non-glaucomatous optic neuropathies from glaucoma.[2,9-13]

Despite these challenges, guidelines for neuroimaging in patients with atypical VFDs remain sparse. This study investigated patients with atypical VFDs, analyzed their clinical characteristics, and identified the risk factors for clinically significant neuroimaging findings. In doing so, it aims to provide recommendations for performing neuroimaging in these patients to enhance diagnostic accuracy and improve clinical decision-making.

MATERIALS AND METHODS

The Institutional Review Board of the Severance Hospital Clinical Research Ethics Committee reviewed and approved the study protocol (IRB protocol number: 4-2023-0180). This study complied with the tenets of the Declaration of Helsinki. The requirement for written informed consent was waived due to the retrospective design and the use of deidentified patient data. To minimize potential selection bias and enhance internal validity, we applied clearly predefined inclusion and exclusion criteria and operationalized key clinical variables.

Participants

We reviewed the medical records of patients who underwent brain magnetic resonance imaging (MRI) for the evaluation of atypical VFDs at the glaucoma clinic of Severance Hospital between January 2013 and December 2022.

The inclusion criteria for the study were 1) age at the time of examination being older than 18 years; and 2) presence of VFDs of unclear etiology not attributable to intraocular pathology.

The exclusion criteria for the study were 1) inability to perform reliable visual field tests of both eyes; 2) abnormal findings in slit lamp, gonioscope, or fundus examinations that could affect the interpretation of intraocular pressure (IOP), visual field testing, or optical coherence tomography (OCT) results; 3) ocular signs suggestive of neurologic pathology, including afferent pupillary defect, dyschromatopsia, disc swelling, ophthalmoplegia, nystagmus, or pain with eye movement; 4) neurologic symptoms other than decreased visual acuity (e.g., headache, hemiparesis, or altered mental status); 5) history of brain lesion, trauma, or surgery; 6) history of systemic medication (e.g., ethambutol, vigabatrin, or digoxin) or nutritional deficiency (e.g., vitamin B_{12}) known to cause optic neuropathy; and 7) history of ocular trauma or intraocular surgery other than uncomplicated cataract extraction.

This study specifically included patients who lacked overt neurological signs or symptoms-except for decreased visual acuity-to explore cases where neuroimaging is considered primarily based on ophthalmic findings. This approach aims to identify clinical factors prompting neuroimaging in patients presenting with atypical VFDs in an ophthalmology clinic setting.

Clinical assessments

All patients underwent comprehensive ophthalmic examination, including best-corrected visual acuity (BCVA) measurement, IOP measurement by Goldmann applanation tonometry, slit-lamp examination, gonioscopy and dilated fundus examination on a single visit. A subjective complaint of visual deterioration, accompanied by at least a two-line decline on the Snellen chart in the absence of corresponding ocular pathology, was defined as a "symptom of decreased visual acuity." Potential causes of visual decline, including anterior segment and retinal pathologies, were carefully excluded.

Standard automated perimetry was performed using the Humphrey field analyzer (Carl Zeiss Meditec, Dublin, CA, USA) with the 24-2 Swedish Interactive Threshold Algorithm Faster protocol. Only tests with fixation losses less than 20%, false positives less than 15%, and false negatives less than 20% were included. All visual field tests were interpreted by glaucoma specialists (BHW and LJH). Visual field patterns were categorized according to the Ocular Hypertension Treatment Study classification.[14] Incomplete homonymous hemianopsia was defined as any partial homonymous VFD, including quadrantanopia, macular sparing, scotomatous, or sectoral patterns, as previously described by Kedar, et al.[15] For patients with prior perimetry, the rate of VFD progression was estimated using changes in mean deviation (MD). A progression rate exceeding 1.5 dB per year was defined as "rapid progression."[10,16]

Atypical VFDs were classified into three categories based on their clinical presentation and rationale for neuroimaging: 1) vertical VFDs: defects respecting the vertical meridian; 2) rapidly progressive VFDs: those progressing >1.5 dB per year in MD despite stable IOP; 3) structurally inconsistent VFDs: defects incongruent with optic disc or retinal nerve fiber layer (RNFL), or cases in which functional impairment exceeded what should be expected based on structural findings. These predefined criteria were used to identify patients for whom neuroimaging was clinically indicated to evaluate possible neurological causes of visual dysfunction.

OCT imaging was conducted using the Cirrus HD-OCT system (Carl Zeiss Meditec, Inc., Dublin, CA, USA), and the thicknesses of the peripapillary RNFL and macular ganglion cell–inner plexiform layer (GCIPL) were quantitatively assessed using 6 mm × 6 mm scan cubes.

The diagnosis of glaucoma was based on characteristic optic disc changes [e.g., vertical cup-to-disc ratio (CDR) >0.6, rim thinning or notching, or disc hemorrhage] with corresponding glaucomatous VFDs. A glaucomatous VFD was defined as: 1) three or more adjacent points in the same hemifield with $p<0.01$ on the pattern deviation plot, including at least one point with $p<0.005$; 2) a glaucoma hemifield test result "outside nor-

https://doi.org/10.3349/ymj.2025.0089

mal limits" on at least two consecutive examinations.

All patients underwent contrast-enhanced brain MRI. Magnetic resonance angiography was additionally performed when indicated. The primary indications for neuroimaging corresponded to the three atypical VFD categories: vertical VFDs, structurally inconsistent VFDs, and rapidly progressive VFDs. Brain MRI findings were categorized according to their clinical relevance to the patient's VFD as follows: 1) significant findings, defined as intracranial lesions considered causative of the VFDs (e.g., compressive masses, ischemic or hemorrhagic strokes involving the visual pathway); 2) incidental findings, defined as abnormalities not related to VFDs (e.g., benign cysts or microvascular changes not affecting the visual pathway); and 3) negative findings, defined as radiologic interpretations without notable pathological features.

Statistical analysis

Continuous variables were expressed as mean±standard deviation, and categorical variables as frequencies and percentages. The normality of continuous variables was assessed prior to analysis. Univariate analyses were conducted using either the independent sample t-test or the Mann–Whitney U test for continuous variables, and the chi-squared test or Fisher's exact test for categorical variables, as appropriate.

Variables with statistically significant differences in univariate analyses (p<0.05) were included in the multivariable logistic regression model. Multicollinearity among the predictors was assessed using the variance inflation factor (VIF), with values <10 considered acceptable. Model fit was evaluated using the Hosmer–Lemeshow test, and discriminative ability was assessed by calculating the area under the receiver operating characteristics curve (AUROC). To avoid intra-subject correlation, only one eye per patient—the eye with the more severely affected visual field (i.e., worse MD)—was included in the analysis, and the patient was considered the unit of analysis.

All statistical analyses were performed using the SPSS version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

A total of 159 patients (87 male, 72 female) underwent brain MRI for the differential diagnosis of atypical VFDs from 2013 to 2022, with a mean age of 50.01±17.10 years. Regarding the reason for neuroimaging, rapidly progressive VFDs were the most common (49.1%), followed by structurally inconsistent VFDs (27.0%) and vertical VFDs (23.9%) (Table 1). The arcuate pattern was the most frequently observed VFD pattern, followed by the vertical VFD and total loss. The frequency of VFDs was significantly different between the glaucoma group and non-glaucoma group (p<0.001) (Fig. 1).

Fig. 2 shows the patients classified according to the diagnosis of glaucoma and neuroimaging results. A total of 82 patients (51.6%) showed positive brain MRI findings. Among them, 53 patients had positive findings that were unrelated to their VFDs (incidental findings), and 29 patients had positive findings that were responsible for their VFDs (significant findings). Representative neuroimaging findings corresponding to significant cases are shown in Figs. 3 and 4.

The most frequent findings among patients with significant

Table 1. Demographics and Clinical Characteristics of Patients (n=159)

Variables	Value
Age (yr)	50.01±17.10 (range, 19–86)
Sex	
Male	87 (54.7)
Female	72 (45.3)
Presence of glaucoma	95 (59.7)
Presence of symptom (decreased visual acuity)	49 (30.8)
BCVA (logMAR)	0.28±0.47
Baseline IOP (mm Hg)	15.45±2.8
Disc morphology	
Vertical CDR	0.67±0.18
PPA	48 (30.2)
Disc pallor	14 (8.8)
Pale disc	12 (7.5)
Global indices of visual field test	
VFI	70.93±27.16
MD	-10.92±8.82
PSD	7.06±4.29
Presence of incomplete homonymous hemianopia	40 (15.7)
Reason for brain MRI	
Vertical VFDs	38 (23.9)
Structurally inconsistent VFDs	43 (27.0)
Rapidly progressive VFDs	78 (49.1)
Thickness of RNFL (μm)	
Superior	86.68±23.19
Temporal	56.90±17.21
Inferior	83.46±26.88
Nasal	62.47±13.17
Average	72.31±15.50
Thickness of GCIPL (μm)	
Superior	65.36±15.10
Superonasal	67.99±15.67
Inferonasal	65.09±14.44
Inferior	62.63±13.05
Inferotemporal	63.94±14.04
Superotemporal	64.27±13.88
Average	64.86±12.60
Minimum	55.02±14.71

Data are presented as mean±standard deviation or n (%).
BCVA, best-corrected visual acuity; IOP, intraocular pressure; CDR, cup-to-disc ratio; PPA, peripapillary atrophy; VFI, visual field index; MD, mean deviation; PSD, pattern standard deviation; MRI, magnetic resonance imaging; VFDs, visual field defects; RNFL, retinal nerve fiber layer; GCIPL, ganglion cell–inner plexiform layer.

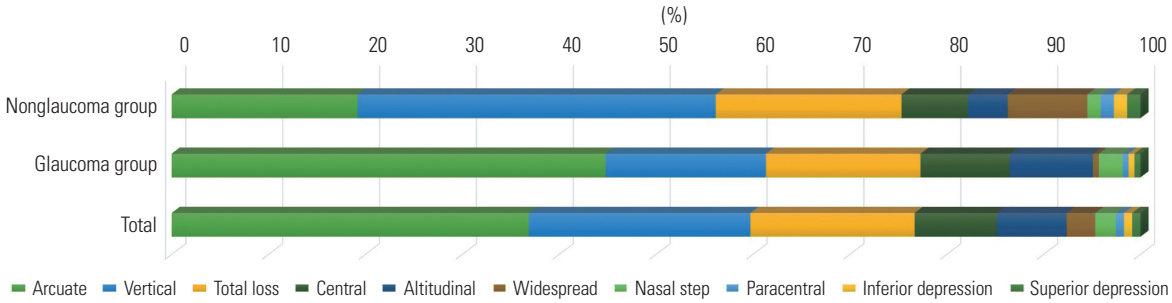

Fig. 1. Frequency distribution of visual field defects.

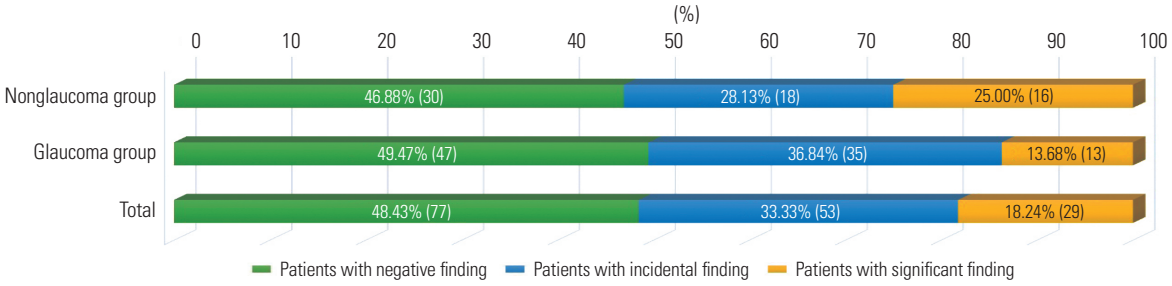

Fig. 2. Classification of patients. Values in parentheses indicate the number of patients.

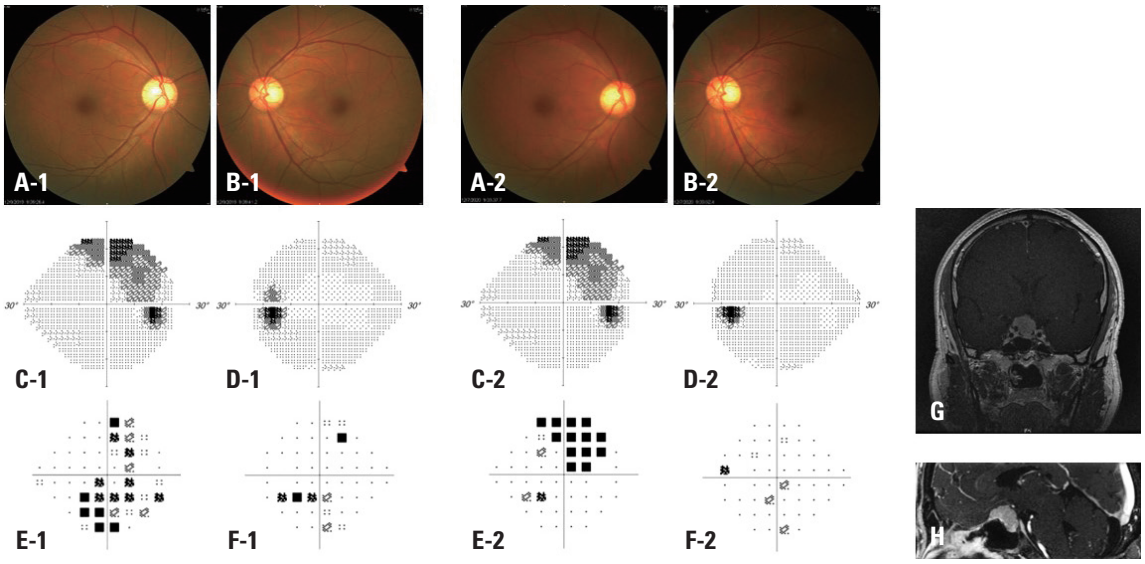

Fig. 3. A representative case of a non-glaucoma patient who showed a significant finding on brain MRI. (A and B) Fundus photographs; (C and D) visual sensitivity maps; and (E and F) pattern deviation maps obtained at the first visit are labeled "-1," and those obtained at the second visit are labeled "-2." (G) T1-weighted coronal brain MRI. (H) T1-weighted fast spoiled gradient-echo sagittal image of the sella. A 45-year-old male visited our hospital for a check-up. At the first visit, vertical cup-to-disc ratio was 0.6 in the right eye (A-1) and 0.5 in the left eye (B-1). The visual field test showed an arcuate visual field defect in the right eye (C-1 and E-1) and a paracentral scotoma in the left eye (D-1 and F-1). Since there was no definite sign of retinal nerve fiber layer defect, he was diagnosed as a glaucoma suspect in both eyes. After 1 year, he showed a more definite arcuate visual field defect in the right eye (C-2 and E-2) and underwent brain MRI due to rapid progression of the visual field defect in the right eye (mean deviation: -4.25 dB → -6.86 dB). MRI showed an approximately 20-mm meningioma at the tuberculum sellae, with compression of both optic nerves and the optic chiasm (G and H). He was referred to the neurosurgery department and underwent tumor removal via a transsphenoidal approach. MRI, magnetic resonance imaging.

results were intracranial tumors (9 patients), and the brain MRI results are presented in Table 2. Thirteen patients (44.83%) with significant findings underwent therapeutic interventions, including surgery (7 patients), anti-thrombotic medication (4 patients), radiotherapy (1 patient), and steroid medication (one patient). Additionally, 7 patients (13.21%) with incidental findings required anti-thrombotic medication for cerebrovascular accidents.

The clinical presentations were compared between patients with negative and significant findings (Table 3). Compared to those with negative findings, patients with significant findings were older (p<0.001), more frequently reported symptoms of

https://doi.org/10.3349/ymj.2025.0089

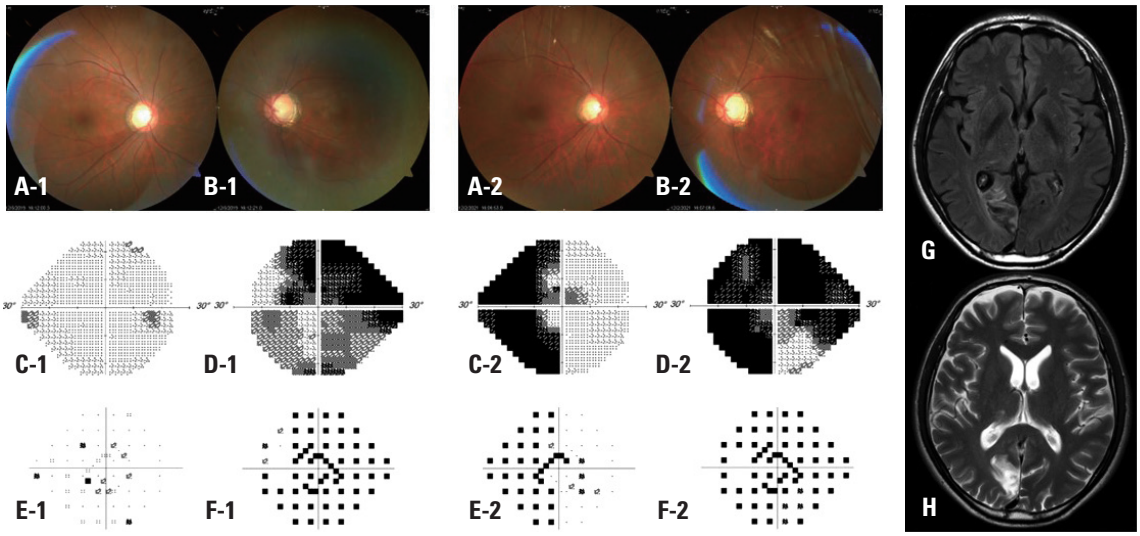

Fig. 4. A representative case of a glaucoma patient who showed a significant finding on brain MRI. (A and B) Fundus photographs; (C and D) visual sensitivity maps; (E) pattern deviation map of the right eye; and (F) total deviation map of the left eye. Images obtained in 2019 are labeled "-1," and those obtained in 2021 are labeled "-2." (G) T2 fluid-attenuated inversion recovery horizontal brain MRI; (H) T2-weighted horizontal brain MRI. Due to reliability issues, images obtained in 2019 are presented for comparison with those obtained in 2021. A 51-year-old male who had been using IOP-lowering medication for over 6 years for primary open-angle glaucoma in both eyes visited our hospital every 6 months. In 2021, the vertical cup-to-disc ratio was 0.7 in the right eye (A-2) and 0.9 in the left eye (B-2). Compared with his previous visual field test (C-1, D-1, E-1, and F-1), right homonymous hemianopia was identified (C-2, D-2, E-2, and F-2), which prompted brain MRI. MRI showed an old infarct with residual hemorrhage in the right occipital lobe (G abd H). Since he had been taking warfarin for aortic graft replacement, regular neuroimaging was recommended. MRI, magnetic resonance imaging; IOP, intraocular pressure.

Table 2. Results of Brain MRI Findings

Results	Significant findings (n=29)	Incidental findings (n=29)
Intracranial tumor	9	4
Cerebrovascular accident	6	18
Cerebral aneurysm	4	5
Optic nerve atrophy	4	0
Pituitary gland lesion	3	2
Brain atrophy	1	3
Optic neuritis	1	0
Intraorbital lesion	1	1
Arachnoid cyst	0	4
Nonspecific hyperintensities	0	16

MRI, magnetic resonance imaging.

decreased visual acuity (p<0.001), and less frequently exhibited peripapillary atrophy (PPA) (p=0.004). Regarding VFDs, patients with significant findings had more instances of incomplete homonymous hemianopsia (p<0.001).

Multivariate logistic regression analysis showed that the factors with statistically significant differences were independent risk factors for significant findings (Table 4). No significant multicollinearity was observed among the included predictors (VIFs <10). The model demonstrated acceptable goodness-of-fit based on the Hosmer–Lemeshow test (p=0.820). The AUROC was 0.843 [95% confidence interval (CI), 0.782–0.904], indicating good discriminative ability. In cases with worsening visual acuity symptoms, the risk was increased 5.79 times [odds ratio (OR) 5.790, 95% CI 2.361–14.195]. In patients with incomplete homonymous hemianopsia, the risk increased 15.167 times (OR 15.167, 95% CI 3.096–74.300). Additionally, for each additional year of age, the risk was increased by a factor of 1.049 (OR 1.049, 95% CI 1.018–1.081). Among the reasons for MRI imaging, the risk was 4.385 times higher in cases where MRI was performed due to the rapidly progressive VFDs compared to structurally inconsistent VFDs (OR 4.385, 95% CI 1.266–15.189). The presence of PPA was associated with a 65% reduction in the relative risk of significant findings on brain MRI (OR 0.353, 95% CI 0.136–0.919, p=0.033).

The patients were classified based on the presence of glaucoma, and the characteristics of the negative and the significant groups were compared (Table 5). Statistically significant differences in age and worsening visual acuity symptoms were observed, which were consistent with the overall analysis. Among non-glaucoma patients, the significant group had a higher pattern standard deviation (PSD, p=0.003) than the negative group. In glaucoma patients, the significant group had a lower IOP (p<0.001), fewer instances of PPA (p=0.004), and more cases of incomplete homonymous hemianopsia (p=0.001).

DISCUSSION

Differential diagnosis of atypical VFDs, and the decision whether to perform neuroimaging, is challenging across subspecialties, ranging from glaucoma to neuro-ophthalmology. In this study, "atypical VFDs" were defined as VFDs that deviated from the classic glaucomatous patterns and warranted neuroimag-

Table 3. Comparison of Clinical Characteristics of Patients according to Brain MRI Findings

Variables	Negative findings (n=77)	Significant findings (n=29)	*p*
Age (yr)	43.50±15.99	54.49±17.35	<0.001*
Sex			0.338
Male	40 (51.9)	17 (58.6)	
Female	37 (48.1)	12 (41.4)	
Presence of symptom (decreased visual acuity)	18 (23.4)	15 (51.7)	<0.001*
BCVA (logMAR)	0.27±0.46	0.25±0.33	0.317
Baseline IOP (mm Hg)	15.52±2.64	14.69±2.67	0.926
Disc morphology			
Vertical CDR	0.69±0.18	0.63±0.20	0.451
PPA	34 (44.2)	4 (10.5)	0.004*
Disc pallor	4 (5.2)	4 (13.8)	0.210†
Pale disc	6 (7.8)	4 (13.8)	0.456†
Global indices of visual field test			
VFI	74.81±24.99	64.64±27.88	0.155
MD	-9.66±8.34	-12.68±8.85	0.442
PSD	7.06±4.30	7.90±4.25	0.503
Presence of incomplete homonymous hemianopia	16 (12.9)	18 (42.9)	<0.001*
Reasons for brain MRI			
Structurally inconsistent VFDs	30 (39.0)	4 (13.8)	0.012*
Rapidly progressive VFDs	36 (46.8)	17 (58.6)	
Vertical VFDs	11 (14.2)	8 (27.6)	
Thickness of RNFL (μm)			
Superior	86.16±23.95	82.13±22.54	0.361
Temporal	57.31±18.13	53.74±13.09	0.262
Inferior	83.27±26.86	85.16±24.61	0.799
Nasal	62.26±12.92	62.37±11.72	0.964
Average	72.20±15.60	70.79±14.19	0.619
Thickness of GCIPL (μm)			
Superior	65.13±13.81	65.87±12.42	0.769
Superonasal	68.38±15.28	67.61±13.17	0.779
Inferonasal	65.31±14.36	66.45±12.34	0.661
Inferior	62.93±11.17	64.71±11.43	0.394
Inferotemporal	63.58±13.10	67.18±11.83	0.132
Superotemporal	63.72±13.53	64.92±10.62	0.618
Average	64.89±12.03	66.03±10.66	0.604
Minimum	55.94±13.77	58.74±12.51	0.266

BCVA, best-corrected visual acuity; IOP, intraocular pressure; CDR, cup-to-disc ratio; PPA, peripapillary atrophy; VFI, visual field index; MD, mean deviation; PSD, pattern standard deviation; MRI, magnetic resonance imaging; VFDs, visual field defects; RNFL, retinal nerve fiber layer; GCIPL, ganglion cell–inner plexiform layer.
Data are presented as mean±standard deviation or n (%).
*p<0.05; †Fischer's exact test.

Table 4. Logistic Regression Analysis of Factors Associated with Significant Findings on Brain MRI

	β	*p*	OR	95% CI
Age	0.048	0.002*	1.049	1.018–1.081
Presence of symptom of decreased visual acuity	1.756	<0.001*	5.790	2.361–14.195
PPA	-1.041	0.033*	0.353	0.136–0.919
Presence of incomplete homonymous hemianopia	2.719	0.001*	15.167	3.096–74.300
Reason for brain MRI (rapidly progressive VFDs vs. structurally inconsistent VFDs)	1.478	0.020*	4.385	1.266–15.189

OR, odds ratio; CI, confidence interval; PPA, peripapillary atrophy; MRI, magnetic resonance imaging; VFDs, visual field defects.
*p<0.05.

https://doi.org/10.3349/ymj.2025.0089

Table 5. Comparison of Clinical Presentations of Patients according to Their Findings on Neuroimaging in the Glaucoma and Non-Glaucoma Groups

Variables	Non-glaucoma group			Glaucoma group		
	Negative findings (n=30)	Significant findings (n=16)	*p*	Negative findings (n=47)	Significant findings (n=13)	*p*
Age (yr)	40.87±17.17	50.94±17.07	0.010*	45.2±14.96	58.73±17.03	<0.001*
Sex						
Male	14 (46.7)	8 (50.0)	0.821	26 (55.3)	9 (69.2)	0.124
Female	16 (53.3)	8 (50.0)		21 (44.7)	4 (30.8)	
Presence of symptom (decreased visual acuity)	8 (28.3)	8 (50.0)	0.025*	10 (21.3)	7 (53.8)	0.001*
BCVA (logMAR)	0.33±0.54	0.22±0.35	0.418	0.25±0.42	0.27±0.33	0.796
Baseline IOP (mm Hg)	15.35±2.11	16.15±2.83	0.273	15.6±2.88	13.36±1.73	<0.001*
Disc morphology						
Vertical CDR	0.54±0.19	0.48±0.20	0.326	0.76±0.12	0.74±0.11	0.372
PPA	2 (6.7)	1 (6.3)	1.000†	32 (68.1)	3 (23.1)	0.004*†
Pallor of disc	2 (6.7)	2 (12.5)	0.602†	2 (4.3)	2 (15.4)	0.202†
Pale disc	3 (10.0)	2 (12.5)	1.000†	3 (6.4)	2 (15.4)	0.295†
Global indices of visual field test						
VFI	82.78±26.25	69.95±25.13	0.076	71.02±23.6	59.82±29.92	0.114
MD	-7.11±9.38	-10.80±8.59	0.145	-10.88±7.55	-14.39±8.94	0.065
PSD	4.48±3.75	7.85±4.33	0.003*	8.29±4.01	7.95±4.27	0.726
Presence of incomplete homonymous hemianopia	8 (20.0)	8 (50.0)	0.131	8 (9.5)	10 (45.45)	0.001*†
Reasons for brain MRI						
Structurally inconsistent VFDs	19 (42.1)	2 (12.5)	0.041*	11 (23.4)	2 (15.4)	0.114†
Rapidly progressive VFDs	5 (26.3)	9 (56.2)		31 (66.0)	8 (61.5)	
Vertical VFDs	6 (31.6)	5 (31.3)		5 (10.6)	3 (23.1)	
Thickness of RNFL (μm)						
Superior	100.18±25.78	92.63±26.82	0.335	79.81±20.23	74.50±15.37	0.255
Temporal	58.97±18.35	59.38±13.97	0.938	56.56±18.09	49.64±10.98	0.090
Inferior	106.11±26.09	100.88±22.81	0.489	72.94±20.03	73.73±19.25	0.869
Nasal	66.87±9.95	61.48±10.10	0.026*	60.18±13.61	64.77±12.57	0.155
Average	82.84±16.84	77.94±16.40	0.329	67.39±12.38	65.59±9.78	0.529
Thickness of GCIPL (μm)						
Superior	69.74±16.07	73.50±14.64	0.424	63.05±12.20	60.32±6.48	0.160‡
Superonasal	71.05±17.49	75.00±15.44	0.437	67.17±14.11	62.23±7.95	0.112‡
Inferonasal	70.92±17.95	73.88±13.62	0.558	62.77±11.67	61.05±7.94	0.419‡
Inferior	69.84±13.57	71.50±9.89	0.661	59.80±8.24	59.77±9.99	0.990
Inferotemporal	71.32±14.94	73.38±13.62	0.625	60.08±10.54	62.86±7.25	0.301
Superotemporal	69.71±16.31	70.50±12.14	0.863	61.01±11.15	60.86±7.25	0.940‡
Average	70.53±15.34	72.88±11.28	0.584	62.35±9.22	61.05±6.90	0.539
Minimum	63.05±17.92	65.63±14.26	0.613	52.73±9.98	53.73±8.24	0.666

BCVA, best-corrected visual acuity; IOP, intraocular pressure; CDR, cup-to-disc ratio; PPA, peripapillary atrophy; VFI, visual field index; MD, mean deviation; PSD, pattern standard deviation; MRI, magnetic resonance imaging; VFDs, visual field defects; RNFL, retinal nerve fiber layer thickness; GCIPL, ganglion cell–inner plexiform layer.

Continuous variables are presented as mean±SD and compared using the Mann–Whitney U test. Categorical variables are presented as counts (percentages) and compared using the chi-square test or Fisher's exact test as appropriate.

*p<0.05; †Fisher's exact test; ‡Mann-Whitney U test.

ing based on clinical judgment. Some patients with known glaucoma were included if their visual field changes met the predefined criteria for atypical VFDs, as described in the Methods section. This reflects real-world referral patterns in tertiary care, where glaucoma patients may still require neuroimaging to rule out concurrent neurologic pathology.

We investigated the results of brain MRI in patients with atypical VFDs to identify the clinical presentations associated with significant findings. The yield of significant findings related to VFDs was 18.23%. Age, visual acuity symptoms, absence of PPA, incomplete homonymous hemianopsia, and rapidly progressive VFD were identified as significant risk factors. Al-

though the events-per-variable ratio in our model was below the conventional threshold, the model showed acceptable discrimination (AUROC=0.843) and consistent results across different selection methods, supporting its robustness.

Based on the anatomy of the visual pathway from ganglion cells to the visual cortex in the occipital lobe and its retinotopic organization, a vertical VFD indicates a brain lesion in the visual pathway. Previous studies have analyzed the correlation between vertical VFDs and the anatomical location of lesions along the visual pathway,[15,17] and have provided a scoring system to identify potential brain lesions.[18] In our study, the presence of incomplete homonymous hemianopsia was identified as an independent risk factor for significant findings in neuroimaging and the yield of vertical VFD was about 24%.

Depending on the presence of pre-existing glaucomatous VFDs, significant differences were observed in visual field test indicators between the negative and significant groups. In glaucoma patients who already had glaucomatous VFD, there were no significant differences in the global indices of the visual field test. However, there was a significant difference in the presence of incomplete hemianopsia between the negative group (9.5%) and the significant group (45.5%). In previous studies on neuroimaging of atypical normal-tension glaucoma (NTG) patients, Kosior-Jarecka, et al.[10] reported that 71.4% of vertical VFD cases were associated with brain pathology, while Güvenç, et al.[19] found that abnormal results were more frequent in cases of VFD incompatible with glaucoma. Therefore, in patients with glaucoma, detecting vertical patterns of VFDs is more important than determining absolute values, and neuroimaging is recommended for glaucoma patients exhibiting VFDs inconsistent with IOP or structural changes.

By contrast, patients without glaucoma showed significant differences in the global indices of the visual field test between the negative and the significant groups. In the significant group, PSD was significantly higher, and the proportion of patients with a faster progression rate calculated by MD was also higher than that in the negative group. Thus, the extent and progression rate of VFDs may serve as discriminating features in patients without glaucoma.

In the clinical setting, the visual field test is not the only diagnostic factor. A comprehensive assessment incorporating patient history and ophthalmic examination is essential to identify potential intracranial pathology.[10,11,13,20,21] Greenfield, et al.[13] reported that patients with compressive optic neuropathy had lower visual acuity than those with glaucoma. Kosior-Jarecka, et al.[10] reported that 50% of patients with atypical NTG and worsening BCVA had brain pathology. In this study, subjective worsening of visual acuity symptoms was also analyzed as a risk factor for significant findings on brain MRI, highlighting the necessity for thorough history-taking.

Disc morphology, such as vertical CDR, rim color, disc asymmetry between the two eyes, and PPA, has been widely studied as a criterion for the differential diagnosis of glaucoma and other optic neuropathies.[13,21-25] In this study, patients with significant findings showed significantly less PPA than those with negative findings, a result more attributable to glaucoma patients. In contrast, disc pallor, a sign of non-glaucomatous optic neuropathy, did not show a significant difference in this study. PPA is considered a morphological feature of the optic disc that reflects glaucomatous optic nerve damage.[26] Compared to normal eyes, glaucomatous eyes show a significantly larger area of the optic disc and PPA, which correlates with the size of the blind spot.[27] Therefore, the presence of PPA suggests glaucomatous changes rather than visual tract issues, indicating a lower risk of intracranial pathology. Clinicians must differentiate VFDs caused by morphological variables of intraocular etiologies, as these can present as an enlarged blind spot or even mimic a temporal VFD.

The development of OCT has introduced quantitative measures, such as the thickness of the RNFL[28,29] and GCIPL,[30] Bruch's membrane opening minimum rim width,[31] and the density of the microvasculature around the disc and macula,[32,33] to differentiate between neuropathies. Gupta, et al.[29] reported that in patients with non-glaucomatous optic nerve cupping, the nasal and temporal RNFL thicknesses, as well as macular thickness and volume, were lower than in patients with glaucomatous optic nerve cupping. Xiao, et al.[30] reported that, compared to non-glaucoma patients, those with glaucoma exhibited thinning of the inferior and superior RNFL, as well as more severe GCIPL reduction in the inferotemporal and inferior sectors. Unlike previous studies, this study focused on atypical VFDs and approximately two-thirds (110 patients, 69.2%) of the patients showed VFDs that were inconsistent with the RNFL structure. There were no significant differences in RNFL and GCIPL thicknesses between the groups. However, among non-glaucoma patients, the significant group showed thinner nasal RNFL compared to the negative group. Further research with a larger sample size is needed to explore whether non-glaucomatous etiologies might affect the nasal RNFL.

Age is an important factor in determining whether neuroimaging should be performed. Older age is a risk factor for glaucoma,[34] while optic nerve damage in young patients is regarded as a risk factor for non-glaucomatous optic neuropathy.[13,21] Unlike previous studies focusing on patients with clear diagnoses, studies involving patients with atypical NTG have identified older age as a risk factor for positive neuroimaging results. In cases of atypical NTG, young patients are more likely to show normal neuroimaging results.[10,19] In this study, older age was also found to be a risk factor for significant findings on neuroimaging. Neuroimaging in older patients is important for identifying diagnoses affecting the visual pathway.

Incidental findings unrelated to the VFDs were observed in 53 patients. The most common finding was a cerebrovascular accident (18 patients), which led to the initiation of antithrombotic medication in seven patients. Silent cerebral infarcts are known to be a risk factor for visual field progression in patients

https://doi.org/10.3349/ymj.2025.0089

with NTG.[35] Therefore, the incidental finding of a cerebrovascular accident requires attention, regardless of its direct impact on the visual pathway, as it is both a sign of a systemic problem and a risk factor for the progression of NTG.

This study had several limitations. First, the study was limited by its retrospective design. Missing the diagnosis of non-glaucomatous optic neuropathy can result in overlooking potentially life-threatening conditions, which is a limitation of this study given its retrospective design. Second, owing to the relatively small sample size, subgroup analysis was limited. Future studies with a larger sample size, analyzing the overlap of glaucoma and non-glaucomatous optic neuropathies, and investigating whether specific VFDs are associated with particular brain lesions, would contribute to a deeper understanding of the relationship between pathophysiology and function. Third, our results do not fully establish the diagnosis in patients with atypical VFDs who showed negative neuroimaging findings. Further tests, such as genetic examinations, may help differentiate this heterogeneous group. Fourth, although incomplete homonymous hemianopsia was identified as a significant risk factor, we did not compare its diagnostic yield with that of complete homonymous hemianopsia. Future studies should investigate their relative diagnostic value to better guide imaging decisions. Nevertheless, this study is the first to identify the neuroimaging results and clinical features of atypical VFDs and aims to establish a rationale for performing neuroimaging in such cases.

In conclusion, when deciding whether to perform neuroimaging for atypical VFDs, it is essential to consider the patient's age, presence of symptoms (worsening visual acuity), disc morphology, and the pattern and progression rate of the defect. Neuroimaging is recommended for elderly patients or those with worsening visual acuity symptoms. If findings are suggestive of glaucoma, assessment for the vertical pattern is important. If there are no findings suggestive of glaucoma, close monitoring of the severity and progression of VFDs is crucial.

ACKNOWLEDGEMENTS

This work was supported by a grant from the National Research Foundation of Korea (NRF), funded by the Korean government (MSIT) (No. 2022R1F1A107625911), and by a research grant from Samil Pharmaceutical Co., Ltd. (Seoul, Republic of Korea) (No. 4-2024-0341).

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