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Assessment of the optic nerve, optic disc, and perineural area using shear-wave elastography in patients with multiple sclerosis

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Abstract

Purpose: To observe and describe the stiffness changes of the optic nerve in the patients with multiple sclerosis (MS) with or without optic neuritis and healthy adults via shear wave elastography (SWE).

Methods: 70 optic nerves from 35 patients with MS and 60 optic nerves from 30 healthy subjects were included prospectively in the study. The optic nerve (ON), optic disc (OD), and perineural area were evaluated with SWE and optic nerve sheat diameter (ONSD) was measured by ultrasound.

Results: The mean age of patients was 39.68 ± 9.99 years. There was no statistically significant difference between the groups in terms of ONSD, SWE ON, SWE OD, and SWE perineural area levels ($P > .05$). In the MS group; No statistically significant difference was found between patients with and without optic neuritis for the mean age, gender distribution, duration of MS, types of MS, ONSD, SWE ON, SWE OD, SWE perineural area, and Expanded Disability Status Scale (EDSS) scores ($P > .05$). No statistically significant difference in terms of ONSD, SWE ON, SWE OD, and SWE perineural area between the MS patients with or without optic neuritis and the control group ($P > .05$).

Conclusion: Shear wave elastography measurements of the optic nerve, optic disc, and perineural area do not contribute to the evaluation of optic neuritis in a patient with MS.

1 | INTRODUCTION

Multiple sclerosis is a chronic inflammatory disease and one of the most common causes of neurological disability in young adults globally.[1,2] Many genetic and environmental factors, demyelination, and iron-related abnormalities are the aetiological and pathological causes of the MS.[3-5]

MS can affect all the anatomical parts of the visual system. The most often seen presentations are optic neuritis, brainstem, and spinal cord syndromes.[1] Optic neuritis may be the first manifestation of multiple sclerosis.[6] Acute demyelinating optic neuritis is the presenting symptom in about 20% of MS patients and affects about half of MS patients at some point in the disease course.[7]

Computerised tomography has limited applications in optic nerve pathologies because of the ionising radiation and low resolution of soft tissue. Conventional and non-conventional Magnetic Resonance Imaging (MRI) such as diffusion tensor imaging, diffusion-weighted imaging provide high-resolution images. Whereas it is time-consuming, expensive, less obtainable, and often requires the use of gadolinium contrast. A more practical method is needed to evaluate the optic nerve for the initial diagnosis and follow-up of patients.[8-10]

Sonoelastography is an advanced sonographic technique and a non-invasive method for evaluating the different elasticity characteristics of tissues. There are two main sonoelastographic techniques that include strain elastography (SE), which display the local strain of a given sample of tissue (relative strain) and compresses the tissues axially, and shear wave elastography (SWE), which uses waves that are generated by transducers and interact with the tissue and a less operator-dependent method. Shear wave elastography can allow visualisation and documentation of absolute stiffness in kilopascals or meters per second objectively without a maneuvre.[10,11]

Sonoelastography has been used in the evaluation of internal organ pathology, and more recently, its clinical application to optic nerve tissue has been a growing area of interest.[12] As far as we know, there is only one reported study about the sonoelastography of the optic nerve in MS patients in the English medical literature.[13]

The main purpose of the study is to assess the elasticity features of the optic nerve, optic disc, and perineuronal area using SWE in patients with MS (with or without optic neuritis), compare with healthy volunteers and describe the contribution of SWE findings for visual dysfunction in MS.

2 | MATERIAL AND METHODS

2.1 | Participants

This prospective study was approved by the local ethics committee and was conducted according to the Helsinki Declaration. All adult participants provided written informed consent to participate in the study.

Between February 2019 and August 2019, both optic nerves of patients with MS and healthy participants who were referred by the Neurology Clinic of our institution were examined. MS was diagnosed by an experienced neurologist in compliance with the revised McDonald criteria, and duration of the disease and the clinical rating scale called "Expanded Disability Status Scale (EDSS)" score was also recorded. Patients diagnosed with two types of MS; Relapsing-Remitting MS (RRMS) or Secondary-Progressive MS (SPMS) were included in the study. Patients had previous optic neuritis diagnosed based on typical history, clinical and radiological findings.

Patients with a history of orbital surgical intervention and trauma, systemic diseases (hypertension, diabetes mellitus), infections with optic nerve involvement (meningitis, syphilis, tuberculosis), disorders that cause optic nerve damage (cranial vasculitis, Graves' disease, autoimmune diseases, etc) were excluded from the study. Patients with or without an optic neuritis attack in previous history were included the study, but there were no patients with acute optic neuritis attack in the patients included the study. Seventy optic nerves from 35 patients with MS and sixty optic nerves from 30 healthy subjects were included prospectively in the study.

2.2 | Equipment and scanning

We used The Esaote QElaXto 2D sonography system (Esaote S.p.A.) with SWE software sonoelastographic evaluations. A linear array probe of 6-9 MHz was used in the SWE examinations. The participants had a supine position with closed eyes during the examination. We applied the coupling gel between the eyelids of all the participants and instructed them not to move their eyes during the examination. We measured the optic nerve diameter (OND) for each eye between the external hypoechogenic borders of the optic nerve without hyperechogenic space surrounding that nerve by the B-mode US and then we applied SWE without compression. We standardised the examination technique based on literature.[9,13,14] In addition to the optic nerve, we obtained the measurements of the perineural area and optic disc by SWE. We used the transverse plane from inside the equator of the eyeball and longitudinal axis of the optic nerve for measurements and then saved static images.

2.3 | Data analysis

One radiologist performed sonoelastography measurements for all subjects. Two radiologists (SSE and A.K with 2 years of experience in elastography and 30 years of conventional US experience, respectively) determined the final interpretations through consensus. The radiologists were blind to the clinical information of the patients with MS (with or without optic neuritis).

Quantitatively analysis of optic nerve, optic disc, and perineural area stiffness was expressed as kPa with a colour scale of 0-150 kPa and a region of interest at an interval of 2 to 3 mm. Three measurements for the quantitative value of each optic nerve, optic disc, and perineural area were acquired and the average values were used for the statistical analysis. (Figures 1 and 2).

2.4 | Statistical analysis

IBM SPSS Statistics 22 (IBM SPSS, Turkey) programme was used in the analysis of the data obtained in the study. The suitability of the parameters to the normal distribution was evaluated by the Shapiro Wilks test. Besides descriptive statistical methods (mean, standard deviation, frequency), a student *t* test was used for comparing normally distributed parameters between two groups, and the Mann–Whitney *U* test was used for comparing non-normally distributed parameters between two groups while evaluating the study data. Pearson correlation analysis was used to examine the relationships between parameters that are suitable for normal distribution, and Spearman's rho correlation analysis was used to examine the relationships between parameters not compatible with a normal distribution. Continuity (yates) correction was used to compare qualitative data. Results were evaluated within the 95% confidence range at $P < .05$ significance level.

3 | RESULTS

The study was conducted with 130 eyes of 65 patients, 44 (67.7%) male and 21 (32.3%) female, whose ages ranged from 18 to 59. The mean age was 39.68 ± 9.99 years. The cases were divided into two groups as "MS Group" (n = 70) and "Control Group" (n = 60). The duration of the disease in the MS group ranges between 2 and 25 years, with a mean of 14.74 ± 5.85 years and a median of 15 years. According to MS types; 29 (44.6%) of the cases had RRMS and six (9.2%) had SPMS type. There was no statistically significant difference between the groups in terms of ONSD, SWE ON, SWE OD, and SWE perineural area levels ($P > .05$) (Table 1).

In the MS group; there is no statistically significant difference between patients with and without optic neuritis, in terms of mean age, gender distribution, MS duration, MS types, ONSD, SWE ON, SWE OD, SWE perineural area, and EDSS levels ($P > .05$) (Table 2). There is no statistically significant difference in terms of ONSD, SWE ON, SWE OD, and SWE perineural area between the MS patients with optic neuritis and the control group ($P > .05$) (Table 3). There is no statistically significant difference in terms of ONSD, SWE ON, SWE OD, and SWE perineural area between the MS patients without optic neuritis and the control group ($P > .05$) (Table 4).

4 | DISCUSSION

MS is an autoimmune, chronic, inflammatory, and demyelinating disease. While MS can lead to optical neuritis, internuclear ophthalmoplegia, nystagmus, and saccadic dysmetria as visual dysfunction, optic neuritis is the most frequently detected one.[15] It is often associated with severe visual loss. Therefore, early diagnosis of optic nerve damage is extremely important. Recently, ultrasonography has become an important adjuvant in the evaluation of the optic

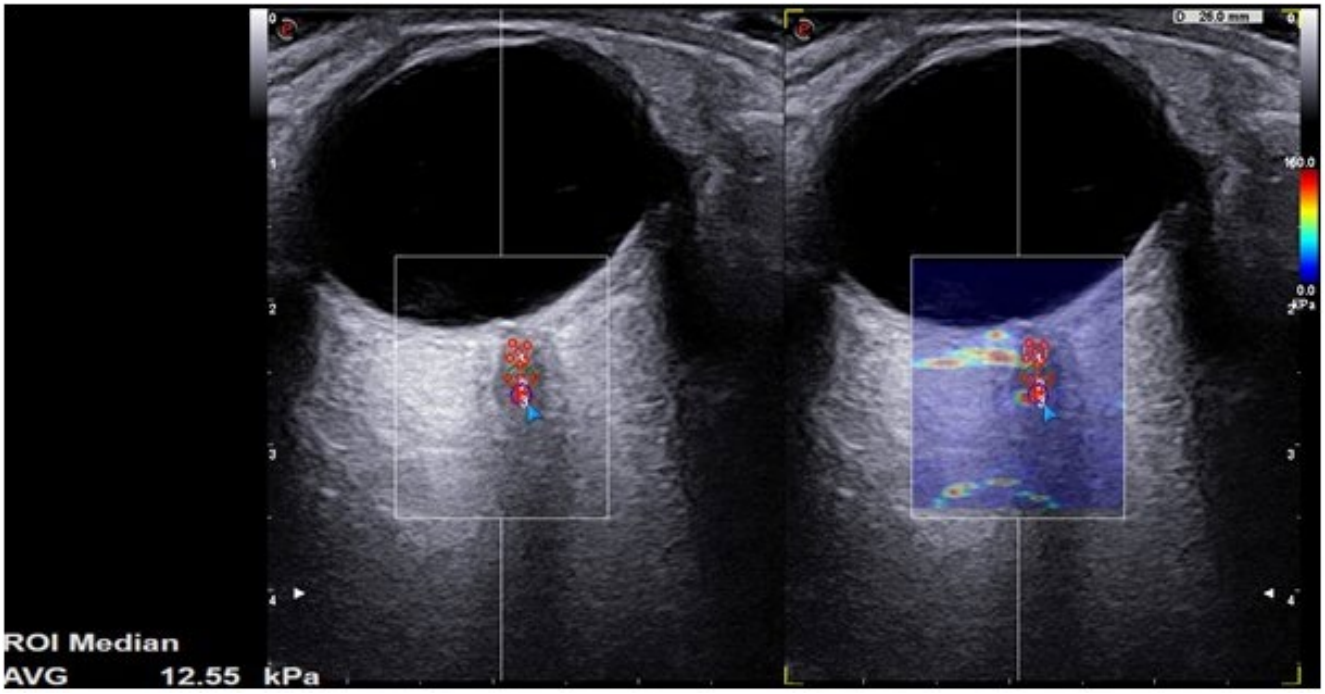

FIGURE 1 Grayscale (left) and colour (right) SWE images of the optic nerve and circular regions of interest (box). Elasticity measurement with SWE of the optic nerve of a 38-year-old female patient with MS revealed a mean score of 12.55 kPa

TABLE 1 The detailed SWE findings of both groups are described

	MS (n = 70)	Control (n = 60)	*P*
ONSD $_{\text{Mean ± SD}}$	2.94 ± 0.50	3.03 ± 0.58	.319[a]
SWE ON $_{\text{Median (IQR)}}$	7.31 (18.5)	7.30 (6.1)	.957[b]
SWE OD $_{\text{Median (IQR)}}$	7.07 (15.6)	7.28 (9.2)	.724[b]
SWE perineural area $_{\text{Median (IQR)}}$	8.59 (17.1)	11.3 (16.8)	.154[b]

Abbreviations: IQR, interquartile range; MS, multiple sclerosis; OD, optic disc; ON, optic nerve; ONSD, optic nerve sheat diameter; SD, standard deviation; SWE, shearwave elastography.

[a]Student *t* test.

[b]Mann–Whitney *U* test.

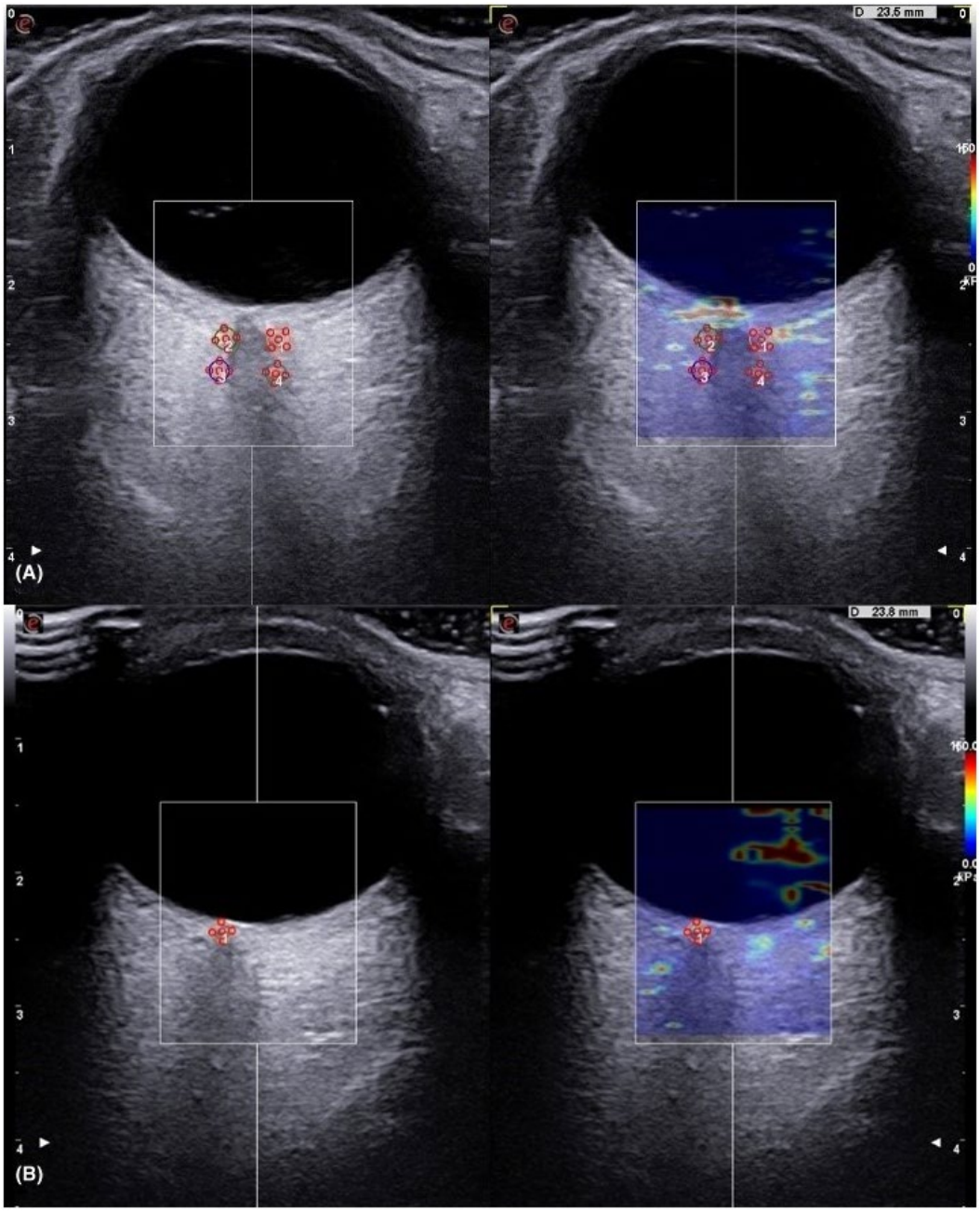

FIGURE 2 FIGURE Grey-scale (left) and colour (right) SWE images showing the measurement technique (a) on the perineural area and (b) on the optic disc

nerve.[16] We performed this study considering that SWE can be an effective modality for evaluating the optic nerve in the diagnosis of optic neuritis because of non-invasive and low-cost properties.

Volume loss and axonal damage in the retinal nerve fibres can be observed in MS patients.[15] The optic disc usually appears normal but is mildly edematous in one-third of cases.[17] Also, autoimmune-related posterior uveitis or vasculitis of the optic nerve in Wegener's granulomatosis may cause optic disc edema.[18] This effect of autoimmune pathologies on the optic disc may cause damage by similar mechanisms in MS patients. The presence of the vascular network in the perineural area may play a role in the development of optical neuritis by having immune cells in this autoimmune inflammatory process.[19] Thus, we thought that the evaluation of the perineural area might be beneficial and added this area to our research. In the literature, these parameters have been evaluated with MRI in different studies.[20-22] However, there is no study in which all three parameters were evaluated together on SWE.

In the literature, there is only one study evaluating sonoelastographic findings in patients with MS, and only the optic nerve was evaluated in this study.[13] Besides, in another study; Batur et al evaluated both ON and retrobulbar tissue in patients with isolated optic neuritis on SWE and reported that comparison of the normal eye

with isolated optic neuritis. The stiffness of the optic nerve in optic neuritis was found higher than the contralateral normal optic nerve and this difference was statistically significant.[23] In our study, we aimed to develop a different point of view; the optic disc and perineural area were also evaluated in addition to the optic nerve, and quantitative evaluation was made particularly on SWE to increase the reliability of the study. Our study has been the first to evaluate all these parameters together. Besides, we strengthened the clinical effectiveness of our study by comparing our SWE measurements with the EDSS score. EDDS is widely used in clinical trials and for the assessment of MS. Since we thought the EDDS and sonoelastographic parameters might have a relation, we also compared the SWE results with the EDDS scores. Unfortunately, we could not find any significant differences.

In Inal et al's study, the sonoelastographic changes in the optic nerve in patients with MS were evaluated in terms of the elasticity of the optic nerve based on the three main colourings in strain elastography (SE) and SWE.[13] According to this study, both SE and SWE can be used to investigate inflammation in patients with MS and may provide early diagnosis of optic neuritis. In our study, no statistically significant difference was found in the comparison of the optic nerve, optic disc, and perineural area SWE measurements between the MS patients (with or without optic neuritis attack) and healthy volunteers. According to these findings, our study results do not support the results which they reported.

At this point, the disadvantages of SWE arise such as the difficulty of the measurement technique and dependence on the operator. Optic nerve diameter up to 5 mm is considered normal in a healthy population.[24,25] Inal et al found that the mean optic nerve diameter was 5.31 ± 0.48 mm (range, 3.8-6.5) in MS patients, while this value was 5.22 ± 0.58 mm (range, 3.7-7) in healthy volunteers. These findings support the concerns about the measurement. In our

TABLE 2 The detailed findings associated with or without optic neuritis such as duration of MS, type of MS, and SWE findings on the MS group are described

	ON		
	Absence (n = 45)	Presence (n = 25)	*P*
Duration of MS $_{\text{Median (IQR) (year)}}$	12 (9.5)	17 (6)	.243[b]
ONSD $_{\text{Mean ± SD (mm)}}$	2.87 ± 0.52	3.06 ± 0.43	.119[a]
SWE ON $_{\text{Median (IQR)}}$	7.64 (12.7)	6.3 (24.5)	.783[b]
SWE OD $_{\text{Median (IQR)}}$	8.97 (16.0)	5.45 (11.1)	.157[b]
SWE perineural area $_{\text{Median (IQR)}}$	8.44 (12.4)	13.47 (18.4)	.433[b]
EDSS $_{\text{Median (IQR)}}$	2 (0.5)	2 (1)	.979[b]
Type of MS $_{\text{n (%)}}$			
RRMS	36 (80%)	22 (88%)	.517[c]
SPMS	9 (20%)	3 (12%)	

Abbreviations: IQR, interquartile range; MS, multiple sclerosis; OD, optic disc; ON, optic nerve; ONSD, optic nerve sheat diameter; SD, standard deviation; SWE, shearwave elastography.

[a]Student *t* test.

[b]Mann–Whitney U test.

[c]Fisher's Exact test.

TABLE 3 The comparison of SWE values between MS patients with optic neuritis and control group

	ON Presence (n = 25)	Control (n = 60)	*P*
ONSD $_{\text{Mean ± SD}}$	3.06 ± 0.43	3.03 ± 0.58	.819[a]
SWE ON $_{\text{Median (IQR)}}$	6.3 (24.5)	7.30 (6.1)	.981[b]
SWE OD $_{\text{Median (IQR)}}$	5.45 (11.1)	7.28 (9.2)	.101[b]
SWE perineural area $_{\text{Median (IQR)}}$	13.47 (18.4)	11.3 (16.8)	.576[b]

Abbreviations: IQR, interquartile range; MS, multiple sclerosis; ON, optic nerve; OD, optic disc; ONSD, optic nerve sheat diameter; SD, standard deviation; SWE, shearwave elastography.

[a]Student *t* test.

[b]Mann–Whitney *U* test.

TABLE 4 The comparison of SWE values between MS patients without optic neuritis and control group

	ON absence (n = 45)	Control (n = 60)	*P*
ONSD $_{\text{Mean ± SD}}$	2.87 ± 0.52	3.03 ± 0.58	.139[a]
SWE ON $_{\text{Median (IQR)}}$	7.64 (12.7)	7.30 (6.1)	.954[b]
SWE OD $_{\text{Median (IQR)}}$	8.97 (16.0)	7.28 (9.2)	.541[b]
SWE perineural area $_{\text{Median (IQR)}}$	8.44 (12.4)	11.3 (16.8)	.110[b]

Abbreviations: IQR, interquartile range; MS, Multiple Sclerosis; OD, Optic disc; ON, Optic nerve; ONSD, optic nerve sheat diameter; SD, standard deviation; SWE, shearwave elastography.

[a]Student *t* test.

[b]Mann–Whitney *U* test

study, this value was 3.03 ± 0.58 mm in the healthy population and it was compatible with the information in the literature.

Optic neuritis may cause increased or decreased ONSD in the acute and chronic phases.[16,26,27] This may be an early and late sign of optic neuritis. The hypothesis that optic nerve thickness and stiffness may differ in optic neuritis with MS patients is the study's main purpose. However, we could not find any significant difference in ONSD and SWE ON between patient groups with and without optic neuritis and control group. We anticipate that the absence of patients with acute optic neuritis attack in the study may have led to these results. We think that MS patients with acute attack might have different results.

One of the limitations of our study is that SWE is an operator-dependent measurement method. Although our small size of the patient population seems to be a problem, the prospective study design increases the reliability of our results.

5 | CONCLUSION

The measurements of SWE that we recommended as an easily accessible, non-invasive method that might be used in the evaluation of the optic nerve for visual dysfunction of patients with MS do not contribute additionally.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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