Turkish Journal of Neurology

Turk J Neurol 2025;31(2):186-195
Doi: 10.55697/tnd.2025.262

ORIGINAL ARTICLE

Cognitive functions in radiologically isolated syndrome

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ABSTRACT

Objectives: The study aimed to evaluate the cognitive functions of cases diagnosed with radiologically isolated syndrome (RIS), and to analyze the correlation between cognitive functions, lesion location, the number of lesions detected on magnetic resonance imaging, and the presence of oligoclonal bands in cerebrospinal fluid.

Patients and methods: The retrospective study included 28 patients (4 males, 24 females; mean age: 32.1±8.3 years; range, 18 to 50 years) diagnosed with RIS according to the Magnetic Resonance Imaging in Multiple Sclerosis criteria between June 2019 and November 2020 and 28 healthy individuals (5 males, 23 females; mean age: 34.4±10.1 years; range, 20 to 51 years) matched for age, educational level, and sex. The Brief International Cognitive Assessment for Multiple Sclerosis was used for cognitive evaluation.

Results: The scores of the Symbol Digit Modalities Test, California Verbal Learning Test-II, and Brief Visuospatial Memory Test-Revised were significantly lower in the patient group compared to the control group. However, no significant relationship was found between the cognitive test scores of the patients and the total number of lesions, location of lesions, oligoclonal bands, and immunoglobulin G index.

Conclusion: Subclinical cognitive impairment in RIS patients is most likely due to the demyelinating process and RIS is likely to represent a preclinical or subclinical stage of multiple sclerosis. Therefore, all RIS cases should be evaluated and monitored for cognitive impairment to allow for early diagnosis and treatment.

Keywords: Cognitive functions, multiple sclerosis, radiologically isolated syndrome.

Radiologically isolated syndrome (RIS) is a term used for defining a group of asymptomatic subjects with brain magnetic resonance imaging (MRI) abnormalities suggestive of multiple sclerosis (MS). In the largest RIS cohort study to date, it was reported that in patients diagnosed with RIS, the first clinical event developed within five years in 34% of the cases[1] and within 10 years in 51.2% of the cases.[2] These accumulated data have led to the view that RIS represents a preclinical or subclinical stage of MS and that individuals with RIS may have mild and unnoticeable symptoms and signs.[3] This view is supported by the detection of cognitive impairment in RIS by cognitive tests.[4,5] Cognitive impairment has been reported in 40 to 70% of patients with MS,[6] in 20 to 57% of patients with clinically isolated syndrome (CIS),[4,7,8] and in 21-33% of subjects with RIS.[4,5,9] Moreover, the cognitive impairment pattern of RIS and CIS is highly similar to that of MS. Information processing speed, executive functions, and memory are the most impaired cognitive areas in RIS cases, as in MS patients.[4,5,9,10,11] The only recently published study in Türkiye was on pediatric RIS patients.[12] In this study, sustained attention, visual-motor coordination, short-term memory skills, and ability to use visual-spatial information were found to be relatively worse in the RIS group. However, another study showed that cognitive functions were not significantly different between RIS and control groups.[13] Scientists, consortiums, and working groups dealing with MS have been trying to diagnose MS earlier for years since it is commonly known that early diagnosis and early treatment

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Received: September 12, 2024 **Accepted:** April 07, 2025 **Published online:** June 02, 2025
Cite this article as: Soydar P, Mavioğlu H. Cognitive functions in radiologically isolated syndrome. Turk J Neurol 2025;31(2):186-195. doi: 10.55697/tnd.2025.262.

lead to better disease control and also prevent the progression of disability in MS. Radiologically Isolated Syndrome Consortium (RISC) reported that age, positive cerebrospinal fluid (CSF) findings, infratentorial (IT) lesions on MRI, and spinal cord lesions were baseline independent predictors associated with a subsequent clinical event.[2] The presence of gadolinium enhancing lesions during follow-up was also associated with the risk of a clinical event. The Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) working group reviewed the diagnostic criteria of RIS in 2018 and proposed the criteria for distinguishing cases with a high risk of conversion to MS. They defined this group as subclinical MS and published their recommendations.[3] In a very recent report published by RISC suggested that at five years, the risk stratification for presenting a clinical event was <10% in RIS subjects with one or two lesions in two locations without risk factor, 16% with one risk factor, and nearly 50% with more than two risk factors. The presence of spinal cord lesions on the index scan, CSF-restricted oligoclonal bands (OCBs), and the presence of new T2 or gadolinium-enhancing lesions on follow-up scans were risk factors.[14] Cognitive impairment was found to be a predicting factor for conversion from CIS to MS, and the authors reported that 64% of CIS patients failing ≥2 cognitive tests and 88% of patients failing ≥3 cognitive tests converted to MS during the follow-up.[7] On the contrary, in a study conducted with RIS cases, no significant difference was found between patients that converted to MS during the follow-up and those that did not with regard to cognitive functions.[11] Nevertheless, Cortese et al.[15] reported that previously healthy Norwegian males developed their first clinical MS symptoms within the first two years after the cognitive examination scored significantly lower than the controls.

According to the data of most studies, cognitive dysfunctions are not uncommon in demyelinating pathologies. However, they are likely often overlooked since they are usually not severe enough to be noticed and not included in routine evaluation and measurement. Accumulation of strong evidence about the prevalence and predictive value of cognitive dysfunctions in RIS will allow for early and cost-effective diagnosis of MS. Therefore, there is a need for more and larger studies investigating the prevalence and predictive value of cognitive dysfunction in people diagnosed with RIS. Hence, this study aimed to contribute to the data on this subject.

PATIENTS AND METHODS

The retrospective study included 28 patients (4 males, 24 females; mean age: 32.1±8.3 years; range, 18 to 50 years) who presented to the neurology outpatient clinic of the Manisa Celal Bayar University Faculty of Medicine between June 2019 and November 2020 with a headache or nonspecific complaints along with normal neurological findings and were detected with lesions consistent with MS on MRI. All the patients were at least primary school graduates and were diagnosed with RIS according to the MAGNIMS recommendations for diagnosis and management of RIS and subclinical MS.[16] Subjects with a history of neurological diseases, major depression, other psychiatric diseases, alcohol and substance addiction, and severe metabolic systemic disease that could impair cognition were excluded from the study. No immunological, rheumatologic, or viral diseases were detected in any patient. A control group of 28 healthy individuals (5 males, 23 females; mean age: 34.4±10.1 years; range, 20 to 51 years) who matched the patient group in terms of age, sex, and educational level and did not have any cognitive symptoms, history of any diseases, and vascular risk factors was selected from a study conducted in our clinic, which aimed to gather normative data for the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery. A written informed consent was obtained from each patient. The study protocol was approved by the Manisa Celal Bayar University Faculty of Medicine Ethics Committee (Date: 25.06.2019, No: 27071). The study was conducted in accordance with the principles of the Declaration of Helsinki.

A cranial MRI was performed using two 1.5T MRI scanners (Signa HDx; GE Healthcare, Milwaukee, WI, USA; and Magnetom Area; Siemens Healthineers, Erlangen, Germany) with the same protocol. After three-plane localization and calibration imaging, the MRI protocol included sagittal two-dimensional (2D) T2-FLAIR (fluid-attenuated inversion recovery), axial 2D precontrast T1-weighted turbo spin echo, axial T2-weighted turbo spin echo, and axial 2D FLAIR sequences. In all cases, contrast agent was injected, and after waiting for at least 5 min, postcontrast axial, coronal, and sagittal sequences and axial DWI (diffusion-weighted imaging) sequences were obtained. Images were evaluated by both a neuroradiologist and a MS-specific neurologist. In cases with interreader discrepancy, the subject

TABLE 1
Demographic characteristics of the groups

	RIS group			Control group			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)**			32.1±8.3			34.4±10.1	0.343*
Sex							0.716**
Male	4	14.3		5	17.9		
Female	24	85.7		23	82.1		
Mean education duration**			10.893±3.95			10.750±4.43	0.899

RIS: Radiologically isolated syndrome; SD: Standard deviation; * T-test; ** Chi-square test.

was excluded from the study. In MRI, the number of periventricular (PV), juxtacortical (JC), cortical, IT, corpus callosum (CC), subcortical (SC)/deep white matter, and spinal lesions, as well as the total number of lesions, were visually evaluated and recorded.

In some cases, visual evoked potentials (VEPs) were performed, and OCBs and immunoglobulin G (IgG) indices were examined in CSF. Isoelectric focusing was used in the evaluation of OCBs in CSF, and a nephelometer was used to calculate the IgG index in the Ondokuz Mayıs University, Neuroimmunology Laboratory.

The BICAMS battery,[17] which was validated for Turkish MS patients,[18] was used for cognitive evaluation. The BICAMS battery included the Symbol Digit Modalities Test (SDMT), California Verbal Learning Test-II (CVLT-II), and Brief Visuospatial Memory Test-Revised (BVMT-R) and was administered by a trained neurologist. Cognitive assessment was performed within a maximum period of three months after MRI examination.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 23.0 software (IBM Corp., Armonk, NY, USA). Demographic data of the patients and controls, including age, sex, and mean education period, were evaluated using a t-test and the chi-square test. The SDMT, CVLT-II, and BVMT-R scores of the RIS and control groups were compared using a t-test. The relationship between cognitive tests and demographic characteristics, such as age and education duration, was examined using Pearson's correlation coefficient. Logistic and linear regression analyses were used for multivariate analysis. Correlations between cognitive tests and the number of PV, JC, cortical, IT, CC, spinal,

TABLE 2
Demographic characteristics and MRI findings in patients with RIS

	n	%	Mean±SD
Age (year)			32.1±8.3
Sex			
Male	4	14.3	
Female	24	85.7	
Mean education duration (year)			10.9±4.0
MRI lesions			
Periventricular lesion	28	100	4.07±2.32*
Juxtacortical lesion	26	92.9	1.67±0.98*
Cortikal lesion	6	21.4	0.50±1.23*
Subcortical-deep white matter lesion	28	100	4.64±3.29*
Corpus callosum lesion	10	35.7	0.53±0.92*
Infratentorial lesion	3	10.7	0.21±0.68*
Spinal lesion	3	10.7	0.25±0.87*

MRI: Magnetic resonance imaging; RIS: Radiologically isolated syndrome; SD: Standard deviation; * Mean number of lesions.

TABLE 3
Cognitive test scores of the RIS and control groups

	RIS group	Control group	
	Mean±SD	Mean±SD	*p**
SDMT	32.929±11.84	41.357±15.39	0.026
CVLT-II	47.821±7.50	53.393±7.95	0.009
BVMT-R	19.500±7.24	25.536±8.67	0.007

RIS: Radiologically isolated syndrome; SD: Standard deviation; SDMT: Symbol Digit Modalities Test; CVLT-II: California Verbal Learning Test-II; BVMT-R: Brief Visuospatial Memory Test-Revised.

TABLE 4
Correlation between cognitive tests and demographics factors in the RIS group

	SDMT	CVLT-II	BVMT-R
Age			
r	−0.428	−0.410	−0.376
p	0.023	0.030	0.049
Education period			
r	0.752	0.540	0.709
p	0.000	0.003	0.000

RIS: Radiologically isolated syndrome; SDMT: Symbol Digit Modalities Test; CVLT-II: California Verbal Learning Test-II; BVMT-R: Brief Visuospatial Memory Test-Revised; Pearson correlation coefficient test.

SC, and deep white matter lesions and the total number of lesions were assessed using Pearson's correlation coefficient. The relationship between cognitive test scores and OCBs, IgG index, and VEP was evaluated using the Kruskal-Wallis test. Since the sample size was small, we performed a post hoc power analysis. According to the post hoc power analysis result, the power of the test was determined as 82% when 28 samples were taken with the effect size obtained in the study findings. This power was within acceptable limits. A p-value <0.05 was considered statistically significant.

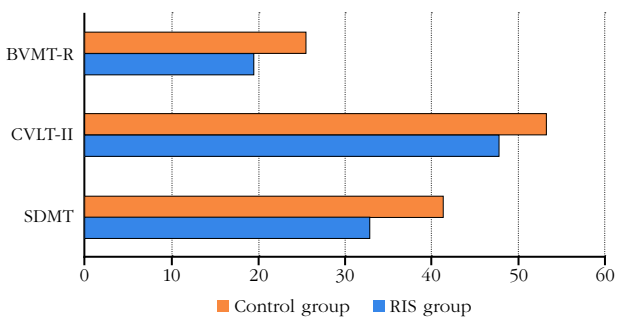

Figure 1. The BICAMS subtest scores of RIS and control groups.

BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis; RIS: Radiologically isolated syndrome; BVMT-R: Brief Visuospatial Memory Test-Revised; CVLT-II: California Verbal Learning Test-II; SDMT: Symbol Digit Modalities Test.

RESULTS

No significant difference was found between the patient and control groups with regard to demographic characteristics including age, educational level, and sex (Table 1). Demographic characteristics and MRI findings in RIS patients are summarized in Table 2. The scores of SDMT, CVLT-II, and BVMT-R were significantly lower in the patient group than in the control group (Table 3, Figure 1). All three cognitive tests showed a mild-to-moderate but significant inverse correlation with age in the RIS group. Moreover, there was a moderate-to-strong positive correlation with the level of education (Table 4). Nevertheless, due to the small number of male patients (n=4) as opposed to female patients (n=24) in the RIS group, the relationship between sex and cognitive tests could not be evaluated statistically. The difference found for SDMT, CVLT-II, and BVMT-R between the two groups in univariate analyzes was reevaluated (Nagelkerke R^2=0.44) with multivariate analysis (variables included in the model were age, sex, education level, SDMT, CVLT-II, and BVMT-R). Compared to do patient group, the control group was found to have a CVLT multivariate OR of 1.125 [95% CI: 1.005-1.258] and BVMT mutivariate OR of 1.173 [95% CI: 1.038-1.326] times higher.

A CSF examination was performed in 46.4% of the patients. Oligoclonal band type 2 was found to be positive in 61.5% of the patients. The IgG index was assessed in 53.6% of the patients, and it was found to be high in 33.3% of these patients. Additionally, VEP was recorded in 71.4% of the patients, and conduction prolongation was found in 20% of them. However, no significant relationship was found between cognitive scores, OCB, and IgG index, and VEP (Table 5). Likewise, no significant relationship was detected between any cognitive test score, the total number of

TABLE 5
Relationship between cognitive tests and OCB and IgG indices and VEP

	Positivity ratio		SDMT	CVLT-II	BVMT-R
	n	%	*p*	*p*	*p*
OCB	8/13	61.5	0.579	0.480	0.678
IgG index	5/15	33.3	0.661	0.458	0.832
VEP	4/20	20	0.363	0.314	0.963

OCB: Oligoclonal banding; IgG: Immunoglobulin G; VEP: Visual evoked potential; SDMT: Symbol Digit Modalities Test; CVLT-II: California Verbal Learning Test-II; BVMT-R: Brief Visuospatial Memory Test-Revised; * Kruskal-Wallis test.

TABLE 6
Correlations between cognitive tests and lesion locations and numbers of lesions

	SDMT	CVLT-II	BVMT-R
Periventricular			
r	0.141	0.205	0.062
p	0.473	0.297	0.756
Juxtacortical			
r	0.-256	−0.419	−0.236
p	0.188	0.076	0.226
Cortical			
r	0.-025	0.222	0.236
p	0.898	0.256	0.226
Infratentorial			
r	0.029	0.080	−0.141
p	0.882	0.687	0.473
Corpus callosum			
r	0.081	0.123	0.043
p	0.686	0.542	0.830
Spinal			
r	−0.036	0.258	0.294
p	0.870	0.234	0.173
Subcortical/deep white matter			
r	0.078	0.057	0.070
p	0.693	0.772	0.724
Total number of lesions			
r	0.070	0.140	0.094
p	0.724	0.477	0.634

SDMT: Symbol Digit Modalities Test; CVLT-II: California Verbal Learning Test-II; BVMT-R: Brief Visuospatial Memory Test-Revised.

lesions, and the number of lesions in different locations (Table 6).

DISCUSSION

Literature indicates that the first clinical event suggestive of MS occurs in 34% of RIS cases within five years[1] and in 51.2% of the cases within 10 years.[2] These data have led to the view that the RIS may be the preclinical or subclinical phase of MS. In 2018, the MAGNIMS working group proposed some recommendations for the diagnosis and management of RIS. At the same time, the authors suggested that individuals with RIS who have MRI risk factors for conversion to MS were likely to have a subclinical form of MS. The authors recommended active monitoring of these patients with periodical (every six to 12 months) clinical and radiological follow-up.[3] They also argued that RIS patients are truly asymptomatic and that subjects with RIS may have mild and unnoticeable symptoms and signs. Accordingly, cognitive impairment, which has been confirmed in 21.4 to 33% of subjects with RIS, may be one of these mild and unnoticeable symptoms and signs.[4,5,9] Moreover, the cognitive impairment pattern of RIS cases is similar to that of MS.[4,5,9,10] Perhaps the first symptoms of individuals with RIS are subclinical cognitive impairment. There are other data to support this view. Patients with MS with isolated cognitive impairment attacks have been reported.[19] Cortese et al.[15] reported that previously healthy Norwegian males developing first clinical MS symptoms within two years after the cognitive examination scored significantly lower than controls.

In the present study, we found that the mean scores of SDMT, CVLT-II, and BVMT-R were significantly lower in the RIS group than in the control group (Table 3, Figure 1). In the literature, some studies on cognitive functions in RIS reported cognitive impairment, while others reported no significant difference when compared to controls. For the first time, Lebrun et al.[10] reported the cognitive functions in a cohort of 26 RIS cases in 2020. They assessed the cognitive functions of 26 patients with RIS and compared them with 26 patients with MS and 26 healthy subjects matched for age, sex, and level of education. The results indicated that information processing speed, executive functions, and short-term memory were found to be the most impaired cognitive areas in RIS patients, similar to those of patients with MS. Likewise, subsequent studies using the Rao-BRNB battery (Rao-Brief Repeatable Neuropsychological Battery) and additional cognitive tests reported cognitive dysfunctions in RIS with a similar profile in patients with MS.[4,9,20] In another study, the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS) battery was applied to 27 patients with RIS, and cognitive impairment was detected in 37% of the cases.[5] By contrast, in some other studies, cognitive test results in patients with RIS were found to be lower than some of the cognitive test results in controls, while no significant difference was found.[12,13] Recently, the cognitive functions of 31 people diagnosed with RIS and 19 control groups were evaluated with BICAMS, and no significant difference was found between the two groups, while CVLT-II scores were found to be lower in patients with RIS than in the control group.[13] From these findings, it can be inferred that while most of the studies on cognitive functions in RIS reported cognitive impairment compared to controls, some reported no significant difference. In addition, the numbers of cases in all of these studies were remarkably low.

Radiologically isolated syndrome is not yet accepted as a disease or as a distinct MS phenotype and thus has no standard treatment. Early diagnosis and disease-modifying treatment have been shown to reduce disease activity and disability accumulation in MS and to delay conversion from CIS to MS. Detecting RIS with high risk for conversion to MS and initiating early treatment may prevent conversion from RIS to CIS and MS. To predict conversion, there is a need for strong predictors. Studies reported that MRI parameters were the strongest predictors of conversion from RIS to MS and that contrast-enhancing lesions, T2 lesion load, and the presence of IT lesions, particularly spinal lesions, had a predictive value in conversion from RIS to MS.[2,14,19,21] Nevertheless, data on other MRI parameters such as PV, JC,[1,22,23] cortical,[24] and CC lesions and general or focal atrophy of the brain[23,25] are contradictory. In the largest RIS cohort study to date, other predictive factors were found to include positive CSF findings and age.[2] The authors reported that the probability of a first clinical event within a 10-year follow-up was 29% in individuals with at least one risk factor, 54% in individuals with two risk factors, 68% in individuals with three risk factors, and 87% in individuals with four risk factors. In a very recent report published by RISC, it was suggested that at five years, the risk stratification for presenting a clinical event was <10% in RIS subjects with one or two lesions in two locations without a risk

factor, 16% with one risk factor, and nearly 50% with more than two risk factors.[14] Additionally, the presence of spinal cord lesions on the index scan, CSF-restricted OCBs, and the presence of new T2 or gadolinium-enhancing lesions on follow-up scans were reported as risk factors. Nevertheless, the predictive value of cognitive functions was not evaluated in these studies. Cognitive impairment was found as a predicting factor for conversion from CIS to MS, and the authors reported that 64% of patients with CIS failing ≥2 cognitive tests and 88% of patients failing ≥3 cognitive tests converted to MS during the follow-up.[7] In a follow-up study conducted with 1500 patients with MS with the MSGA (MindStreams GA) battery, Achiron et al.[26] detected cognitive impairment with a similar profile to that of CIS, relapsing-remitting MS (RRMS), primary-progressive MS, and, particularly, secondary-progressive MS. Menascu et al.[11] suggested that cognitive impairment started 1.2 years before the onset of MS with the regression model, whereas no significant difference was found between the cognitive functions of patients with RIS who converted to MS during the follow-up and those who did not. In that study, however, the number of cases that converted to MS was small, and the cognitive functions of the cases with RIS were poorer than those of controls at baseline, although no significant difference was found. In a study conducted with the Rao-BRNB battery in 2021, the cognitive functions of 17 patients with RIS and 17 controls were compared, and a significant decrease was found in at least two cognitive tests in 35.5% of patients with RIS.[20] In the same study, during the 4.5-year follow-up period, it was observed that the group with cognitive dysfunction had a high rate of conversion to MS. This suggests that cognitive impairment may be an independent risk factor for conversion to MS. In another study, olfactory test scores of RRMS and RIS patients were significantly different from those in the control group ($p<0.05$).[27] Of note, there was a significant difference between the odor threshold scores of patients in the RRMS and RIS groups. In addition, there was a significant correlation between memory-oriented cognitive tests and olfactory tests in the RRMS and RIS groups.

In our study, no significant correlation was found between the cognitive test scores of the patients with RIS and the number of PV, JC, IT, spinal, cortical, CC, SC, and deep white matter lesions and the total number of lesions on MRI (Table 6). To our knowledge, only a few studies investigated the relationship between cognitive impairment and MRI parameters in RIS, and the findings were contradictory.[5,9,10] Some of these studies found a relationship,[5,9,20] while others did not find any relationship between cognitive impairment and MRI parameters.[10,13] Lebrun et al.[10] found no significant correlation between the cognitive functions and the number of PV, JC, and IT lesions, total number of lesions, and contrast enhancement. A more recent study also found no relationship between gadolinium-enhanced lesions or spinal lesions and cognitive impairment.[13] Amato et al.[9] reported that the cognitive impairment detected in RIS cases was associated with high T1 lesion volume and low cortical volume. Domingo-santos et al.[20] assessed 17 patients with RIS and 17 matched healthy controls with a neuropsychological battery and a 3T MRI. Six patients (35.3%) fulfilled their criterion for cognitive impairment (ci-RIS). The ci-RIS subgroup showed lower values of normalized brain and gray matter volumes compared to healthy controls. After a median follow-up of 4.5 years, the ci-RIS subgroup presented a higher conversion rate to MS, suggesting that cognitive impairment might be an independent risk factor for conversion to MS. Stromillo et al.[28] reported that N-acetylaspartate-to-creatine ratio was significantly lower in the brain of 23 patients with RIS compared to that of healthy controls, suggesting that the pathologic process was active in patients with RIS. In a study conducted with quantitative MRI techniques, lesion load, distribution, number, and brain volume were found to be similar in the RIS and RRMS groups, whereas the magnetization transfer (MT) ratio in the lesion was found to be lower in the RRMS group compared to the RIS group.[29] Although the MT ratio in normal-appearing white matter and cortex was low in RRMS, it was similar in RIS and controls. Based on their findings, the authors suggested that more than 70% of cases with RIS could be classified as RRMS based on brain volume and lesion MT ratios and logistic regression analysis. Literature indicates that permanent and progressive cognitive impairment in MS is due to diffuse axonal damage, brain atrophy, and, hence, neurodegeneration.[30] Additionally, deterioration in information processing speed is also considered to be due to disconnection.[31,32] In our study, brain volume could not be calculated, and thus, its relationship with cognitive performance could not be examined. We consider that the findings reported on this subject are controversial, which could be due to three reasons. First, the number of studies and cases are low. Second, the number of lesions in RIS patients is remarkably low.

Third, the demyelinating and degenerative process may have started in the normal-appearing brain tissue. The lack of prospective MRI scanning or quantitative imaging techniques (e.g., volumetric analysis or diffusion tensor imaging) in our study limits the scope of the findings. Future directions should consider advanced imaging approaches.

In our study, a CSF examination was performed in 15 out of 28 patients with RIS, OCB was examined in 13 cases, and the IgG index was examined in 15 cases. Of these, eight cases were positive for OCB type 2, and the IgG index was high in five cases, although no significant correlation was found between OCB and IgG indices and cognitive test scores (Table 5). In most studies, it was reported that OCB positivity in CSF was predictive in terms of conversion to MS.[1,22,33-35] In some other studies, however, the predictive value of IgG index was found to be lower compared to that of OCB positivity.[19,36] In the largest RIS cohort study that evaluated RIS patients over a 10-year follow-up period, abnormalities were found in 65% of cases that underwent CSF examination.[2] In the same study, 30.4% of cases had OCB positivity, 7.7% only had IgG index elevation, and 61.8% of them both were found to be abnormal. The authors also noted that positive CSF was predictive in terms of conversion to MS. By contrast, in a similar way to our study, a more recent study reported that SDMT, CVLT-II, and BVMT-R scores did not differ significantly in patients with positive OCB compared to other patients.[13]

In the present study, VEP was performed in 71.4% of the patients and a pathology was detected in 20% of them. However, no significant relationship was found between VEP pathologies and cognitive test scores. Similarly, Lebrun et al.[10] found no significant relationship between VEP and cognition. In a similar study, authors reported that abnormal VEP findings had a predictive value in conversion to MS.[19]

The present study was limited since it had a small number of patients. Additionally, the MRI scans were not performed prospectively, and lesion assessment was based on visual evaluation rather than a specific study protocol.

In conclusion, consistent with the findings of most previous studies, our study showed that cognitive functions in patients with RIS were significantly lower than those of controls. This finding once again confirmed the necessity of routine monitoring of cognitive functions in patients with RIS, as well as those with CIS and MS. The recommendation for the evaluation and monitoring of cognitive functions of patients with RIS is likely to be incorporated into clinical guidelines in the near future for identifying people at high risk of conversion to MS. We could not find any significant relationship between cognitive scores and MRI parameters, as well as OCB and IgG indices in CSF and VEP pathologies, which may be due to the small number of cases. If the relationship between cognitive disorders and these parameters in the RIS stage can be demonstrated through larger-scale and well-designed studies, the predictive value of all parameters in terms of conversion to MS is likely to increase, allowing early diagnosis and treatment of MS.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Both authors contributed equally to this article.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Okuda DT, Siva A, Kantarci O, Inglese M, Katz I, Tutuncu M, et al. Radiologically isolated syndrome: 5-Year risk for an initial clinical event. PLoS One 2014;9:e90509. doi: 10.1371/journal.pone.0090509.
2. Lebrun-Frenay C, Kantarci O, Siva A, Sormani MP, Pelletier D, Okuda DT, et al. Radiologically isolated syndrome: 10-Year risk estimate of a clinical event. Ann Neurol 2020;88:407-17. doi: 10.1002/ana.25799.
3. De Stefano N, Giorgio A, Tintoré M, Pia Amato M, Kappos L, Palace J, et al. Radiologically isolated syndrome or subclinical multiple sclerosis: MAGNIMS consensus recommendations. Mult Scler 2018;24:214-21. doi: 10.1177/1352458517717808.
4. Labiano-Fontcuberta A, Martínez-Ginés ML, Aladro Y, Ayuso L, Mitchell AJ, Puertas-Martín V, et al. A comparison study of cognitive deficits in radiologically and clinically isolated syndromes. Mult Scler 2016;22:250-3. doi: 10.1177/1352458515591072.
5. Oh J, Suthiphosuwan S, Sati P, Absinta M, Dewey B, Guenette M, et al. Cognitive impairment, the central vein sign, and paramagnetic rim lesions in RIS. Mult Scler 2021;27:2199-208. doi: 10.1177/13524585211002097.
6. Rocca MA, Amato MP, De Stefano N, Enzinger C, Geurts JJ, Penner IK, et al. Clinical and imaging assessment of cognitive dysfunction in multiple sclerosis. Lancet Neurol 2015;14:302-17. doi: 10.1016/S1474-4422(14)70250-9.

7. Zipoli V, Goretti B, Hakiki B, Siracusa G, Sorbi S, Portaccio E, et al. Cognitive impairment predicts conversion to multiple sclerosis in clinically isolated syndromes. Mult Scler 2010;16:62-7. doi: 10.1177/1352458509350311.
8. Feuillet L, Reuter F, Audoin B, Malikova I, Barrau K, Cherif A, et al. Early cognitive impairment in patients with clinically isolated syndrome suggestive of multiple sclerosis. Mult Scler 2007;13:124-7. doi: 10.1177/1352458506071196
9. Amato MP, Hakiki B, Goretti B, Rossi F, Stromillo ML, Giorgio A, et al. Association of MRI metrics and cognitive impairment in radiologically isolated syndromes. Neurology 2012;78:309-14. doi: 10.1212/WNL.0b013e31824528c9.
10. Lebrun C, Blanc F, Brassat D, Zephir H, de Seze J. Cognitive function in radiologically isolated syndrome. Mult Scler 2010;16:919-25. doi: 10.1177/1352458510375707.
11. Menascu S, Stern M, Aloni R, Kalron A, Magalshvili D, Achiron A. Assessing cognitive performance in radiologically isolated syndrome. Mult Scler Relat Disord 2019;32:70-3. doi: 10.1016/j.msard.2019.04.030.
12. Okumuş A, Kara B, Sakarya Güneş A, Anık Y, Efendi H, Çoskun A. Evaluation of mental performance and cognitive functions of children and adolescents diagnosed with radiologically isolated syndrome. Mult Scler Relat Disord 2024:88:105735. doi: 10.1016/j.msard.2024.105735.
13. Carvalho V, Soares C, Gomes I, Carvalho A, Serrazina F, Rodrigues SG, et al. RISCOP-Cognitive profile in a Portuguese cohort of radiological isolated syndrome patients: A case-control study. Mult Scler Relat Disord 2021;50:102832. doi: 10.1016/j.msard.2021.102832.
14. Lebrun-Frénay C, Okuda DT, Siva A, Landes-Chateau C, Azevedo CJ, Mondot L, et al. The radiologically isolated syndrome: Revised diagnostic criteria. Brain 2023;146:3431-43. doi: 10.1093/brain/awad073.
15. Cortese M, Riise T, Bjørnevik K, Bhan A, Farbu E, Grytten N, et al. Preclinical disease activity in multiple sclerosis: A prospective study of cognitive performance prior to first symptom. Ann Neurol 2016;80:616-24. doi: 10.1002/ana.24769.
16. 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. doi: 10.1016/S1474-4422(15)00393-2.
17. Langdon DW, Amato MP, Boringa J, Brochet B, Foley F, Fredrikson S, et al. Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Mult Scler 2012;18:891-8. doi: 10.1177/1352458511431076.
18. Ozakbas S, Yigit P, Cinar BP, Limoncu H, Kahraman T, Kösehasanoğulları G. The Turkish validation of the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) battery. BMC Neurol 2017;17:208. doi: 10.1186/s12883-017-0993-0.
19. Lebrun C, Bensa C, Debouverie M, Wiertlevski S, Brassat D, de Seze J, et al. Association between clinical conversion to multiple sclerosis in radiologically isolated syndrome and magnetic resonance imaging, cerebrospinal fluid, and visual evoked potential: Follow-up of 70 patients. Arch Neurol 2009;66:841-6. doi: 10.1001/archneurol.2009.119.
20. Domingo-Santos Á, Labiano-Fontcuberta A, Aladro-Benito Y, Martínez-Ginés ML, Ayuso-Peralta L, Puertas-Martín V, et al. Predicting conversion to multiple sclerosis by assessing cognitive impairment in radiologically isolated syndrome. Mult Scler Relat Disord 2021;49:102749. doi: 10.1016/j.msard.2021.102749.
21. Okuda DT, Mowry EM, Cree BA, Crabtree EC, Goodin DS, Waubant E, et al. Asymptomatic spinal cord lesions predict disease progression in radiologically isolated syndrome. Neurology 2011;76:686-92. doi: 10.1212/WNL.0b013e31820d8b1d.
22. Makhani N, Lebrun C, Siva A, Brassat D, Carra Dallière C, de Seze J, et al. Radiologically isolated syndrome in children: Clinical and radiologic outcomes. Neurol Neuroimmunol Neuroinflamm 2017;4:e395. doi: 10.1212/NXI.0000000000000395.
23. Rojas JI, Patrucco L, Míguez J, Besada C, Cristiano E. Brain atrophy in radiologically isolated syndromes. J Neuroimaging 2015;25:68-71. doi: 10.1111/jon.12182.
24. Giorgio A, Stromillo ML, Rossi F, Battaglini M, Hakiki B, Portaccio E, et al. Cortical lesions in radiologically isolated syndrome. Neurology 2011;77:1896-9. doi: 10.1212/WNL.0b013e318238ee9b.
25. Azevedo CJ, Overton E, Khadka S, Buckley J, Liu S, Sampat M, et al. Early CNS neurodegeneration in radiologically isolated syndrome. Neurol Neuroimmunol Neuroinflamm 2015;2:e102. doi: 10.1212/NXI.0000000000000102.
26. Achiron A, Chapman J, Magalashvili D, Dolev M, Lavie M, Bercovich E, et al. Modeling of cognitive impairment by disease duration in multiple sclerosis: A cross-sectional study. PLoS One 2013;8:e71058. doi: 10.1371/journal.pone.0071058.
27. Arici Duz O, Saatci O, Karakulak EZ, Birday E, Hanoglu L. Olfactory dysfunction and cognition in radiologically isolated syndrome and relapsing-remitting multiple sclerosis. Eur Neurol 2021;84:175-82. doi: 10.1159/000514433.
28. Stromillo ML, Giorgio A, Rossi F, Battaglini M, Hakiki B, Malentacchi G, et al. Brain metabolic changes suggestive of axonal damage in radiologically isolated syndrome. Neurology 2013;80:2090-4. doi: 10.1212/WNL.0b013e318295d707.
29. De Stefano N, Stromillo ML, Rossi F, Battaglini M, Giorgio A, Portaccio E, et al. Improving the characterization of radiologically isolated syndrome suggestive of multiple sclerosis. PLoS One 2011;6:e19452. doi: 10.1371/journal.pone.0019452.
30. Costa BK, Sato DK. Time to target brain atrophy and neurodegeneration in multiple sclerosis. Arq Neuropsiquiatr 2016;74:181-2. doi: 10.1590/0004-282X20160028.

31. Calabrese P, Penner IK. Cognitive dysfunctions in multiple sclerosis--a "multiple disconnection syndrome"? J Neurol 2007;254 Suppl 2:II18-21. doi: 10.1007/s00415-007-2006-5.
32. Dineen RA, Vilisaar J, Hlinka J, Bradshaw CM, Morgan PS, Constantinescu CS, et al. Disconnection as a mechanism for cognitive dysfunction in multiple sclerosis. Brain 2009;132:239-49. doi: 10.1093/brain/awn275.
33. Etemadifar M, Janghorbani M, Koushki MM, Etemadifar F, Esfahani MF. Conversion from radiologically isolated syndrome to multiple sclerosis. Int J Prev Med 2014;5:1379-86.
34. Lebrun SA, Kantarci C, Azevedo C, Sormani MP, Pelletier D, Okuda D. Multi-center, randomized, double-blinded assessment of teriflunomide in extending the time to a first clinical event in radiologically isolated syndrome (RIS) (TERIS study). Multiple Sclerosis. Conference: 32nd Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS. 2016.
35. Matute-Blanch C, Villar LM, Álvarez-Cermeño JC, Rejdak K, Evdoshenko E, Makshakov G, et al Neurofilament light chain and oligoclonal bands are prognostic biomarkers in radiologically isolated syndrome. Brain 2018;141:1085-93. doi: 10.1093/brain/awy021.
36. Thouvenot E, Hinsinger G, Demattei C, Uygunoglu U, Castelnovo G, Pittion-Vouyovitch S, et al. Cerebrospinal fluid chitinase-3-like protein 1 level is not an independent predictive factor for the risk of clinical conversion in radiologically isolated syndrome. Mult Scler 2019;25:669-77. doi: 10.1177/1352458518767043.