Original Article

Restricted Diffusion of the Optic Nerves in Patients with Acute Optic Neuritis: A Diagnostic Accuracy Study

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Objective: To evaluate the diagnostic accuracy of restricted diffusion of the optic nerves in patients with acute optic neuritis (ON).

Materials and Methods: The present study was a diagnostic accuracy study, including all acute ON patients, admitted to Ramathibodi Hospital in Thailand, between January 2014 and December 2018 (ID 075739). Patients were divided into acute ON and non-optic neuritis condition (non-ON) groups. The acute ON group was divided further into neuromyelitis optica spectrum disorder-associated optic neuritis (NMOSD-ON) group and other types of ON (other-ON) group. Patients' clinical information and MRI scans were reviewed retrospectively. Restricted diffusion of the optic nerves was present if hyperintense signals were observed on diffusion-weighted imaging (DWI) and hypointense signals were observed on the apparent diffusion coefficient (ADC) map.

Results: A total of 102 patients were included in the present study (141 optic nerves). Of all patients, 78 had acute ON (76.5%), and 24 had non-ON (23.5%). Of all optic nerves, there were 95 optic nerves in the acute ON group (67.4%) and 46 in the non-ON group (32.6%). Of 95 optic nerves in the acute ON group, there were 52 optic nerves in the NMOSD-ON group (54.7%) and 43 in the other-ON group (45.3%). Restricted diffusion of the optic nerves demonstrated a sensitivity of 77.9%, specificity of 95.7%, positive predictive value of 97.4%, and negative predictive value of 67.7% in identifying acute ON. It had a sensitivity of 86.5%, specificity of 32.6%, positive predictive value of 60.8%, and negative predictive value of 66.7% in differentiating NMOSD-ON from other-ON.

Conclusion: The diffusion MRI can be a marker of acute ON. The test is most useful for ruling in acute ON when restricted diffusion is positive. However, further investigations might be required in negative tests. Restricted diffusion is positive in several types of ON. It is difficult to differentiate NMOSD-ON from other ON types using diffusion MRI alone.

Keywords: Neuromyelitis optica spectrum disorders, Optic neuritis, Diffusion-weighted imaging, Apparent diffusion coefficient, Restricted diffusion

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Optic neuritis (ON) is an inflammatory disorder of the optic nerves. It is clinically diagnosed but can mimic other types of optic neuropathy. Contrast-enhanced T1-weighted images with fat suppression of the orbits (CE-T1W/FS) can be used to confirm the diagnosis of acute ON[1-4]. Enhancement of the optic nerve is highly sensitive for acute ON[5]. Such enhancement might be associated with disruption of the blood-nerve barrier of the optic nerve[5]. However, gadolinium injection is prohibited in some patients, particularly those with renal impairment. The enhancement may not be visible following steroid treatment. An alternative tool with which to assess acute ON may be helpful.

Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) mapping are other magnetic resonance imaging (MRI) techniques

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that provide more information about microscopic water diffusion in tissue[5]. There is increasing evidence that acute ON can cause high DWI signal with corresponding low ADC (restricted diffusion) of the optic nerve. Some patients with ON do not have enhancement of the optic nerve and DWI/ADC map could be a useful marker in those. The sensitivities and specificities of restricted diffusion to detect inflamed optic nerves vary markedly among studies[5-8]. In patients with chronic ON, increased ADCs were reported and correlated well with visual parameters[9,10]. It has been proposed that ADC values could be a surrogate marker of axonal degeneration of chronic ON. Recently, two case reports revealed restricted diffusion of the optic nerves in patients with neuromyelitis optica spectrum disorder-associated optic neuritis (NMOSD-ON) [11,12]. A study also found that the mean ADC value of NMOSD-ON is lower than that in multiple sclerosis-associated- ON. ADC may help differentiate NMOSD-ON from multiple sclerosis ON[13]. The present study aimed to evaluate the diagnostic accuracy of DWI/ADC map in the diagnosis of acute ON.

Materials and Methods

Patients

The present study was a diagnostic accuracy study, including all consecutive acute ON patients, admitted to Ramathibodi Hospital, a university hospital, in Bangkok, Thailand, between January 1, 2014 and December 30, 2018. The patients' demographic, clinical information, and initial visual acuity (VA) were obtained retrospectively from medical records. Patients were divided into two groups, namely, acute ON and non-optic neuritis condition (non-ON) groups. The inclusion criteria of acute ON were first-time acute presentations of decreased vision, unilateral or bilateral involvement, signs of optic nerve dysfunctions, and all patients underwent thorough visual examinations by neuro-ophthalmologists. The acute ON group was divided further into NMOSD-ON group and other types of ON (other-ON) group. The inclusion criteria for NMOSD-ON were clinical presentations consistent with acute ON; all patients underwent thorough visual examinations by neuro-ophthalmologists, aquaporin4-IgG seropositivity (cell-based assay), no evidence of infection nor sinusitis. All NMOSD-ON patients met Wingerchuck 2015 criteria[14]. The other-ON group was comprised of myelin oligodendrocyte glycoprotein antibody-IgG-positive ON (MOG-ON), multiple sclerosis-associated ON (MS-ON), systemic autoimmune disorder-associated-ON (autoimmune-ON), infectious ON, post-infectious ON, and idiopathic ON. All patients with MS-ON met 2017 Mcdonald criteria[15]. Patients with idiopathic ON had neither MS-typical brain lesions nor any specific antibodies and causes. They also did not have further episodes of other neurological deficits. The inclusion criteria for the non-ON group were patients who developed other diseases of the visual pathway/normal vision; all patients underwent thorough visual examinations by neuro-ophthalmologists. The study was approved by the Ethical Clearance Committee on Human Rights Related to Research Involving Human Subjects, Faculty of Medicine Ramathibodi Hospital, Mahidol University (ID 075739) with written informed consent obtained from each patient or their representative.

MRI protocols

MRI scans were reviewed by two neuro-radiologists (Tritanon O and Laothamatas J with 8 and 25 years of experience, respectively). They were masked to the diagnoses. The scans were performed within 45 days after the symptom onset. The MRI examinations were performed on two different scanners: a 3.0T scanner (Ingenia; Philips Healthcare, Best, the Netherlands) and a 1.5T scanner (Signa TwinSpeed; GE Healthcare) using the authors' standard, routine brain and orbit MRI protocols that included axial and coronal CE-T1W/FS, T2W images with fat suppression (T2W/FS), axial fluid-attenuation inversion recovery images, axial DWI, and calculation of the ADC. DWI and ADC mapping were performed as part of the brain MRI protocol. Axial and coronal CE-T1W/FS and T2W/FS were employed as part of the orbital MRI protocol. DWI was performed using a single-shot spin-echo echo-planar image with the following parameters. On 3.0T MRI: TR/TE 3,000/90 ms, flip angle 90 degrees, section thickness 4 mm without gap, matrix size 160×160 mm, and FOV 240×240 mm. On 1.5 MRI: TR/TE 8,000/90 ms, section thickness 5 mm and intersection gap 1.5 mm, matrix size 128×128 mm, and FOV 240×240 mm. Diffusion sensitizing gradients were applied sequentially in the x, y, and z directions with b=0 and 1,000 seconds/mm² on both 3.0T and 1.5 T MRI. Restricted diffusion of the optic nerves was present if hyperintense signals were observed on DWI relative to the surrounding intraconal fat and extraocular muscles and hypointense signals were observed on the ADC map (Figure 1, 2).

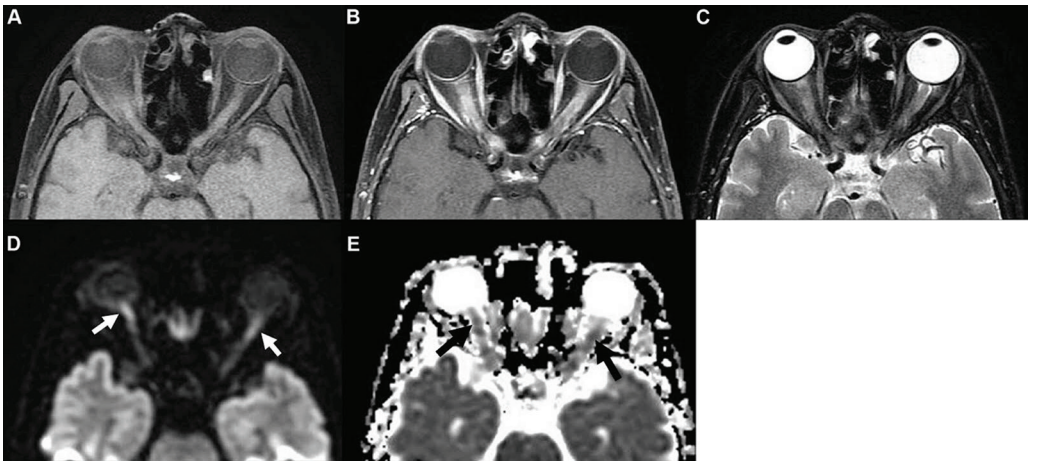

Figure 1. A) 53-year-old woman with NMOSD presented with bilateral optic neuritis. A) and B) axial, pre- and post-contrast T1-weighted images with fat saturation of the orbits showed enhancement in both optic nerves, C) T2-weighted image of the orbits demonstrated high signal intensity of both optic nerves, D) and E) Axial DWI and ADC map showed restricted diffusion of both optic nerves, predominantly at the proximal part.

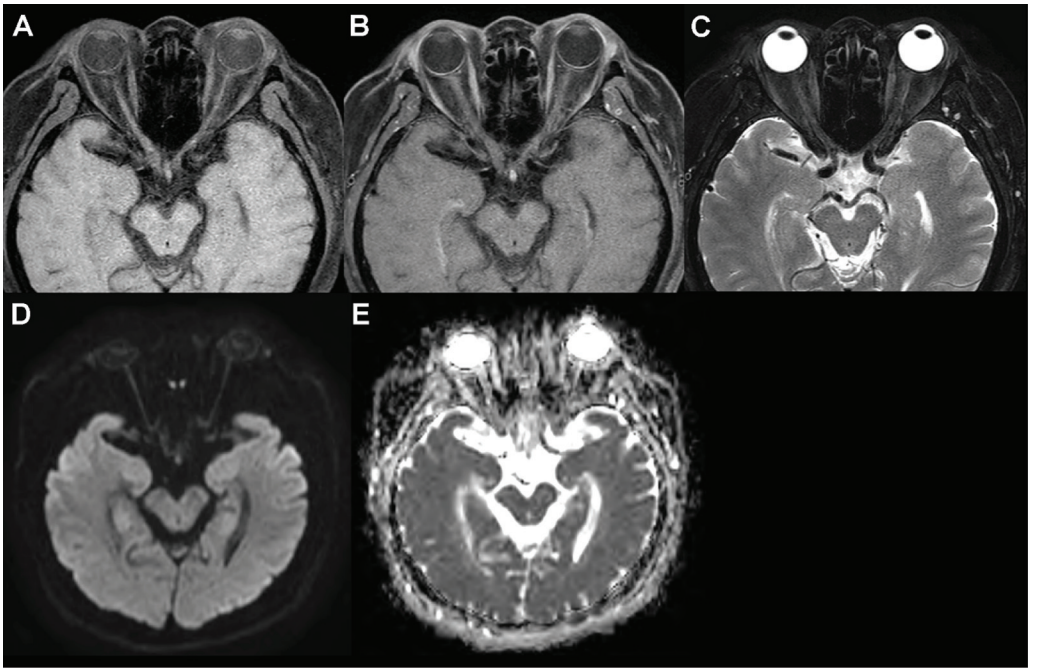

Figure 2. A) patient presented with non-optic neuritis condition and normal vision. A) and B) axial, pre- and post-contrast T1-weighted images with fat saturation of the orbits showed healthy optic nerves, C) T2-weighted image of the orbits demonstrated normal optic nerves, D) and E) Axial DWI and ADC map showed no restricted diffusion of both optic nerves.

Statistical analysis

All statistical analyses were performed using Stata Statistical Software, version 15.1 (StataCorp LLC, College Station, TX, USA). The sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive values, and negative predictive value, were assessed for DWI and ADC mapping. The index test was restricted diffusion in DWI/ADC map. The reference standard was clinical diagnoses. The index test and the reference standard were performed at the same time. A p-value of less than 0.05 was considered statistically significant for all analyses.

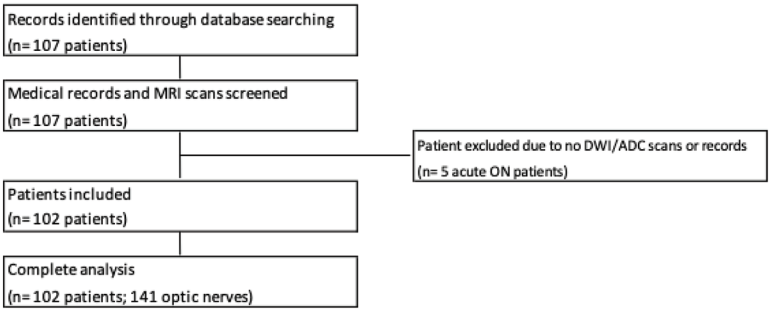

Figure 3. Patient flow diagram.

Table 1. Demographic and clinical features

		Number of optic nerves	Bilateral (patients)	Initial VA	Optic nerves with restricted diffusion; n (%)
1.	Acute ON	95	17	20/20 to NPL	74 (77.9)
1.1	NMOSD-ON	52	8	20/20 to NPL	45 (86.5)
1.2	MOG-ON	9	4	20/70 to CF	9 (100)
1.3	MS-ON	3	0	20/200 to HM	2 (66.7)
1.4	Autoimmune-ON	4	0	20/400 to CF	4 (100)
1.5	Infectious ON	2	0	20/400 to PL	1 (50.0)
1.6	Post-infectious ON	1	0	CF	0 (0.0)
1.7	Idiopathic-ON	24	5	20/20 to NPL	14 (58.3)
2.	Non-ON	46	22	20/20 to NPL	2 (4.3)
Total		141	39		

ON=optic neuritis; NMOSD-ON=neuromyelitis optica spectrum disorder-associated ON; MOG-ON=myelin oligodendrocyte glycoprotein antibody-IgG-positive ON; MS-ON=multiple sclerosis-associated ON; VA=visual acuity; NPL=no perception of light; CF=counting fingers; HM=hand movements; PL=perception of light

Results

The authors found 107 patients identified through database search. Five patients were excluded because of unavailable data (Figure 3). A total of 102 patients were included in the study [141 optic nerves, 81 females (79.4%), 21 males (20.6%), age 15 to 83 years old (mean 44.6, SD 15.9)]. Demographic and clinical features were shown in Table 1.

Of all 102 patients, 78 had acute ON (76.5%), and 24 had non-ON (23.5%). Of all 141 optic nerves, there were 95 optic nerves in the acute ON group (67.4%, 17 participants with bilateral involvement) and 46 in the non-ON group (32.6%, 22 participants with bilateral involvement). Of 95 optic nerves in the acute ON group, there were 52 optic nerves in the NMOSD-ON group (54.7%) and 43 in the other-ON group (45.3%). Fourteen patients with acute ON received steroid treatment before the scans. All optic nerves in the acute ON group developed enhancement on CE-T1W/FS except for one nerve with idiopathic ON. The non-ON group was comprised of ethambutol-induced optic neuropathy (n=6 optic nerves), Leber hereditary optic neuropathy (n=2), anterior ischemic optic neuropathy (n=1), optic nerve compression (n=1), traumatic optic neuropathy (n=1), chiasmal compression (n=4), papilledema (n=2), cilioretinal artery occlusion (n=1), retinal vasculitis (n=1), homonymous hemianopia (cerebral infarct, n=2), cranial nerve palsy (n=4), nystagmus (n=2), myasthenia gravis (n=14), and normal vision (n=5). All optic nerves in the non-ON group were healthy on CE-T1W/FS.

Of all 141 optic nerves, restricted diffusion of the optic nerves demonstrated a sensitivity of 77.9% (95% confidence interval [CI] 68.2 to 85.8), specificity of 95.7% (95% CI 85.2 to 99.5), positive likelihood ratio of 17.9 (95% CI 4.6 to 69.8), negative likelihood ratio of 0.2 (95% CI 0.2 to 0.3), positive predictive value of 97.4% (95% CI 90.8 to 99.7), and negative predictive value of 67.7% (95% CI 54.9 to 78.8) in identifying acute ON (Table 2). Two patients with non-ON developed restricted diffusion. They were diagnosed with ethambutol optic neuropathy and

Table 2. A cross tabulation of restricted diffusion (index test) by the reference standard in ON and non-ON groups

Reference standard	Restricted diffusion (index test)		
	Positive	Negative	Total
ON	74	21	95
Non-ON	2	44	46
Total	76	65	141

ON=optic neuritis

Table 3. A cross tabulation of restricted diffusion (index test) by the reference standard in NMOSD-ON and other ON

Reference standard	Restricted diffusion (index test)		
	Positive	Negative	Total
NMOSD-ON	45	7	52
Other ON	29	14	43
Total	74	21	95

NMOSD-ON=neuromyelitis optica spectrum disorder-associated ON; Other ON=other types of optic neuritis

myasthenia gravis.

Among optic nerves with acute ON, restricted diffusion demonstrated a sensitivity of 86.5% (95% CI 74.2 to 94.4), specificity of 32.6% (95% CI 19.1 to 48.5), positive likelihood ratio of 1.3 (95% CI 1 to 1.6), negative likelihood ratio of 0.4 (95% CI 0.2 to 0.9), positive predictive value of 60.8% (95% CI 48.8 to 72), and negative predictive value of 66.7% (95% CI 43 to 85.4) in detecting NMOSD-ON (Table 3).

Discussion

Based on the results, the diffusion MRI can identify 77.9% of acute ON cases and correctly identify 95.7% of those who do not have acute ON. Positive predictive value of 97.4% indicates a high probability that subjects with restricted diffusion truly have acute ON. Negative predictive value of 67.7% indicates a lower chance that subjects with absent restricted diffusion genuinely do not have the disease. Hence, the test is most useful for ruling in acute ON when restricted diffusion is positive. However, further investigations might be required in negative tests.

Among patients with acute ON, the diffusion MRI had high sensitivity but low specificity in the diagnosis of NMOSD-ON. The results indicate that the test is useful for detecting NMOSD-ON but comes with a relatively high false-positive rate. This is because other ON types can develop restricted diffusion in the optic nerves as well.

DWI and ADC map can be an alternative tool for acute ON diagnosis when there are gadolinium injection contraindications. The prognosis of some ON including NMOSD-ON is generally poor without appropriate therapy. Early recognition and treatments of the disease are essential to prevent severe visual loss[16]. The presence of restricted diffusion in the optic nerve, therefore, should alert clinicians for prompt treatments.

The present study limitation was due to it was a retrospective study, and there was no assessment of inter-rater reliability between the two neuro-radiologists.

Conclusion

The diffusion MRI can be a marker of acute ON. It can provide more information for clinical judgment in acute ON, especially when there are contraindications for gadolinium injections. The test is most useful for ruling in acute ON when restricted diffusion is positive. However, further investigations might be required in negative tests. Restricted diffusion is positive in several types of ON. It is difficult to differentiate NMOSD-ON from other ON types using diffusion MRI alone.

What is already known on this topic?

ON is clinically diagnosed and mostly confirmed by contrast-enhanced T1-weighted images with fat suppression of the orbits. Enhancement of the optic nerve is highly sensitive for the diagnosis of acute ON.

What this study adds?

DWI and ADC mapping can be helpful in diagnosing acute ON, particularly in cases of gadolinium contraindications. The test had a sensitivity of 77.9% and a specificity of 95.7%

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Conflicts of interest

The authors declare no conflict of interest.

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