DOI: 10.14744/DAJPNS.2024.00244
Dusunen Adam J Psychiatr Neurol Sci
2024;37:94-101

RESEARCH ARTICLE

The dilemma of bright spots detected on magnetic resonance imaging of the brain for the diagnosis of multiple sclerosis: A retrospective evaluation of nonspecific white matter lesions

Nurhan Kaya Tutar[1], Sami Omerhoca[1], Elif Soylemez[1], Sinem Yazici Akkas[2], Nilufer Kale[1]

[1]Bagcilar Training and Research Hospital, Department of Neurology, Istanbul, Turkiye
[2]Department of Neurology, St.-Marien-Hospital, Lunen, Germany

ABSTRACT

Objective: With advances in magnetic resonance imaging (MRI) technology, nonspecific white matter lesions (NSWMH) are often incidentally detected on T2-weighted images. The origin of these lesions is unknown. In younger individuals, these findings may prompt consideration of multiple sclerosis (MS) as a possible diagnosis. In the presence of these lesions, the misinterpretation of radiological diagnostic criteria can lead to the overdiagnosis of MS. This study aims to address the management of patients with NSWMH.

Method: This retrospective study involved patients referred to our MS outpatient clinic, suspected of having MS following the detection of T2-hyperintense lesions, who were subsequently diagnosed with NSWMH between 2017 and 2021. We collected data on patients' medical complaints, neurological examinations, brain MRI findings, and results from additional investigations from our hospital's data system.

Results: The study included 70 patients (87.1% female), with an average age of 40.87±8.13 years (range, 19 to 55 years). The average follow-up period was 22.1±16.5 months. MRI analysis showed the number and location of lesions to be subcortical (12.06±14.01), cortical/juxtacortical (1.2±2.2), periventricular (0.91±1.42), in the corpus callosum (0.38±0.23), and in the posterior fossa (0.05±0.07). Lesions were bilaterally located in 63% of cases. Only two patients developed new lesions, as observed in the first follow-up MRI, with no further changes in subsequent MRIs during the long-term follow-up.

Conclusion: Neurologists need to distinguish between NSWMH and MS lesions. Ultimately, MRI serves as a supportive diagnostic tool, with clinical findings taking precedence over all other diagnostic methods.

Keywords: Magnetic resonance imaging, multiple sclerosis, nonspecific white matter lesions, T2-hyperintense lesions

INTRODUCTION

With advances in magnetic resonance imaging (MRI), nonspecific white matter hyperintensities (NSWMHs) are often incidentally detected in T2-weighted images (1). When patients visit a neurology outpatient clinic for common symptoms like headache and dizziness, finding these T2-hyperintense lesions on a brain MRI scan can cause confusion for both the physician and the patient.

How to cite this article: Kaya Tutar N, Omerhoca S, Soylemez E, Yazici Akkas S, Kale N. The dilemma of bright spots detected on magnetic resonance imaging of the brain for the diagnosis of multiple sclerosis: A retrospective evaluation of nonspecific white matter lesions. Dusunen Adam J Psychiatr Neurol Sci 2024;37:94-101.

Correspondence: Nurhan Kaya Tutar, Bagcilar Training and Research Hospital, Department of Neurology, Istanbul, Tukiye
E-mail: nurhantutar@gmail.com
Received: November 21, 2023; **Revised:** February 24, 2024; **Accepted:** April 19, 2024

The differential diagnosis for white matter hyperintensities is extensive, including age-related small vessel disease, vasculitis, migraines, and infectious or inflammatory processes (2). In older individuals, risk factors such as hypertension, diabetes, and cerebrovascular disease may contribute to these lesions (3–5). Conversely, in young adults, multiple sclerosis (MS) may be considered (6, 7). These young patients with visible bright spots on brain MRIs are often referred to MS specialists.

The diagnosis of MS is determined using the McDonald criteria, which have evolved over the years based on clinical presentations and MRI scans of the brain and spinal cord, assessing dissemination in time and space (8–11). The integration of imaging with clinical findings facilitates the early diagnosis of MS. However, MS diagnosis mandates that the lesions meet specific criteria outlined by the Magnetic Resonance Imaging in MS (MAGNIMS) study group, not just any T2 lesions identified in neuroimaging (12). Notably, lesions indicative of demyelination possess unique characteristics that, without typical MS symptoms, may lead to a diagnosis of radiologically isolated syndrome (RIS), a condition that could potentially evolve into MS (13).

Currently, the most common cause of MS misdiagnosis is the misinterpretation of NSWMH on brain MRIs (14–16). As such, diagnosing and managing MS should involve consultations with MS specialists and, when necessary, neuroradiologists, rather than relying solely on radiological reports.

Even when it is determined that patients do not have MS, their concerns and questions about the management of these lesions often remain unresolved. Key questions that require answers include: 1. What is the pathophysiology behind these lesions? 2) What steps should be taken if these lesions increase?

This study aims to review the initial clinical and MRI findings and the long-term follow-up of patients diagnosed with NSWMH who were referred to our MS outpatient clinic after the detection of T2 hyperintensities suspected to be MS.

METHODS

Study Design, Participants and Procedure

In this retrospective study, we evaluated patients referred to our MS outpatient clinic between 2017 and 2021 for potential MS diagnosis after detection of T2-hyperintense lesions on brain MRI, who were ultimately diagnosed with NSWMH. The revised 2017 McDonald criteria were employed for the differential diagnosis of MS, and the 2009 RIS criteria were used for RIS differential diagnosis (11, 13). The study protocol was approved by the Ethical Committee of Medipol University in Istanbul (IRB Approval Date: 06/01/2022, Number: E-10840098-772.02-108). Informed consent was obtained from each participant.

Table 1: Medical records of patients

	Frequency	%
Initial Presentation		
Headache	58	82.9
Dizziness	10	14.3
Fatigue	2	2.9
Speech Disorder	2	2.9
Blurred Vision	1	1.4
Paresthesia	2	2.8
Medical History		
None	37	52.9
Hypertension	13	17.2
Hypothyroidism	10	14.3
Diabetes Mellitus	7	10.0
Diplopia	3	4.3
Arrhythmia	3	4.3
Miscarriage	3	4.3
Migraine	3	4.3
Major Depression	2	2.9
Hepatitis C	2	2.9
Uveitis	1	1.4
Ulcerative Colitis	1	1.4
Rheumatoid Arthritis	1	1.4
Oral Aphthae	1	1.4
Neurological Examination		
Normal	63	90
Deep Tendon Hyperreflexia	5	7.1
Tremor	1	1.42
Hemihypoesthesia	1	1.42

The analysis included patients' complaints, neurological examinations, and additional tests such as vasculitis markers (serum C-reactive protein, antinuclear antibody, anti-double-stranded DNA (anti-dsDNA), rheumatoid factor), coagulopathic testing (protein C and protein S levels, homocysteine), cerebrospinal fluid (CSF) analysis for oligoclonal bands (OCB) and CSF immunoglobulin G (IgG) index, visual evoked potentials (VEP), transthoracic echocardiography (TTE), and spinal cord

Table 2: Number and distribution of lesions on baseline brain MRI

	n	Mean±SD	Mean (Min–Max)
Subcortical	70	12.06±14.01	7 (0–80)
Periventricular	70	0.91±1.42	0 (0–8)
Cortical/Juxtacortical	70	1.2±2.2	0 (0–12)
Posterior Fossa	70	0.05±0.07	0 (0–1)
Corpus Callosum	70	0.38±0.23	0 (0–3)
Contrast Enhancement	70	0	0

MRI: Magnetic Resonance Imaging; SD: Standard Deviation.

neuroimaging. Data for these were extracted from our hospital's system. All imaging was performed using a 1.5 T scanner and included T1-weighted, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) sequences in axial, coronal, and sagittal planes. Contrast material was administered in all MRI scans.

The white matter lesions (WMLs) detected on MRI were categorized by location, considering unilaterality/bilaterality, symmetry/asymmetry, and specific regions such as supratentorial, infratentorial, periventricular white matter, subcortical white matter, cortical/juxtacortical, and the corpus callosum. The count of lesions in these areas was recorded. The MRIs were also assessed for evidence of periventricular capping (PVC). In follow-up MRIs, both the emergence of new WMLs and the resolution of existing ones were documented. Patients with concomitant neurological diseases, ischemia, and cardiac conditions were excluded from the study.

Statistical Analysis

Statistical analysis was conducted using IBM SPSS (Statistical Package for the Social Sciences) version 23.0 (IBM Corporation, Armonk, NY, USA). Descriptive statistics were presented in the form of frequency tables and cross tables for categorical variables, and through mean, median, standard deviation, minimum, and maximum values for numerical variables.

RESULTS

A total of 70 patients (87.1% female) were enrolled in the study. The mean age was 40.87±8.13 years (range: 19–55), and the average follow-up duration was 22.1±16.5 months. The initial complaints reported by patients included headache (82.9%), dizziness (14.3%), fatigue (2.9%), speech disorders (2.9%), blurred vision (1.4%), and paresthesias (4.1%). No medical history was reported in 52.9% of the patients. The most common comorbidities included hypertension (17.2%), hypothyroidism (14.3%), and diabetes mellitus (10.0%). Neurological examinations at the initial MRI scan were normal in 63 (90%) patients. Pathological neurological examination findings included deep tendon hyperreflexia (7.1%), tremor (1.42%), and hemihypoesthesia (1.42%) (Table 1).

Table 3: Characteristics of lesions on baseline brain MRI

	Frequency	%
Unilateral	7	10.0
Bilateral	63	90.0
Symmetrical	43	61.5
Asymmetrical	27	38.5
Number of Lesions on T1 Sequence		
0–1	58	82.9
1–6	12	17.1
Ventricular Capping Sign		
No	14	20.0
Yes	56	80.0

MRI: Magnetic Resonance Imaging.

MRI analysis revealed the following average number and location of lesions: subcortical (12.06±14.01), cortical/juxtacortical (1.2±2.2) periventricular (0.91±1.42), corpus callosum (0.38±0.23), and posterior fossa (0.05±0.07). No contrast enhancement was observed (Table 2). None of the patients met the MAGNIMS criteria for dissemination in space on baseline brain MRI. Lesions were bilaterally localized in 63% of cases and tended to be symmetrical in 61.5%. Only 12% of patients had more than one lesion on the T1 sequence. PVC was noted in 56% of the patients (Table 3, Fig. 1).

Routine biochemical tests showed that 93.2% of the patients had a vitamin D deficiency, 49.52% had a vitamin B12 deficiency, and 72.8% had hyperlipidemia. A vasculitis profile was conducted for 49 patients, with 88% showing negative results. However, 4% exhibited hyperhomocysteinemia, 2% tested positive for antinuclear antibodies (ANA), 2% had positive anti-dsDNA antibodies, and 4% showed decreased levels of protein S (Table 4).

Lumbar puncture results from 11 patients were analyzed retrospectively. The CSF profile was evaluated, and all patients displayed normal parameters with no findings suggestive of MS (normal IgG index and oligoclonal band type 1). Cervical spinal MRI was conducted on 64 patients, none of whom had cervical spinal cord lesions. Thoracic spinal MRI was performed on 51 patients, and similarly, no thoracic spinal cord

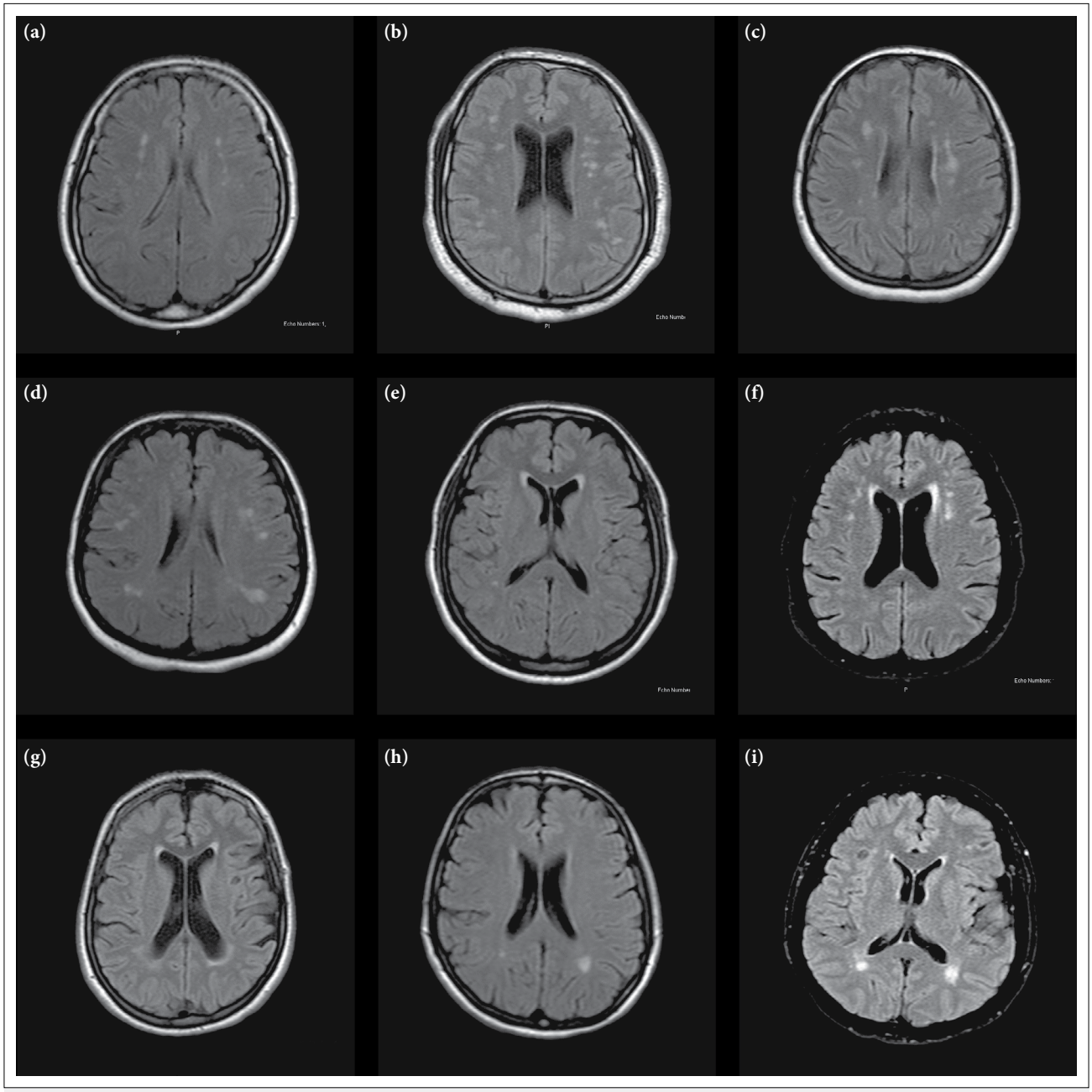

Figure 1. Brain MRI Lesions: Predominantly subcortical with a tendency for bilateral localization and symmetry **(a–d)**. Periventricular capping; increased signal intensity around the poles of the lateral ventricles **(e–g)**. Lesions not in contact with the ventricles **(h–i)**.

lesions were found. VEP studies were conducted on 37 patients, with 91.7% showing normal results (Table 4).

Transthoracic echocardiography was performed on 21 patients, revealing no potential cardiac sources of embolism. Magnetic resonance angiography (MRA) of the carotid and vertebral arteries was performed in 22 patients, and none showed stenosis exceeding 50%.

The initial follow-up brain MRI for 46 patients was conducted at an average of 19.32±9.24 months, during which only 2 (4.34%) patients developed a new lesion on the MRI. A reduction in the number of WMLs was observed in 1 patient (2.17%). The second follow-up brain MRI for 28 patients occurred at an average of 31±8.59 months, with no changes noted. The third follow-up brain MRI for 14 patients, conducted at an average of 36.4±2.88 months, also showed no changes. The fourth brain MRI follow-up for 4 patients, at an average of 44±0 months, similarly revealed no changes (Tables 5 and 6).

Table 4: Further laboratory and imaging findings

	Frequency	%
Routine Biochemistry		
Normal	2	3.03
Vitamin B12 Deficiency	34	49.52
Vitamin D Deficiency	55	93.2
Hyperlipidemia	43	72.8
Vasculitic Markers		
Normal	44	88
Hyperhomocysteinemia	2	4
ANA +	1	2
Anti-dsDNA +	1	2
Low Protein S Level	2	4
Cerebrospinal Fluid		
Normal	9	81.9
OCB Type 1	11	100
Normal IgG Index	11	100
Increased Protein Level	2	18.1
MRI Angiography		
Normal	18	81.8
Abnormal	4	18.2
Echocardiography		
Normal	16	76.2
Left Atrium Dilatation	2	9.5
Right Ventricular Hypertrophy	1	4.8
Hypokinesia	1	4.8
Mitral Valve Prolapse	1	4.8
VEP		
Normal	33	91.7
Latency Prolongation	3	8.4
Decreased Amplitude	1	2.8
Lesions on Cervical MRI		
No	64	100.0
Yes	0	0
Lesions on Thoracic MRI		
No	51	100.0
Yes	0	0

VEP: Visual Evoked Potential; OCB: Oligoclonal bands; MRI: Magnetic Resonance Imaging.

Table 5: Time taken for follow-up brain MRI

	n	Mean±SD	Mean (Min–Max)
First MRI Follow-up (Months)	46	19.32±9.24	18 (6–52)
Second MRI Follow-up (Months)	28	31±8.59	32.5 (16–48)
Third MRI Follow-up (Months)	14	36.4±2.88	36 (33–41)
Fourth MRI Follow-up (Months)	5	44±0	44 (44–44)
Fifth MRI Follow-up (Months)	1	–	–
Sixth MRI Follow-up (Months)	1	–	–

MRI: Magnetic Resonance Imaging; SD: Standard Deviation.

Table 6: Changes in follow-up brain MRI

	Frequency	%
First MRI Follow-up		
No change	43	93.4
Newly developed lesion	2	4.34
Disappeared	1	2.17
Second MRI Follow-up		
No change	28	100.0
Third MRI Follow-up		
No change	14	100.0
Fourth MRI Follow-up		
No change	5	100.0
Fifth MRI Follow-up		
No change	1	100.0
Sixth MRI Follow-up		
No change	1	100.0

MRI: Magnetic Resonance Imaging.

DISCUSSION

The diagnostic process for MS begins with a comprehensive history and neurological examination when a patient is referred to MS specialists due to suspected clinical or imaging findings indicative of MS. MS is more common in women, with the sex ratio now approaching 3:1 (female to male) in most developed countries (17, 18). Consequently, MS is often suspected in female patients presenting with T2 hyperintensity on MRI. In our study, we noted that patients with NSWMHs referred to our MS outpatient clinic were predominantly female. However, while MS typically affects individuals aged 20–40 years, the average age of our patients with NSWMH was over 40 years (19). Therefore, although late-onset MS is possible, diagnosis in such cases requires a thorough and cautious approach (20).

Typical clinical manifestations of a demyelinating episode in MS include optic neuritis, brainstem syndromes, and transverse myelitis (21). In contrast, the primary symptoms reported by our NSWMH patients were predominantly headaches (82.9%). Studies have

shown that women are more frequently affected by chronic headaches than men (22), tend to have a lower pain threshold than men, and seek medical treatment more frequently (23). Consequently, it is more common for women to seek medical attention for headache complaints. In our patient cohort, other symptoms such as visual impairment (blurring), dizziness, speech difficulties, and numbness were rare. In neurological outpatient clinics, it has been observed that up to one-third of "normal" individuals aged 20 to 45 years may present to the hospital with transient neurological symptoms that have no clinical significance and no underlying abnormalities (24, 25). Therefore, a patient presenting with neurological complaints does not necessarily have an underlying organic pathology upon further investigation.

Misinterpretation of radiological diagnostic criteria when nonspecific neurological symptoms are present can erroneously suggest a diagnosis of MS, potentially leading to unnecessary treatment initiation and consequent economic burden (14). Even in the absence of clinical findings indicative of MS, these radiological images may lead to overdiagnosis of RIS. In our study, the T2 hyperintensities that were incidentally detected were mostly located subcortically. Localizations characteristic of MS, such as periventricular (hyperintensities touching the ventricles), corpus callosum, juxtacortical/cortical, and posterior fossa, were rarely observed. Predominantly subcortical lesions suggest the need for careful consideration of an MS diagnosis, even if typical MS localizations are affected (12). Notably, the lesions were bilaterally located and exhibited a symmetrical pattern, which is uncommon in MS. Another significant observation was the absence of contrast enhancement in any of the lesions. While contrast agents can be crucial in diagnostic processes, their unnecessary use should be avoided to prevent accumulation in the deep nuclei of the brain with repeated exposure (26).

MS lesions that appear hypointense on T1-weighted images are commonly referred to as "T1 black holes," which indicate axonal loss and tissue destruction (27). Studies have demonstrated that these black holes in MRI scans of MS patients correlate with clinical outcomes and disease progression (28). Thus, in individuals with a high capacity for remyelination at an early age, black holes may not be present in the initial stages of MS. In our study, only 12% of patients had more than one lesion on the T1 sequence. The two patients who developed new lesions on follow-up MRI also had lesions on T1-weighted images. Closer monitoring may be warranted for such patients, who display an important radiological sign of MS.

PVCs, characterized by increased signal around the poles of the lateral ventricles (primarily the frontal horns) bilaterally, are a frequent finding on brain MRIs (29). Although this common signal change is reported to increase with age, it occurs in more than half of asymptomatic individuals, even in those under 55 years old (30). Pathological studies have indicated that PVCs are not associated with ischemic-gliotic changes but are instead linked to areas of finely textured myelin and denudation of the ventricular ependymal lining (31). In our study, PVCs were noted in 56% of patients. Although periventricular lesions are typical for MS, their symmetrical appearance helps differentiate these conditions.

The etiology of NSWMH is not yet fully understood. However, association with factors such as migraines, aging, and hypertension have been reported (32, 33). Our data show that the most common comorbidities were hypertension (17.2%), hypothyroidism (14.3%), and diabetes mellitus (10.0%), which is consistent with the literature. In routine biochemical tests, 72.8% of patients exhibited hyperlipidemia, identifying it as a vascular risk factor. Additional investigations into ischemic causes, including assessments for vasculitis markers and transthoracic echocardiography (TTE), yielded no significant results.

Research has shown a consistent link between vitamin D deficiency and white matter lesions (34). In our study, 93.2% of patients were found to be deficient in vitamin D, aligning with findings from previous studies. Furthermore, vitamin D has been reported to influence the development of MS and to increase the frequency of its attacks (35). Thus, maintaining adequate vitamin D levels appears crucial for both MS and NSWMH.

According to the McDonald criteria, the spinal cord is a key location for demonstrating dissemination in space (11). However, in our study, no spinal cord lesions were observed in any of the patients who underwent spinal imaging to assess for demyelinating features. Additionally, CSF findings from all patients who underwent lumbar puncture were normal, with only OCB type 1 detected.

Published data on NSWMH are sparse, leading to a lack of consensus on the required frequency of MRI follow-ups when NSWMHs are detected. In our study, the development of new lesions was noted in two patients during the first follow-up MRI, but no further changes were observed in subsequent MRIs over a prolonged period. In each case, the newly developed lesion was subcortical and did not alter the initial diagnosis.

While conventional structural MRI is highly sensitive in detecting white matter hyperintensities, it does not specifically pinpoint the underlying cause of these changes (36). However, there is growing evidence suggesting that new imaging techniques may be able to differentiate between MS lesions and NSWMHs more effectively. Recent studies have highlighted the utility of functional MRI, which measures changes in the blood oxygen level-dependent (BOLD) signal and cerebral blood flow (CBF), in distinguishing MS lesions from NSWMHs (37).

Additionally, optical coherence tomography (OCT) has proven effective in differentiating between MS and NSWML patients. Siger et al. (38) found that the ganglion cell-inner plexiform layer and the macular retinal nerve fiber layer were significantly thinner in MS patients compared to those with NSWML. In addition to exploring novel diagnostic methods, our previous study reported on the utility of VEP, which has been used for many years to diagnose demyelinating diseases. VEPs may demonstrate decreased amplitude or prolonged latency (or both) in MS patients, while typically yielding normal results in patients with NSWMH (39).

The strength of our study lies in providing data on the long-term follow-up of patients with NSWMH. However, our study has limitations due to its observational cohort design and the lack of a controlled setting. Another limitation could be its retrospective nature. Particularly concerning MRI, different protocols could have been employed. Prospective studies with comprehensive follow-ups are warranted.

CONCLUSION

Today, MRI stands as the most sensitive diagnostic tool for MS, yet it can sometimes lead to diagnostic confusion. Nonetheless, MS is primarily diagnosed based on clinical evaluation, where a detailed history and routine neurological examination are crucial. Careful interpretation and integration of MRI findings are essential in diagnosing a patient, and MS neurologists are needed in challenging cases.

Contribution Categories		Author Initials
Category 1	Concept/Design	N.K.
	Data acquisition	S.O., S.Y.A., E.S.
	Data analysis/Interpretation	S.Y.A., N.K.T.
Category 2	Drafting manuscript	N.K.T.
	Critical revision of manuscript	N.K.
Category 3	Final approval and accountability	N.K.
Other	Technical or material support	S.O.

Ethical Approval: The Medipol University Clinical Research Ethics Committee granted approval for this study (date: 06.01.2022, number: E-10840098-772.02-108).

Conflict of Interest: The authors declare that they have no conflict of interest.

Informed Consent: Informed consent was obtained from all participants.

Use of AI for Writing Assistance: Not declared.

Financial Disclosure: The authors declare that they have no financial support.

Peer-review: Externally peer-reviewed.

REFERENCES

1. Schmidt R, Berghold A, Jokinen H, Gouw AA, van der Flier WM, Barkhof F, et al. White matter lesion progression in LADIS: frequency, clinical effects, and sample size calculations. Stroke 2012; 43:2643-2647. [CrossRef]
2. Aliaga ES, Barkhof F. MRI mimics of multiple sclerosis. Handb Clin Neurol 2014; 122:291-316. [CrossRef]
3. de Leeuw FE, de Groot JC, Achten E, Oudkerk M, Ramos LM, Heijboer R, et al. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. J Neurol Neurosurg Psychiatry 2001; 70:9-14. [CrossRef]
4. Liao D, Cooper L, Cai J, Toole JF, Bryan NR, Hutchinson RG, et al. Presence and severity of cerebral white matter lesions and hypertension, its treatment, and its control. The ARIC Study. Atherosclerosis Risk in Communities Study. Stroke 1996; 27:2262-2270. [CrossRef]
5. Longstreth WT Jr, Manolio TA, Arnold A, Burke GL, Bryan N, Jungreis CA, et al. Clinical correlates of white matter findings on cranial magnetic resonance imaging of 3301 elderly people. The Cardiovascular Health Study. Stroke 1996; 27:1274-1282. [CrossRef]
6. Toledano M, Weinshenker BG, Solomon AJ. A Clinical approach to the differential diagnosis of multiple sclerosis. Curr Neurol Neurosci Rep 2015; 15:57. [CrossRef]
7. Rolak LA, Fleming JO. The differential diagnosis of multiple sclerosis. Neurologist 2007; 13:57-72. [CrossRef]
8. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, et al. Recommended diagnostic criteria for multiple sclerosis: Guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurol 2001; 50:121-127.
9. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol 2005; 58:840-846. [CrossRef]
10. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011; 69:292-302. [CrossRef]
11. Thompson AJ, Banwell BL, Barkhof F, Carroll WM, Coetzee T, Comi G, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018; 17:162-173. [CrossRef]

12. Filippi M, Rocca MA, Ciccarelli O, De Stefano N, Evangelou N, Kappos L, et al. MRI criteria for the diagnosis of multiple sclerosis: MAGNIMS consensus guidelines. Lancet Neurol 2016; 15:292-303. [CrossRef]

13. Okuda DT, Mowry EM, Beheshtian A, Waubant E, Baranzini SE, Goodin DS, et al. Incidental MRI anomalies suggestive of multiple sclerosis: the radiologically isolated syndrome. Neurology 2009; 72:800-805. [CrossRef]

14. Solomon AJ, Klein EP, Bourdette D. "Undiagnosing" multiple sclerosis: the challenge of misdiagnosis in MS. Neurology 2012; 78:1986-1991. [CrossRef]

15. Solomon AJ, Bourdette DN, Cross AH, Applebee A, Skidd PM, Howard DB, et al. The contemporary spectrum of multiple sclerosis misdiagnosis: A multicenter study. Neurology 2016; 87:1393-1399. [CrossRef]

16. Solomon AJ, Weinshenker BG. Misdiagnosis of multiple sclerosis: frequency, causes, effects, and prevention. Curr Neurol Neurosci Rep 2013; 13:403. [CrossRef]

17. Orton SM, Herrera BM, Yee IM, Valdar W, Ramagopalan SV, Sadovnick AD, et al. Sex ratio of multiple sclerosis in Canada: A longitudinal study. Lancet Neurol 2006; 5:932-936. [CrossRef]

18. Westerlind H, Boström I, Stawiarz L, Landtblom AM, Almqvist C, Hillert J. New data identify an increasing sex ratio of multiple sclerosis in Sweden. Mult Scler 2014; 20:1578-1583. [CrossRef]

19. Leray E, Moreau T, Fromont A, Edan G. Epidemiology of multiple sclerosis. Rev Neurol (Paris) 2016; 172:3-13. [CrossRef]

20. Naseri A, Nasiri E, Sahraian MA, Daneshvar S, Talebi M. Clinical features of late-onset multiple sclerosis: A systematic review and meta-analysis. Mult Scler Relat Disord 2021; 50:102816. [CrossRef]

21. Katz Sand I. Classification, diagnosis, and differential diagnosis of multiple sclerosis. Curr Opin Neurol 2015; 28:193-205. [CrossRef]

22. Marcus DA. Sex hormones and chronic headache in women. Expert Opin Pharmacother 2001; 2:1839-1848. [CrossRef]

23. Hellström B, Lundberg U. Pain perception to the cold pressor test during the menstrual cycle in relation to estrogen levels and a comparison with men. Integr Physiol Behav Sci 2000; 35:132-141.

24. Stone J, Carson A, Duncan R, Coleman R, Roberts R, Warlow C, et al. Symptoms "unexplained by organic disease" in 1144 new neurology out-patients: How often does the diagnosis change at follow-up? Brain 2009; 132:2878-2888. [CrossRef]

25. Carson AJ, Ringbauer B, Stone J, McKenzie L, Warlow C, Sharpe M. Do medically unexplained symptoms matter? A prospective cohort study of 300 new referrals to neurology outpatient clinics. J Neurol Neurosurg Psychiatry 2000; 68:207-210. [CrossRef]

26. U.S. Food and Drug Administration. FDA Drug Safety Communication: FDA evaluating the risk of brain deposits with repeated use of gadolinium-based contrast agents for magnetic resonance imaging (MRI). https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-evaluating-risk-brain-deposits-repeated-use-gadolinium-based. Accessed Apr 25, 2024.

27. Kocsis K, Szabó N, Tóth E, Király A, Faragó P, Kincses B, et al. Two classes of T1 hypointense lesions in multiple sclerosis with different clinical relevance. Front Neurol 2021; 12:619135.

28. Truyen L, van Waesberghe JH, van Walderveen MA, van Oosten BW, Polman CH, Hommes OR, et al. Accumulation of hypointense lesions ("black holes") on T1 spin-echo MRI correlates with disease progression in multiple sclerosis. Neurology 1996; 47:1469-1476. [CrossRef]

29. Neema M, Guss ZD, Stankiewicz JM, Arora A, Healy BC, Bakshi R. Normal findings on brain fluid-attenuated inversion recovery MR images at 3T. AJNR Am J Neuroradiol 2009; 30:911-916.

30. Schmidt R, Schmidt H, Haybaeck J, Loitfelder M, Weis S, Cavalieri M, et al. Heterogeneity in age-related white matter changes. Acta Neuropathol 2011; 122:171-185. [CrossRef]

31. Sze G, De Armond SJ, Brant-Zawadzki M, Davis RL, Norman D, Newton TH. Foci of MRI signal (pseudo lesions) anterior to the frontal horns: Histologic correlations of a normal finding. AJR Am J Roentgenol 1986; 147:331-337. [CrossRef]

32. Bashir A, Lipton RB, Ashina S, Ashina M. Migraine and structural changes in the brain: A systematic review and meta-analysis. Neurology 2013; 81:1260-1268. [CrossRef]

33. Wen W, Sachdev P. The topography of white matter hyperintensities on brain MRI in healthy 60- to 64-year-old individuals. Neuroimage 2004; 22:144-154. [CrossRef]

34. Prager JM, Thomas C, Ankenbrandt WJ, Meyer JR, Gao Y, Ragin A, et al. Association of white matter hyperintensities with low serum 25-hydroxyvitamin D levels. AJNR Am J Neuroradiol 2014; 35:1145-1149. [CrossRef]

35. Pierrot-Deseilligny C, Souberbielle JC. Vitamin D and multiple sclerosis: An update. Mult Scler Relat Disord 2017; 14:35-45.

36. Geraldes R, Ciccarelli O, Barkhof F, De Stefano N, Enzinger C, Filippi M, et al; MAGNIMS study group. The current role of MRI in differentiating multiple sclerosis from its imaging mimics Nat Rev Neurol 2018; 14:199-213. Erratum in: Nat Rev Neurol 2018; 14:213. [CrossRef]

37. Sivakolundu DK, West KL, Zuppichini MD, Wilson A, Moog TM, Blinn AP, et al. BOLD signal within and around white matter lesions distinguishes multiple sclerosis and non-specific white matter disease: A three-dimensional approach. J Neurol 2020; 267:2888-2896. [CrossRef]

38. Siger M, Owidzka M, Świderek-Matysiak M, Omulecki W, Stasiołek M. Optical Coherence tomography in the differential diagnosis of patients with multiple sclerosis and patients with MRI nonspecific white matter lesions. Sensors (Basel) 2021; 21:7127. [CrossRef]

39. Kaya Tutar N, Omerhoca S, Soylemez E, Adatepe T, Kale Icen N. The role of visual evoked potentials in the differential diagnosis of demyelinating diseases. Turk J Neurol 2021; 27:366-370. [CrossRef]