Conversion from Radiologically Isolated Syndrome to Multiple Sclerosis

Masoud Etemadifar, Mohsen Janghorbani[1], Mohammad Mehdi Koushki, Fatemeh Etemadifar, Mahboobeh Fereidan Esfahani

Isfahan Multiple Sclerosis Society, Isfahan University of Medical Sciences, Isfahan, Iran, [1]Department of Epidemiology and Biostatistics, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran

Correspondence to:
Prof. Mohsen Janghorbani, Department of Epidemiology and Biostatistics, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran.
E-mail: janghorbani@hlth.mui.ac.ir

Date of Submission: Jun 30, 2014

Date of Acceptance: Sep 09, 2014

How to cite this article: 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.

ABSTRACT

Background: The aim of this study was to estimate the conversion rate from radiologically isolated syndrome (RIS) to definite multiple sclerosis (MS).

Methods: During a mean (standard deviation [SD]) follow-up period of 17.4 (5.4) (range 8-29) months, 25 subjects with RIS and without neurological symptom aged 22-45 year from a single-center have been examined for the occurrence of definite MS. The mean (SD) age of participants was 35.1 (6.2) years at first brain magnetic resonance imaging (MRI). The definite MS were assessed using the revised McDonald's criteria (2010).

Results: Six of 25 patients developed clinical symptom consistent with criteria for definite MS. The conversion rate from RIS to definite MS was 1.5 (95% confidence interval [CI] 0.54, 3.17) per 100 person-months based on 480 person-months of follow-up. Multivariate analysis revealed that presence of contrast-enhancing lesions on the initial MRI was marginally significantly associated with MS (hazard ratio 1.83, 95% CI 0.98, 3.45, $P = 0.060$).

Conclusions: This is the first estimate of conversion rate from RIS to definite MS in Iran. The conversion rates from RIS to definite MS in these participants are high and intensive follow-up and intervention strategies are recommended for these high-risk individuals. A larger study is warranted to assess this risk in greater detail.

Keywords: Conversion rate, Iran, longitudinal study, multiple sclerosis, predictors, radiologically isolated syndrome

Original Article

INTRODUCTION

Radiologically isolated syndrome (RIS) is defined as magnetic resonance imaging (MRI) findings suggestive of multiple sclerosis (MS) in persons without typical MS symptoms and with normal neurological findings.[1,2] It was first introduced in 2009[2] to define a cohort of individuals routinely encountered in clinical practice who are at risk for future demyelinating events. Evidence is growing that individuals with RIS are more likely to progress to symptomatic MS.[1-5] Approximately, two-third of individuals

with RIS shows radiological progression, and one-third of individuals with RIS develop neurological symptoms during mean follow-up periods of up to 5 years.[3] The conversion rate from RIS to MS was 65% after a mean follow-up of 5.3 years and 88% after a mean follow-up of 14.1 years.[4] Similarly, the risk of conversion to definite MS after 5 years in the optic neuritis treatment trial was 51% for persons with baseline brain MRI scans containing ≥3 lesions, compared with 16% in patients with no MRI lesions.[5]

Although some studies have estimated conversion rates from RIS to definite MS in selected populations,[1-5] none of them were undertaken in developing countries or in Iran. Due to the heterogeneity of MS, its recognized polygenic basis and dependence on environmental factors, there is a need for ethnically focused and country- or continent-specific studies of conversion from RIS to definite MS.

The objective of this study was therefore to estimate the conversion rate from RIS to definite MS and to conduct a preliminary investigation of the determinants of conversion to definite MS in a sample of patients in Iran.

METHODS

A total of 25 patients (17 men and 8 women) aged 22-45 years who fulfilled the Barkhof/Tintoré criteria for RIS[1] were evaluated prospectively during a mean (standard deviation [SD]) follow-up period of 17.4 (5.4) (range 8-29) months at the MS out-patient clinics of Isfahan University of Medical Sciences, Iran. After detection of silent MRI with lesions suggestive of inflammatory/demyelinating nature, all individuals underwent MRI study of the brain and cervical spinal cord that fulfilled dissemination in space (DIS) criteria for RIS.[2,6] A complete neurologic and medical history was obtained, and physical examination and comprehensive neurologic evaluation were performed. None of the patients had previously experienced remitting clinical symptoms consistent with neurologic dysfunction of the central nervous system.

In all cases, MRI abnormalities were identified by radiologists and verified by a neurologist (ME) to ensure DIS criteria were met.[2] A qualitative (i.e. geographical location within the brain or spinal cord, and morphology of lesions) and quantitative analysis (i.e. number of T2-foci, presence or absence of gadolinium enhancement) of the brain and cervical spine imaging studies was performed for all study participants. Cerebrospinal fluid (CSF) profile and longitudinal clinical and imaging data were obtained. The CSF was analyzed to determine cell count and a protein level, and oligoclonal bands were evaluated with an isoelectrofocusing method. The detection of oligoclonal bands was confirmed if more than one band that was not detected in the serum was present in the CSF. Patients with RIS were evaluated every 6 months after the start of the study to monitor conversion to definite MS, according to the revised McDonald's criteria.[6] Patients who had at least one new clinical event with documented new symptoms and signs were classified as having definite MS, defined as the development of an acute neurological episode localized to the optic nerve, brainstem, cerebellum, spinal cord, or long sensory or motor tracts, lasting >24 h followed by a period of symptom improvement or the onset of a clinical symptom (e.g. leg weakness).[6] Other disease processes that might have caused the radiological abnormalities were carefully considered and ruled out. Individuals with a history of neonatal complications, alcohol or drug abuse, anoxic injury or heritable blood dyscrasias were excluded.

The study protocol was approved by the Institutional Review Board of the Isfahan University of Medical Sciences, Iran, and all participants provided written informed consent.

Magnetic resonance imaging examination

Brain and cervical spinal cord MRI with gadolinium were carried out at baseline and 6-month follow-up. We used a standard magnetic field strength of 1.5 T with a 5-min scanning time delay after the injection of a single dose of 0.1 mmol/kg gadolinium (axial and sagittal T1-, T2-weighted and fluid-attenuated inversion recovery images, 5-mm slice thickness).

Analysis

Conversion rate was estimated as the number of cases of progression to definite MS per 100 person-months of follow-up beginning on the date of completion of the baseline examination and continuing until the occurrence of definite MS, the

date of the last completed follow-up, death, or the end of follow-up on December 31, 2012, whichever came first. For ease of interpretability, we report the conversion rates to definite MS as percentages per month.

The statistical methods used included the Mann–Whitney U test, Fisher's exact test, and survival analysis with the Cox proportional hazards model and Kaplan–Meier estimates to assess time-dependent variables, in order to obtain hazard ratios (HRs) with 95% confidence intervals (CI) and *P* values. The time from RIS diagnosis to the definite MS was estimated using Kaplan–Meier survival analysis. Cox proportional hazards model was used to assess the independent predictive value of demographic, clinical, and imaging characteristics on the time from the first MRI to definite MS. We considered the following covariates in the Cox proportional hazards model: Age at first brain MRI, gender, family history of MS, location of the lesions (periventricular, corpus callosum, cervical spinal cord) and gadolinium-enhanced lesions. The association of each covariate with time to the definite MS was quantified by HR along with their 95% CI. Survival curves were compared with the log-rank test. All analyses were done with SPSS software for Windows© (SPSS Inc., Chicago, IL, USA). All tests for statistical significance were two-tailed and were done assuming a type I error probability of <0.05.

RESULTS

A total of 25 patients who met the criteria for RIS were identified. Their mean age (SD) was 35.1 (6.2) years (range 22-45 years) at first brain MRI. The average duration of follow-up was 17.4 (5.4) months (range 8-29 months). Most patients (23/25, 92%) underwent brain MRI for the evaluation of migraine and other types of headache. Three participants had a family history of MS. Of 25 patients with RIS for whom gadolinium was used in the first scan, 9 (36%) had one or more enhancing lesions and 6 (24%) had a cervical spinal cord lesion [Table 1]. All patients met the Barkhof/Tintoré criteria for DIS on baseline brain MRI scans.

The MRI studies comprised 25 brain and cervical spinal cord scans. All patients were regularly followed every 6 months. Longitudinal MRI data were acquired for all 25 patients after the incidental foci were identified, and all patients had two or more MRI. Radiological progression (presence of new T2-foci, gadolinium enhancement or

Table 1: Clinical, radiologic and demographic characteristics of patients with radiologically isolated syndrome

Baseline characteristic	Value
Age at first brain MRI (years), mean (SD)	35.1 (6.2)
Follow-up duration (months), mean (SD)	17.4 (5.4)
Time to first clinical event (months), mean (SD)	13.3 (3.4)
Female, *n* (%)	17 (68.0)
Brain MRI, *n* (%)	25 (100)
Cervical spine MRI, *n* (%)	25 (100)
Reasons for MRI, *n* (%)	
Headache	23 (92.0)
Syncope	1 (4.0)
Forgetfulness	1 (4.0)
Family history of MS, *n* (%)	3 (12.0)
Abnormal CSF, *n* (%)	7 (28.0)
Periventricular lesions, *n* (%)	
5-9 lesions	14 (56.0)
10-16 lesions	11 (44.0)
Juxtacortical lesion, *n* (%)	
1 lesions	13 (52.0)
2 lesions	8 (32.0)
3 lesions	3 (12.0)
4 lesions	1 (4.0)
Corpus callosum lesion, *n* (%)	
No lesions	3 (12.0)
1 lesion	6 (24.0)
2 lesions	9 (36.0)
3 or more lesions	7 (28.0)
Brainstem lesion, *n* (%)	
No lesions	13 (52.0)
1 lesion	9 (36.0)
2 or more lesions	3 (12.0)
Cervical lesion, *n* (%)	
No lesions	19 (76.0)
1 lesion	6 (24.0)
Cerebellum lesion, *n* (%)	
No lesions	23 (92.0)
1 lesion	2 (8.0)
Gadolinium enhanced lesion, *n* (%)	
No lesions	16 (64.0)
1 lesion	4 (16.0)
2 lesions	3 (12.0)
3 or more lesions	2 (8.0)

Data are expressed as mean (SD) or number (%). SD=Standard deviation, MRI=Magnetic resonance imaging, MS=Multiple sclerosis,

enlargement of a preexisting lesion) was identified in longitudinal MRI studies in 84% (21/25) of patients.

Conversion from radiologically isolated syndrome to definite multiple sclerosis

During 408 (148 men and 260 women) person-months of follow-up, 6 (2 men and 4 women, all relapsing-remitting) of 25 (8 men and 17 women) patients developed definite MS. In all subjects experiencing clinical events, symptoms appeared to be consistent with a demyelinating event. The first clinical event occurred 8 months after initial MRI in one patient, after 12 months in two patients, after 14 months in one patient, and after 17 months in two patients. One patient developed optic neuritis; one patient developed diplopia, and four patients developed motor symptoms (weakness in the lower or upper limbs). No progressive forms of MS were detected. Figure 1 shows the Kaplan–Meier curve for the definite MS endpoint. The mean (SD) time between the first brain MRI and definite MS was 13.3 (3.4) months (median, 13; range, 8-17). All six of these patients were prescribed disease-modifying therapy for MS. Lumbar puncture was performed in 10 of 25 patients, and CSF profiles were suggestive of MS in 60% (6/10) of these cases (>1 unique oligoclonal bands not observed in the serum). All patients considered as positive for CSF based on the detection of >1 oligoclonal band experienced MRI progression and developed clinical events.

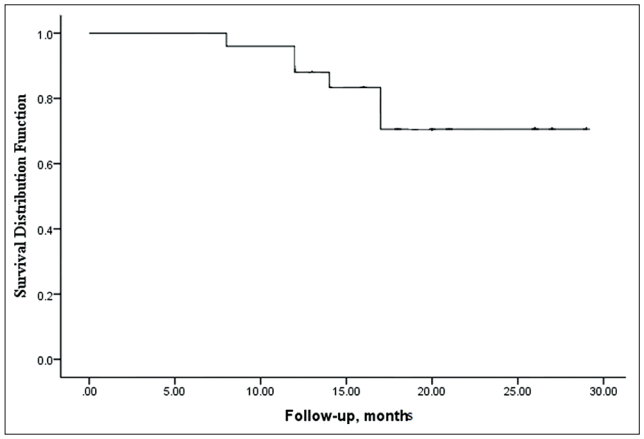

Figure 1: Kaplan–Meier survival curve showing the risk of developing definite multiple sclerosis (MS). At 8 months, 96% of patients did not have MS. At 12 months, 88% of patients did not have MS. At 17 months, 76% of patients did not have MS

Mean age at development of definite MS was 30.2 (5.2) years. The overall conversion rate to definite MS was 1.5% (95% CI: 0.54-3.17) per month. Conversion rates to definite MS were similar in women (1.5%, 95% CI: 0.42-3.9) per month and men (1.4%, 95% CI: 0.17-4.79) per month.

Predictors of conversion to definite multiple sclerosis

The mean and proportional differences between those who did and did not progress to definite MS during a mean follow-up period of 17.4 months are shown in Table 2. Those who progressed to definite MS were younger at first brain MRI (30.2 vs. 36.6 years, $P < 0.05$) and had lower follow-up period (13.3 vs. 18.7 months, $P < 0.05$) and had more gadolinium-enhanced lesions (2.2 vs. 1.0, $P < 0.05$) and CSF abnormalities (1 vs. 6 persons, $P < 0.001$).

The independent predictors associated with conversion to definite MS from RIS were also analyzed with a multivariate model. A step-wise Cox proportional hazards model was run to test seven predictor variables: Age at first brain MRI, gender, family history of MS, location of the lesion (periventricular, corpus callosum, spinal cord) and gadolinium-enhanced lesions. Multivariate analysis showed that the presence of contrast-enhanced lesions on initial MRI was marginally significantly associated with MS (HR 1.83, 95% CI 0.98-3.44, $P = 0.060$), indicating a relative increase of 83% in the HR of conversion to definite MS during the mean follow-up period of 17.4 months in patients who had gadolinium-enhanced lesions compared with those without such lesions. Women also had a nonsignificantly higher risk of progressing to definite MS (HR 2.29, 95% CI 0.65-8.05) [Table 3]. Age at first brain MRI and periventricular, corpus callosum, brainstem, and cervical lesions were not significant predictors of conversion to definite MS.

DISCUSSION

In this cohort study, the conversion rate to MS in patients with RIS at baseline was 1.5%/month; this finding is evidence that individuals with RIS are at increased risk of developing definite MS. To the best of our knowledge, this is the first study to report conversion rates in patient with RIS but

Table 2: Changes in time in patients who did or did not progress to definite multiple sclerosis during a mean follow-up period of 17.4 months

Characteristic	Did not progress (*n*=19)	Progressed (*n*=6)	Difference (95% CI)
Age at first brain MRI (years), mean (SD)	36.6 (5.6)	30.2 (5.2)	6.4 (1.06, 11.87)*
Follow-up duration (months), mean (SD)	18.7 (5.3)	13.3 (3.4)	5.4 (0.58, 10.12)*
Female, *n* (%)	13 (68.4)	4 (66.7)	1.7 (−41.40, 44.90)
Reasons for MRI, *n* (%)			
Headache	17 (89.5)	6 (100.0)	−10.5 (−24.30, 3.27)
Syncope	1 (5.3)	0 (0.0)	5.3 (−4.78, 15.30)
Forgetfulness	1 (5.3)	0 (0.0)	5.3 (−4.78, 15.30)
Family history of MS, *n* (%)	1 (5.3)	2 (33.3)	−28.0 (−67.10, 11.00)
Abnormal CSF, *n* (%)	1 (5.3)	6 (100.0)	−94.7 (−105.0, −84.7)**
Periventricular lesions, *n* (%)			
5-9 lesions	11 (57.9)	3 (50.0)	7.9 (−37.9, 53.6)
10-16 lesions	8 (42.1)	3 (50.0)	−8.9 9 (−53.6, 37.9)
Juxtacortical lesion, *n* (%)			
1 lesion	12 (63.2)	1 (16.7)	46.5 (9.62, 83.40)*
2 lesions	4 (21.1)	4 (60.7)	−45.6 (−87.6, −3.68)*
3 lesions	2 (10.5)	1 (16.7)	−6.2 (−39.0, 26.7)
4 lesions	1 (5.3)	0 (0.0)	5.3 (−4.78, 15.30)
Corpus callosum lesion, *n* (%)			
No lesions	3 (15.8)	0 (0.0)	15.8 (−0.61, 32.2)
1 lesion	3 (15.8)	3 (50.0)	−34.2 (−77.40, 9.03)
2 lesions	7 (36.8)	2 (33.3)	3.5 (−40.00, 47.00)
3 or more lesions	6 (31.6)	1 (16.7)	14.9 (−21.50, 51.30)
Brainstem lesion, *n* (%)			
No lesions	10 (52.6)	3 (50.0)	2.6 (−43.2, 48.5)
1 lesion	7 (36.8)	2 (33.3)	3.5 (−40.0, 47.0)
2 or more lesions	2 (10.5)	1 (16.7)	−6.1 (−39.0, 26.7)
Cervical lesion, *n* (%)			
No lesions	16 (84.2)	3 (50.0)	34.2 (−9.03, 77.4)
1 lesion	3 (15.8)	3 (50.0)	-
Cerebellum lesion, *n* (%)			
No lesions	17 (89.5)	6 (100.0)	−10.5 (−24.30, 3.27)
1 lesion	2 (10.5)	0 (0.0)	-
Gadolinium enhanced lesion, *n* (%)			
No lesions	16 (84.2)	0 (0.0)	84.2 (67.8, 1.01)**
1 lesion	3 (15.8)	1 (16.7)	−0.9 (−34.9, 33.2)
2 lesions	0 (0.0)	3 (50.0)	50.0 (−90.0, −10.0)**
3 or more lesions	0 (0.0)	2 (33.3)	33.3 (−71.1, 4.39)

Data are expressed as mean (SD) or number (%). Difference in the means or proportions of the variables between progressed and did not progress to clinically definite multiple sclerosis. *P<0.05, **P<0.001. CI=Confidence interval, CSF=Cerebrospinal fluid, SD=Standard deviation, MRI=Magnetic resonance imaging, CSF=Cerebrospinal fluid, MS=Multiple sclerosis

absence of neurological symptoms or signs in Iran. A number of studies, with different results, have assessed conversion rate to MS in patients with RIS so far.[2,4,7-10] The differences in the methods used to estimate conversion to clinically definite MS, the duration of undiagnosed RIS, the use of different criteria for the diagnosis of CIS and definite MS, composition of the sample in terms of age and gender and small sample size and short follow-up period may be the reason for the differences. Okuda *et al*.[2] estimated that 59% of individuals with RIS showed radiological progression during a median period of 2.7 years. Brex *et al*.[4] found that clinically definite MS developed in 88% after a

Table 3: Predictors of conversion to definite multiple sclerosis (Cox proportional hazards model)

Covariate	Hazard rate	95% CI
Age at first brain MRI (years)	0.99	0.92-1.08
Gender (men=reference)	2.29	0.65-8.05
Number of gadolinium-enhanced lesions	1.83	0.98-3.45
Family history of multiple sclerosis	1.55	0.43-5.59
Periventricular lesions	1.06	0.91-1.22
Corpus callosum lesions	0.93	0.54-1.60

CI=Confidence interval, MRI=Magnetic resonance imaging

mean of 14.1 years of those with abnormal results on MRI at presentation and in 19% of those with normal MRI results. In a study of 70 patients with RIS during a mean follow-up of 5.2 years, eight patients showed conversion to clinically definite MS.[8] A Brazilian study[9] spanning 49 months found that only two of 12 individuals with RIS developed symptoms of neurological dysfunction as CIS or as recurring symptoms compatible with a diagnosis of definite MS. Recently, Okuda *et al*.[10] found that clinical events were identified in 34% of individuals within 5-year period from the first brain MRI study. In a study similar to ours of a cohort of 30 patients with unexpected MS, 83% showed progression on imaging criteria alone within the first 2 years; clinical symptoms occurred in 37% of patients within 5 years.[7] In our study, the median time to definite MS was 13 months and MRI progression occurred in 84% of the cases. However, it is not known whether the patients were at risk of developing definite MS. The difference of definition of definite MS in this study (the 2010 McDonald criteria) compared with previous studies might be one reason of high conversion rate from RIS to definite MS despite short-term follow-up.

In our series, the presence of contrast-enhanced lesions on initial MRI was marginally significantly associated with MS (HR = 1.83, $P = 0.060$). Other studies[1,2,11-13] also reported that the risk of developing MS was higher in individuals with baseline MRI scans demonstrating gadolinium-enhanced lesions than in individuals without such lesions. As Barkhof *et al*. noted, this risk of enhancement may be related to the existing burden of disease.[14] The presence of gadolinium-enhanced lesions in patients with MS was identified as a predictor of radiological progression[10] and subsequent clinical relapse,[12,13] and as the MRI parameter that most clearly predicted conversion to definite MS.[1] Taken together, these findings confirm the importance of gadolinium-enhanced lesions in patients with RIS.

In our study, mean age of the patients who progressed to definite MS was younger than in patients with RIS who did not progress to MS. This finding is consistent with reports that MS may occur as early as the third decade of life. However, we do not know how long patients who did and did not progress to definite MS may have had undiagnosed RIS. This aspect warrants further investigation.

The high risk of developing MS in individuals with RIS underscores the importance of existing lesions suggestive of demyelinating disease and gadolinium enhancement in the baseline scan regardless of the absence or presence of clinical symptoms. We believe that if the Barkhof/Tintoré criteria are met at the time of the initial brain MRI by an individual suspected of having RIS, paraclinical screening, clinical evaluation, and follow-up MRI should be proposed.

Recently, Okuda *et al*.[15] have reported their findings in 71 individuals with RIS, who had cervical spine MRI scans prior to the first clinical event. Abnormal signals in the cervical spinal cord highly suggestive of MS were found in 25 patients (35%), whereas conversion to clinically isolated syndrome, or primary progressive MS was observed in 21 (29.6%) during a median of 1.6 years. Only three patients out of 46 who did not have spinal cord lesions subsequently had a clinical event. These observations support the view that asymptomatic individuals with abnormal MRI signals in both the brain and cervical spinal cord, in comparison to the brain alone, are at higher risk of developing clinical MS. Unlike Okuda *et al*.,[15] we found that the number of baseline cervical spinal cord lesions was not associated with conversion to definite MS. In our study, cervical spinal cord lesions were present in three of patients who progressed and in three patients who did not progress to MS. This issue warrants further investigation in a larger sample.

The mechanisms underlying the increased risk of MS in patients with RIS are not clear. Persons with RIS may have a milder degree of demyelization or a better repair response to

insult.[16] By using MRI metrics, De Stefano *et al*.[16] found that 13 of 19 patients with RIS had a probability ≥70% of being classified as having MS. Interestingly, the predictive factors they identified included abnormal CSF, dissemination in time in a new MRI scan, and a positive cervical spine MRI.

None of our patients has subsequently been found to have any disease entity other than MS. Nevertheless, a potential limitation of our study is its relatively brief follow-up period of 17.4 (5.4) months (range 8-29), which may be too short to appreciate the real risk of conversion to MS. Assessing the conversion rate after longer follow-up periods is, therefore, warranted. Another limitation is the use of a relatively small sample of patients with RIS. Large and long multicenter prospective studies of RIS need to be performed to determine the actual risk of conversion to MS, and also to search for different biological mechanisms that explain why some cases with demyelinating lesions appear to remain clinically silent for life,[17] or why some patients develop clinical symptoms late in life. The generalizability of the present study is limited by the insufficient number of patient, short period of observation, and single institutional findings of the sample. Despite the above limitations, our findings add to our understanding of the conversion rate to MS in people with RIS in Iran. Furthermore, this study provides new data from Iran, a developing country that has been underrepresented in past studies.

The findings of this study have important implications for clinical practice. Patients with incidental findings of brain abnormalities in their initial MRI studies continue to be at substantial risk for the development of MS. The initiation of prophylactic treatment for RIS is controversial.[18,19] Although treatment with disease-modifying therapies is generally not recommended for individuals with RIS because many may never develop MS, a recent review noted that about 10% of the reported RIS population is treated.[3] It is not known whether early treatment with disease-modifying therapy (as for patients with confirmed MS) improves symptom-free survival for individuals with RIS. For patients with abnormal brain MRI findings, one must balance their risk of developing MS with the potential side-effects and cost of disease-modifying agents. Treatment may be appropriate, but the evidence is insufficient, partly because of the lack of controlled trials of treatments and partly because the long-term prognosis is unknown. Randomized controlled trials designed to test the efficacy of early initiation of disease-modifying therapies in relapsing MS, and to determine whether such treatment delays the conversion of RIS to MS, will aid in defining the role of disease-modifying therapies in the high-risk RIS population.

CONCLUSIONS

The findings of this study expand a still very limited body of evidence supporting the hypothesis that the presence of RIS increases the risk of conversion to MS. Our findings strongly support regular screening and follow-up for patients with RIS. A larger and longer multicenter prospective study of RIS is warranted to assess the actual risk of conversion to MS in greater detail.

ACKNOWLEDGMENTS

We thank K. Shashok (author AID in the Eastern Mediterranean) for improving the use of English in the manuscript.

REFERENCES

1. Barkhof F, Filippi M, Miller DH, Scheltens P, Campi A, Polman CH, *et al*. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. Brain 1997;120(Pt 11):2059-69.
2. 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;72:800-5.
3. Granberg T, Martola J, Kristoffersen-Wiberg M, Aspelin P, Fredrikson S. Radiologically isolated syndrome – incidental magnetic resonance imaging findings suggestive of multiple sclerosis, a systematic review. Mult Scler 2013;19:271-80.
4. Brex PA, Ciccarelli O, O'Riordan JI, Sailer M, Thompson AJ, Miller DH. A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. N Engl J Med 2002;346:158-64.
5. Optic Neuritis Study Group. The 5-year risk of MS after optic neuritis. Experience of the optic neuritis treatment trial. Neurology 1997;49:1404-13.
6. 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.
7. Lebrun C, Bensa C, Debouverie M, De Seze J, Wiertlievski S, Brochet B, *et al.* Unexpected multiple sclerosis: Follow-up of 30 patients with magnetic resonance imaging and clinical conversion profile. J Neurol Neurosurg Psychiatry 2008;79:195-8.
8. 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.
9. Lana-Peixoto MA. How much radiologically isolated syndrome suggestive of multiple sclerosis is multiple sclerosis? Arq Neuropsiquiatr 2012;70:2-4.
10. 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.
11. Kermode AG, Thompson AJ, Tofts P, MacManus DG, Kendall BE, Kingsley DP, *et al.* Breakdown of the blood-brain barrier precedes symptoms and other MRI signs of new lesions in multiple sclerosis. Pathogenetic and clinical implications. Brain 1990;113:1477-89.
12. Kappos L, Moeri D, Radue EW, Schoetzau A, Schweikert K, Barkhof F, *et al.* Predictive value of gadolinium-enhanced magnetic resonance imaging for relapse rate and changes in disability or impairment in multiple sclerosis: A meta-analysis. Gadolinium MRI Meta-analysis Group. Lancet 1999;353:964-9.
13. Koudriavtseva T, Thompson AJ, Fiorelli M, Gasperini C, Bastianello S, Bozzao A, *et al.* Gadolinium enhanced MRI predicts clinical and MRI disease activity in relapsing-remitting multiple sclerosis. J Neurol Neurosurg Psychiatry 1997;62:285-7.
14. Barkhof F, Held U, Simon JH, Daumer M, Fazekas F, Filippi M, *et al.* Predicting gadolinium enhancement status in MS patients eligible for randomized clinical trials. Neurology 2005;65:1447-54.
15. 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.
16. 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.
17. Georgi W. Multiple sclerosis. Anatomopathological findings of multiple sclerosis in diseases not clinically diagnosed. Schweiz Med Wochenschr 1961;91:605-7.
18. Frohman EM, Havrdova E, Lublin F, Barkhof F, Achiron A, Sharief MK, *et al.* Most patients with multiple sclerosis or a clinically isolated demyelinating syndrome should be treated at the time of diagnosis. Arch Neurol 2006;63:614-9.
19. Pittock SJ, Weinshenker BG, Noseworthy JH, Lucchinetti CF, Keegan M, Wingerchuk DM, *et al.* Not every patient with multiple sclerosis should be treated at time of diagnosis. Arch Neurol 2006;63:611-4.

Source of Support: Nil, **Conflict of Interest:** None declared.