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ORIGINAL RESEARCH

Accuracy of Diagnosing Optic Neuritis Using DANTE TI-SPACE Imaging

Ayaka Shimada^{1,2}, Kenji Suda^{1,2}, Eri Nakano¹, Miho Tagawa¹, Manabu Miyata¹, Satoshi Kashii¹, Takuya Hinoda^{1,2}, Yasutaka Fushimi³, Kimitoshi Kimura⁴, Ryusei Nishigori⁴, Sinyeob Ahn⁵, John Grinstead⁶, Akitaka Tsujikawa¹

¹Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, Kyoto, Japan; ²Department of Ophthalmology, Shimane University Faculty of Medicine, Izumo, Shimane, Japan; ³Department of Diagnostic Imaging and Nuclear Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan; ⁴Department of Neurology, Kyoto University Graduate School of Medicine, Kyoto, Japan; ⁵MR Research and Development, Siemens Healthineers, San Francisco, CA, USA; ⁶MR Research and Development, Siemens Healthineers, Portland, OR, USA

Correspondence: Kenji Suda, Department of Ophthalmology and Visual Sciences, Kyoto University Graduate School of Medicine, 54 Shougoin Kawahara-cho, Sakyo-ku, Kyoto, 606-8507, Japan, Tel +81-75-751-3248, Fax +81-75-752-0933, Email qwm04525@kuhp.kyoto-u.ac.jp

Purpose: To evaluate the use of delay alternating with nutation for tailored excitation-prepared T1-weighted turbo spin echo (DANTE T1-SPACE) imaging for diagnosing optic neuritis and to analyze its correlation with clinical findings before and after treatment. **Patients and Methods:** Patients diagnosed with optic neuritis or non-arteritic anterior ischemic optic neuropathy (NA-AION) were evaluated at the Ophthalmology Department of Kyoto University Hospital. All patients underwent magnetic resonance (MR) studies before treatment initiation and ophthalmic examinations before and after treatment. Three ophthalmologists independently reviewed the MR scans for abnormalities. The magnetic resonance imaging (MRI) assessments included post-contrast DANTE T1-SPACE, post-contrast volumetric interpolated breath-hold examination (VIBE), and short T1 inversion recovery (STIR) scans. The presence of abnormalities in each sequence was determined.

Results: Of 36 eyes from 30 patients, 21 eyes from 17 patients were diagnosed with optic neuritis, and 15 eyes from 13 patients were diagnosed with NA-AION. DANTE T1-SPACE sequences showed better sensitivity for detecting optic neuritis than STIR sequences (100% vs 67%, p = 0.009). VIBE images did not confirm enhancement of lesions in some cases with optic neuritis. No differences were observed among the sequences for NA-AION. Lesion length evaluated by DANTE T1-SPACE sequences was associated with circumpapillary retinal nerve fiber layer thickness at the initial visit, eye pain, and the time interval from symptom onset to MRI scan. **Conclusion:** Contrast-enhanced DANTE T1-SPACE was better than other sequences of MRI for diagnosing optic neuritis. **Keywords:** Optic neuritis, magnetic resonance imaging, retinal nerve fiber layer, visual field test

Introduction

Optic neuritis is an inflammatory optic neuropathy characterized by subacute vision loss, visual field loss, dyschromatopsia, and pain associated with eye movement.¹ The incidence of optic neuritis in Japan has been estimated to be 1.03 per 100,000 population,² and the disease can manifest with unilateral or bilateral involvement. Clinical examination may reveal optic disc edema, albeit only in one-third of patients with typical optic neuritis, alongside other objective findings such as an afferent pupillary defect.³

The diagnosis of acute optic neuritis relies on clinical history and features, along with additional investigations, including blood tests, lumbar puncture, and magnetic resonance imaging (MRI).⁴ Atypical cases of optic neuritis require examination for anti-aquaporin 4 antibody (AQP4-Ab), which is included in the diagnostic criteria for neuromyelitis optica. Another subtype of seropositive optic neuritis is myelin-oligodendrocyte glycoprotein antibody (MOG-Ab)-associated disease, which is known to exhibit high sensitivity to steroid treatment. However, because of the time required for immunological testing, the sensitivity of MRI in the initial examination has gained much importance.⁵

According to previous studies, the sensitivity of contrast-enhanced MRI for optic neuritis is 95%; however, approximately 5% of optic neuritis cases do not show enhancement.^{6,7} The orbital region is surrounded by bone and sinus cavities, making it difficult to obtain images with highly uniform fat suppression. However, recent technological advances have led to the development of a black-blood technique, the so-called delay alternating with nutation for tailored excitation (DANTE) pulse, which can achieve signal suppression of the moving spin and cerebrospinal fluid in comparison with conventional methods.⁸ There has been few reports on the usefulness of the black-blood technique for diagnosing or prediction of prognosis of optic neuritis.⁸

The purpose of this study was to evaluate the usefulness of DANTE-prepared T1-weighted turbo spin echo (DANTE T1-SPACE) for the diagnosis of optic neuritis and its correlation with visual function and optical coherence tomography (OCT) findings before and after treatment.

Methods

Ethics Approval

This prospective observational study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board and Ethics Committee of Kyoto University Graduate School of Medicine (approval number [R0134]). Written informed consent was obtained from all the participants in this study. The retrospective study also adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board and Ethics Committee of Kyoto University Graduate School of Medicine (approval number [R2652]). We have publicly disclosed this retrospective research on the clinical courses of optic neuropathies on our faculty's website and provided the participants an opportunity to opt out. Under this condition, the Institutional Review Board and Ethics Committee of Kyoto University Graduate School of Medicine approved the waiver of informed consent. Patient data were stored and handled safely and securely to ensure patient confidentiality in this study.

Patients

The study participants were patients who visited the Ophthalmology Department of Kyoto University Hospital between December 2017 and September 2021 for optic neuritis and between January 2017 to May 2024 for non-arteritic anterior ischemic optic neuropathy (NA-AION). For recruitment of cases with optic neuritis, we included consecutive patients with a first episode of subacute vision loss or visual field progression accompanied by relative afferent pupillary defect (RAPD) and no ophthalmologic findings suspicious for diseases other than optic neuritis by slit-lamp microscopy, color fundus photography, and OCT. This study included cases in which contrast-enhanced MRI of the optic neuropathy, genetic diseases, and retinal diseases based on examinations such as MRI, fluorescein angiography, laboratory blood tests, and biopsy were excluded. We retrospectively enrolled patients with NA-AION who met the diagnostic criteria.

Diagnosis of Optic Neuropathy

In this study, the patients were eventually diagnosed as exhibiting optic neuritis or NA-AION. Diagnoses were determined according to the following diagnostic criteria with reference to previous reports: optic neuritis was characterized by visual field abnormalities, decreased visual acuity, RAPD positivity, decreased critical flicker frequency, and a clinical course consistent with that of optic neuritis. In most cases, patients with typical optic neuritis develop visual loss within hours to days, which typically reaches the nadir within 2 weeks.¹ In this study, detection of anti-AQP4-Ab or anti-MOG-Ab was used to confirm the diagnosis of optic neuritis. A lumbar puncture was performed in all cases, and we used the detection of oligoclonal bands as a reference for diagnosis. NA-AION is an optic neuropathy characterized by a small optic disc (disc at risk) accompanied by disc swelling with papillary hemorrhage and delayed filling of the optic disc and/or choroid on fluorescence angiography, and it has an acute-onset clinical course, with no marked improvement.⁹ The clinical diagnoses of all patients were collected retrospectively from conference records of the neuro-ophthalmology division.

Magnetic Resonance Imaging

MRI was performed using a 3-T magnetic resonance scanner (MAGNETOM Skyra, Prisma or Vida; Siemens Healthineers, Erlangen, Germany) with a 32-channel head coil. All MRI studies for optic nerve examination included whole-brain diffusion-weighted imaging, fluid-attenuated inversion recovery, pre- and post-contrast T1-volumetric interpolated breath-hold examination (VIBE), pre- and post-contrast DANTE T1-SPACE, and pre-contrast 2D short T1 inversion recovery (STIR) sequences of the orbital region with axial and coronal sections. The image-acquisition parameters have been previously reported.¹⁰ The parameters for the DANTE pulse were as follows: flip angle, 10°; radiofrequency pulse duration, 0.08 ms; number of pulses, 148; total pulse train duration, 167.24 ms; spoiler gradient area, 18 mT/m × ms; with whole-brain coverage. Acquisition time was 5 min 44s for DANTE T1-SPACE.

To evaluate the sensitivity of each modality in detecting abnormalities in optic neuritis, three ophthalmologists (A. S., K. S., and M. T). examined the presence of contrast enhancement in DANTE T1-SPACE and T1-VIBE images (Figure 1e and f) and the presence of high-signal areas in the STIR images. Each case was marked as contrast-enhancing/high intensity when the three ophthalmologists reached consensus. In addition, the length of the lesion showing contrast in DANTE T1-SPACE was evaluated by measuring luminance with ImageJ.¹¹ Based on the brightness of the brain white matter, the lesion length was quantified by the number of MRI slices according to a previous report.¹²

Clinical Examinations

Age, sex, best-corrected visual acuity (BCVA), and the interval from symptom onset to MRI examination were recorded during the initial visit to our hospital. For cases diagnosed as optic neuritis, the levels of anti-AQP4-Ab and anti-MOG-Ab and circumpapillary retinal nerve fiber layer thickness (cpRNFLT) were measured using Spectralis HRA + OCT (Heidelberg Engineering, Heidelberg, Germany), and ganglion cell complex (GCC) thickness was measured using RS-3000 (Nidek, Gamagori, Japan). The results of BCVA, cpRNFLT, and GCC thickness measurements at the initial visit and at 1 and 3 months after treatment as well as the best BCVA during the clinical course were collected.



Figure I Representative magnetic resonance images of optic neuritis in this study. (a and b) Coronal magnetic resonance imaging (MRI) scans of optic neuritis. (a) Volumetric interpolated breath-hold examination (VIBE) scan shows no clear difference between the right and left optic neurons. (b) Delay alternating with nutation for tailored excitation sampling perfection with application-optimized contrasts using different flip-angle evolutions (DANTE TI-SPACE) showing a high signal in the right optic neuron. (c and d) Coronal MRI scans of non-arteritic anterior ischemic optic neuropathy. (c) VIBE image showing contrasting effects on the left optic neuron. (d) DANTE TI-SPACE showing no difference between the right and left sides. (e and f) Coronal MRI scans of optic neurons without abnormalities. (e) VIBE image showing high signals in the blood vessels around the bottom of optic nerve. (f) DANTE TI-SPACE suppressing the signal of blood vessels.

Statistical Analyses

Comparisons of the clinical characteristics between optic neuritis and NA-AION or diagnostic performance among MRI modalities were performed using the *t*-test and Fisher's exact test. Lesion length and clinical findings on contrast-enhanced MRI using DANTE T1-SPACE sequence were analyzed using generalized estimating equations (GEE). In the GEE framework, each eye was considered individually dependent. All p-values were two-sided. Statistical significance was defined as a p-value <0.05. All analyses were performed using the R version 4.2.1. (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 36 eyes from 30 patients were included in this study. The diagnoses included optic neuritis in 21 eyes from 17 patients and NA-AION in 15 eyes from 13 patients. Flowcharts illustrating the process of patient inclusion and exclusion are presented in Figure 2. Comparison of the cases with optic neuritis and NA-AION (Table 1) showed no significant differences in male-to-female ratio or number of days after symptom onset at the time of MRI; however, patients with NA-AION were older and had better initial visual acuity than patients with optic neuritis. Among those with optic neuritis, 5 eyes were anti-AQP4-Ab-positive, 8 eyes were anti-MOG-Ab-positive, and 8 eyes were seronegative. No patient had multiple sclerosis (MS) or AQP4-MOG double-positive disease. Three cases were positive for oligoclonal bands, 1 case was positive for antinuclear antibodies, and 1 case was positive for anticentromere antibodies. Additionally, comorbidities included 1 case of rheumatoid arthritis and 1 case of Hashimoto disease.

The diagnostic performance of the three sequences (STIR, VIBE, and DANTE T1-SPACE) for differentiating optic neuritis from NA-AION is presented in Table 2. The sensitivities were 67% for STIR, 90% for VIBE, and 100% for DANTE; the



Figure 2 Patient inclusion and exclusion in this study. (a) Flowchart of patient inclusion and exclusion for optic neuritis between December 2017 and September 2021. (b) Flowchart of patient inclusion and exclusion for NA-AION between January 2017 to May 2024. Abbreviation: NA-AION, non-arteritic anterior ischemic optic neuropathy.

	Total	Optic Neuritis	NA-AION	p-value
No. of patients/eyes	30/36	17/21	13/15	
Sex (male/female)	17:16	7:10	7:6	0.21
Age (years)	60.3 ± 22.9	49.4 ± 23.2	72.8 ± 10.3	0.005
Type of disease				
AQP4-Ab		5		
MOG-Ab		8		
Others		8		
BCVA at first visit (logMAR)	0.90 ± 0.93	1.26 ± 1.00	0.40 ± 0.48	0.005
Disc edema	26	11	15	
Interval from the onset to MRI (days)	14.9 ± 13.4	12.5 ± 12.7	18.3 ± 13.7	0.21

 Table I Clinical Characteristics of the Patients at the First Visit

Note: Data are presented as m/m, ratio, mean \pm standard deviation, or n.

Abbreviations: AQP4-Ab, anti-aquaporin 4 antibody; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; MOG-Ab, anti-myelin oligodendrocyte glycoprotein antibody; NA-AION, non-arteritic anterior ischemic optic neuropathy.

Table 2 Diagnostic Performance of Each MRISequence for Differentiating Optic Neuritisfrom Non-Arteritic Ischemic Optic Neuropathy

	STIR	VIBE	DANTE
Optic neuritis (eyes)			
CE(+)	14	19	21
CE(-)	7	2	0
NA-AION (eyes)			
CE(+)	0	4	0
CE(-)	15	11	15

Abbreviations: CE, contrast enhancement; DANTE, delay alternating with nutation for tailored excitation; MRI, magnetic resonance imaging; NA-AION, non-arteritic anterior ischemic optic neuropathy; STIR, short TI inversion recovery; VIBE, volumetric interpolated breath-hold examination.

specificities were 100% for STIR, 73% for VIBE, and 100% for DANTE; the detection rates were 100% for STIR, 83% for VIBE, and 100% for DANTE. When comparing the sensitivity of each MRI sequence, no significant difference was observed between DANTE T1-SPACE and VIBE sequences (p = 0.49) or between VIBE and STIR sequences (p = 0.13) for optic neuritis. However, DANTE T1-SPACE showed significantly higher sensitivity than STIR for detection of optic neuritis (p = 0.009). Two of these cases showed no abnormalities in VIBE sequence but showed abnormal enhancement in DANTE T1-SPACE sequence (Figure 1a and b). In contrast, for NA-AION, only VIBE sequence revealed enhanced lesions (Figure 1c and d). There was no significant difference for specificities and detection rates between the sequences.

The detailed characteristics of the 17 patients with optic neuritis are presented in Table 3. The length from the optic papilla to the junction of the optic nerve and optic chiasm was 39.3 ± 3.3 mm, and the average length showing high signal on DANTE T1-SPACE sequence was 15.3 ± 10.1 mm. The GCC thickness measurements at the initial visit, at 1 month, and at 3 months were 97.4 ± 12.7 , 85.4 ± 12.2 , and 78.7 ± 11.8 µm, respectively. The cpRNFLTs at the initial visit, at 1 month, and at 3 months were 125.9 ± 50.8 , 98.6 ± 18.8 , and 77.2 ± 13.7 µm, respectively.

The length showing a high signal in DANTE T1-SPACE sequence was analyzed by dividing it into two groups: a shortlesion group (<11 mm) and a long-lesion group (>11 mm) (Table 3). The cpRNFLT at the initial visit was significantly greater and the number of patients with eye pain was higher in the group with long lesions (p = 0.004). On the contrary, the time interval from symptom onset to MRI scan was longer in the short-lesion group (18.7 ± 18.0 and 8.7 ± 2.6 days respetcively; p =0.03). The two groups showed no significant differences in corrected visual acuity at the initial visit, BCVA after treatment, GCC thickness throughout the entire period, or cpRNFLT at 1 month and 3 months following the initial visit.

	Total (21 Eyes)	Short-Lesion Group (10 Eyes)	Long-Lesion Group (11 Eyes)	p-value
Lesion length evaluated by DANTE sequence (mm)		6.84 ± 2.36	22.99 ± 8.14	<0.001
BCVA at the first visit	1.26 ± 1.00	1.32 ± 1.09	1.02 ± 0.91	0.79
BCVA after treatment	0.15 ± 0.64	0.28 ± 0.88	0.025 ± 0.22	0.37
Disc swelling (%)	12 (57)	4 (33)	8 (67)	0.19
Eye pain (%)	7 (33)	1 (10)	6 (54)	0.06
GCC thickness at the first visit (µm)	97.36 ± 12.65	108 ±12.14	99.89 ± 12.65	0.39
GCC thickness at 1 month after treatment (μ m)	85.42 ± 12.21	80.5 ±13.46	84.25 ± 10.45	0.74
GCC thickness at the last visit (μ m)	78.71 ± 11.84	68.5 ±13.67	75.5 ± 8.54	0.33
cpRNFL thickness at the first visit (μ m)	125.85 ± 50.76	97.22 ±17.63	149.27 ± 56.67	0.004
cpRNFL thickness at 1 month after treatment (μm)	98.6 ± 18.80	94 ±18.08	102.63 ± 18.49	0.36
cpRNFL thickness at the last visit (μm)	77.18 ± 13.74	79.33 ±19.69	76.38 ± 10.58	0.81
AQP4-Ab (%)	5 (24)	3 (30)	2 (18)	0.63
MOG-Ab (%)	8 (43)	4 (40)	4 (36)	1.00
Interval from onset to MRI scan (days)	12.5 ± 12.7	18.7 ±18.02	6.73 ± 2.63	0.03

 Table 3 MRI and OCT Findings for Optic Neuritis with Short (<11 mm) and Long (>11 mm) Lesions Showing High Signals in DANTE MRI

Note: Data are presented as mean ± standard deviation or n (%).

Abbreviations: AQP4-Ab, anti-aquaporin 4 antibody; BCVA, best-corrected visual acuity; cpRNFL, circumpapillary retinal nerve fiber layer; DANTE, delay alternating with nutation for tailored excitation; GCC, ganglion cell complex; MOG-Ab, anti-myelin oligodendrocyte glycoprotein antibody; MRI, magnetic resonance imaging; OCT, optical coherence tomography; SD, standard deviation.

A comparison of the clinical characteristics between the groups that showed better BCVA (logarithm of the minimum angle of resolution [logMAR] <0) and worse BCVA (logMAR >0) after treatment is provided in <u>Supplementary Table 1</u>. The GCC thickness at 1 month and at the last visit decreased significantly in the group showing worse BCVA after treatment. No significant differences between the two groups were observed in BCVA at the initial visit, GCC thickness at the initial visit, or cpRNFLT at any time point. Comparisons of the clinical characteristics among anti-AQP4-positive, anti-MOG-positive, and seronegative patients are presented in <u>Supplementary Table 2</u>.

Discussion

Two cases with optic neuritis showed a high signal only with DANTE T1-SPACE sequence. In addition, the sensitivity for detection of optic neuritis was 100% with DANTE T1-SPACE sequence, and none of the 13 cases of NA-AION showed a high signal with DANTE T1-SPACE sequence. Despite the relatively small sample size, the results suggest that optic neuritis can be diagnosed with higher sensitivity and specificity using DANTE T1-SPACE sequence.

One possible reason for the high sensitivity of DANTE T1-SPACE sequence is the differences in the MRI sequences. VIBE is a 3D gradient-echo (GRE) sequence, and DANTE T1-SPACE is a 3D spin echo sequence with variable flip angles. As a train of refocusing pulses creates the magnetization transfer effects from a wide radio-frequency field, DANTE T1-SPACE sequence may show greater enhancement than VIBE sequence.^{13–15} Furthermore, DANTE T1-SPACE sequence provides high contrast with fat suppression in the orbit or cavernous sinus, where fat suppression tends to be insufficient. Tsubouchi et al reported contrast enhancement of the abducens and facial nerves using DANTE T1-SPACE sequence in herpes simplex virus-associated cranial neuritis; thus, DANTE T1-SPACE sequence may be superior in detecting inflammation of the cranial nerves.¹⁶ The sensitivity of VIBE sequence for optic neuritis was 90% in this study, which is consistent with that of a previous report.¹⁷

In the assessments of NA-AION in this study, 4 of 13 cases showed a high signal with VIBE sequence. In a previous report, 5 of 32 NA-AION cases were reported to show a contrast-enhancement effect on gadolinium-enhanced MRI.⁷ In this study, no cases of NA-AION showed high signal intensity with DANTE T1-SPACE sequence. This may be because blood flow is suppressed with DANTE preparation, and blood flow can be misjudged as showing a high signal with VIBE sequence (Figure 1a and b). In addition, this research did not include the arteritic anterior ischemic optic neuropathy (A-AION), but according to the study by Sommer et al, arteritic posterior ciliary artery involvement can

be detected using black-blood MRI in patients with A-AION,¹⁸ indicating that black-blood MRI techniques such as DANTE T1-SPACE sequence are powerful tools in the differential diagnosis of acute-onset optic neuropathy.

In terms of the length showing a high signal with DANTE T1-SPACE sequence, the two groups showed significant differences in the cpRNFLT at the initial visit, the time interval from symptom onset to MRI examination, and eye pain, although the significance was only marginal (p = 0.06). The finding that the cpRNFLT at the initial visit was significantly thicker in the group with long lesions may be attributed to optic disc swelling.¹⁹ Disc edema was present in 4 (33%) of the 12 eyes in the short-lesion group and 8 (67%) of the 12 eyes in the long-lesion group, but the two groups showed no significant difference. The lesion length has been reported to be longer in NMO-Ab- or MOG-Ab-positive optic neuritis than in MS.^{20,21} No patients with MS were included in this study; however, the two groups showed no significant differences in the proportions of AQP4-Ab or MOG-Ab. Notably, the number of days from symptom onset to MRI examination was significantly longer in the short-lesion group because of the absence of eye pain. Fazzone et al reported that the length of enhancement was correlated with eye pain or pain with eye movement,²² which was consistent with the findings of the current study. Eye pain accompanied by optic neuritis can precede visual dysfunction,^{1,23} thus, the influence of lesion length on visual prognosis can be altered by the timing of treatment initiation.

In this study, we found that the factor affecting the prognosis of BCVA was not lesion length but the positive rate of AQP4-Ab. A previous study reported that visual acuity at the initial visit was significantly lower in the long-lesion group than in the short-lesion group;⁵ however, the current study showed no significant difference between these groups after 1 month and at the final visit. As mentioned earlier, the number of days from onset to treatment may have influenced the visual outcomes. The average number of days from onset to the MRI scan was 8.33 days in the better-BCVA group and 17.22 days in the worse-BCVA group. Patients with recurrent optic neuritis episodes reportedly showed better BCVA and less axonal degeneration if they received corticosteroid treatment within 2 days,²⁴ whereas the results did not improve significantly if the treatment delay was more than 5 days.²⁵ Regarding the OCT findings in this study, the GCC thickness at the initial visit and at 1 month decreased significantly in the group with worse BCVA after treatment. The GCC thickness was thought to be reduced because of increased damage to the optic nerve in the worse-BCVA group. Patients with MS have been reported to show a correlation between visual acuity and macular retinal nerve fiber layer thickness or GCL + inner plexiform layer (IPL) thickness,²⁶ which was consistent with the results of this study. As the thinning of the GCL + IPL had already progressed 1 month after the onset of optic neuritis,²⁷ the number of days from onset might have caused the difference in GCC thickness at the initial visit between the two groups.

This study has a few limitations. We compared DANTE T1-SPACE and VIBE sequences, but imaging conditions used for the analyses, such as resolution, voxel size, and slice thickness, were different between the sequences; thus, the influence of differences in imaging conditions on the superiority of the DANTE sequence cannot be ruled out. In accordance with a previous report, the lesion length was evaluated by the luminance of the optic nerve in the coronal section; however, this method does not consider the perineural enhancement often seen in optic neuritis with anti-MOG-Ab. Thus, the results for the lesion length may vary depending on the measurement method. The periods from the onset to the initial visit were also variable (19.0 ± 9.03 days). This time interval can change not only the results of MRI scans or other ophthalmic examinations but also the treatment outcomes, as discussed previously. Regarding the proportion of optic neuritis cases, there were no patients diagnosed with MS in this study. In Japan, optic neuritis caused by MS is rare, and the epidemiological study in Japan has shown that MS was the cause in only 4% of optic neuritis cases.²

In conclusion, our study demonstrated the use of DANTE T1-SPACE sequence with contrast enhancement for diagnosing optic neuritis. However, we were unable to establish its superiority in predicting visual prognosis in comparison with previous studies. Further investigations are warranted to validate and determine the potential utility of DANTE T1-SPACE sequence in the context of optic neuritis.

Data Sharing Statement

The data that support the findings of this study are not publicly available because they include information that could compromise the privacy of research participants, but they are available from the corresponding author (K.S.) upon reasonable request.

Ethics Approval

This prospective observational study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board and Ethics Committee of the Kyoto University Graduate School of Medicine (approval number [R0134]). Written informed consent was obtained from all the participants in this study. The retrospective study also adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board and Ethics Committee of Kyoto University Graduate School of Medicine (approval number [R2652]). We have publicly disclosed this retrospective research on the clinical courses of optic neuropathies on our faculty's website and provided the participants an opportunity to opt out. Under this condition, the Institutional Review Board and Ethics Committee of Kyoto University Graduate School of Medicine approved the waiver of informed consent. Patient data were stored and handled safely and securely to ensure patient confidentiality in this study.

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Disclosure

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