Incidental MRI anomalies suggestive of multiple sclerosis

The radiologically isolated syndrome

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ABSTRACT

Background: The discovery and broad application of MRI in medicine has led to an increased awareness in the number of patients with incidental white matter pathology in the CNS. Routinely encountered in clinical practice, the natural history or evolution of such individuals with respect to their risk of developing multiple sclerosis (MS) is unclear.

Objective: To investigate the natural history of patients who exhibit incidental imaging findings highly suggestive of MS pathology.

Methods: Detailed clinical and radiologic data were obtained from asymptomatic patients with MRI anomalies suggestive of MS.

Results: The cohort consisted of 41 female and 3 male subjects (median age = 38.5, range: 16.2–67.1). Clinical evaluations were performed in 44 patients at the time of initial imaging; longitudinal clinical follow-up occurred for 30 patients, and longitudinal MRI data were acquired for 41 patients. Neurologic examination at the time of the initial MRI scans was normal in nearly all cases. While radiologic progression was identified in 59% of cases, only 10 patients converted to either clinically isolated syndrome or definite MS. The presence of contrast-enhancing lesions on the initial MRI was predictive of dissemination in time on repeat imaging of the brain (hazard ratio [HR] = 3.4, 95% confidence interval [1.3, 8.7], $p = 0.01$).

Conclusion: Individuals with MRI anomalies highly suggestive of demyelinating pathology, not better accounted for by another disease process, are very likely to experience subsequent radiologic or clinical events related to multiple sclerosis. Additional studies will be necessary to fully define this risk. ***Neurology*® 2009;72:800–805**

GLOSSARY

CI = confidence interval; **CIS** = clinically isolated syndrome; **EDSS** = Expanded Disability Status Scale; **FLAIR** = fluid-attenuated inversion recovery; **HR** = hazard ratio; **MS** = multiple sclerosis; **ONTT** = Optic Neuritis Treatment Trial; **RIS** = radiologically isolated syndrome.

The invention of MRI, together with technological advances in magnet field strengths and the increasing use of noninvasive structural neuroimaging techniques in clinical and research practice, has led to frequent, incidental identification of abnormalities in the CNS. Many of the detected abnormalities are nonspecific in etiology and are classified in medical parlance as unidentified bright objects or UBOs, or are indicative of pathologies other than multiple sclerosis (MS).[1-4]

However, some observed changes are highly suggestive of demyelinating pathology based both upon their location and morphology in the CNS (i.e., periventricular geography, involvement of the corpus callosum, ovoid, well-circumscribed, homogeneous). Although routinely encountered in clinical practice, only limited data exist on the natural history or evolution of such individuals. Previous data in clinically isolated syndromes (CIS) stratified the risk of conversion to MS based on the severity of the initial brain MRI,[5,6] emphasizing the importance and prognostic relevance of identified baseline abnormalities to long-term clinical outcomes.

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e-Pub ahead of print on December 10, 2008, at www.neurology.org.
From the University of California, San Francisco, Department of Neurology, UCSF Multiple Sclerosis Center.
Disclosure: The authors report no disclosures.

Table 1 Proposed diagnostic criteria for the radiologically isolated syndrome

A. The presence of incidentally identified CNS white matter anomalies meeting the following MRI criteria:
1. Ovoid, well-circumscribed, and homogeneous foci with or without involvement of the corpus callosum
2. T2 hyperintensities measuring >3 mm and fulfilling Barkhof[7] criteria (at least 3 out of 4) for dissemination in space
3. CNS white matter anomalies not consistent with a vascular pattern
B. No historical accounts of remitting clinical symptoms consistent with neurologic dysfunction
C. The MRI anomalies do not account for clinically apparent impairments in social, occupational, or generalized areas of functioning
D. The MRI anomalies are not due to the direct physiologic effects of substances (recreational drug abuse, toxic exposure) or a medical condition
E. Exclusion of individuals with MRI phenotypes suggestive of leukoaraiosis or extensive white matter pathology lacking involvement of the corpus callosum
F. The CNS MRI anomalies are not better accounted for by another disease process

Conversion rates to MS of 65% and 88% at mean follow-up times of 5.3 and 14.1 years, respectively, for patients identified with an abnormal brain MRI at baseline have been described.[5] Similarly, the risk of converting from CIS to clinically definite MS (CDMS) after 5 years in the Optic Neuritis Treatment Trial (ONTT) was 51% for patients with baseline brain MRI scans containing ≥3 lesions.[6]

We propose that this unique and at risk cohort of individuals without overt clinical symptoms but with MRI features highly suggestive of MS be identified as having a radiologically isolated syndrome (RIS). However, the implication of having RIS on subsequent neurologic outcome measures is unclear. It is the purpose of this study, therefore, to provide insight into the natural history of asymptomatic individuals with MRI anomalies suggestive of demyelinating disease.

METHODS **Study participants.** All patients fulfilling criteria for RIS (table 1) were evaluated at the UCSF Multiple Sclerosis Center. Each patient had incidentally identified white matter anomalies on structural neuroimaging studies that were highly suggestive of MS based both upon their location and morphology within the CNS. In all cases, a detailed clinical history and comprehensive neurologic evaluation, including a determination of the Expanded Disability Status Scale (EDSS) score, were obtained. All attempts were made to ensure that another disease process was not causative for the radiologic aberrations identified. Serologic studies were performed to evaluate for the presence of a vascular, metabolic, inflammatory, infectious, connective tissue, mixed connective tissue, or other demyelinating process. CSF profiles, electrophysiologic tests, and longitudinal clinical and imaging data were available only in select cases when ordered at the discretion of the treating physician. RIS patients were invited for prospective evaluation at the UCSF MS Center to monitor for conversion to CIS or CDMS. For those patients referred with an existing diagnosis of either CIS or CDMS, if a history of RIS was identified, retrospective data were reviewed and collected if study criteria were fulfilled. The protocol was approved by the Committee on Human Research at the University of California, San Francisco. Informed consent was obtained from study participants.

Structural neuroimaging. All patients included had previously undergone MRI studies of the brain at magnetic field strengths of 1.5 Tesla (T) or 3.0 T at multiple institutions, yielding images from nonuniform protocols. All examinations included T1- and T2-weighted spin-echo sequences in multiple planes of view (axial, coronal, and sagittal) with and without gadolinium. In several cases, spinal cord imaging (cervical or thoracic) or a head CT scan was performed prior to the acquisition of brain MRI sequences; the latter, in select cases, was first performed because initial scanning was done prior to the introduction of MRI in clinical practice or recommended following traumatic events.

Incidental MRI abnormalities were identified by radiologists and verified by at least two MS specialists. A qualitative analysis of the available brain imaging studies was performed on all study participants. Imaging studies were deemed significant after fulfilling the following criteria: 1) ovoid, well-circumscribed, and homogeneous foci observed with or without involvement of the corpus callosum; 2) T2 hyperintensities measuring ≥3 mm and fulfilling Barkhof criteria (at least three out of four) for dissemination in space[7]; 3) anomalies not following a clear vascular pattern; and 4) structural neuroimaging abnormalities identified not explained by another disease process. Individuals with MRI features suggestive of leukoaraiosis or extensive white matter changes lacking clear involvement of the corpus callosum were excluded. Patients with a significant history for neonatal complications, recreational or prescription substance abuse, anoxic injury, or heritable blood dyscrasias were also excluded.

Survival analysis. Two survival models were generated to explore the natural history of RIS. In the first, the time to the first clinical event (i.e., CIS) was defined as the outcome. For the second model, the outcome was defined as the time to the first new, ≥3 mm, T2-weighted focus, the presence of contrast enhancement, or enlargement of an existing T2-weighted focus on the follow-up MRI scan. Potential predictors of conversion to CIS or for acquiring new brain MRI lesions were analyzed using the Cox regression model, generating hazard ratios (HR) with 95% confidence interval (CI) and p values. All predictors were included in the univariate analyses; those that were thought to be important were included in the multivariate models. Exposure to disease-modifying therapy was treated as a time-dependent covariate. Tests for interaction were performed for age and race, race and sex, age and sex, race and CSF status, and race and enhancement status on the initial MRI. Model checks were performed using the Schoenfeld test to evaluate the proportional hazards assumption for each of the predictor models. Potential predictors that demonstrated non-proportionality were evaluated using a χ^2 analysis.

RESULTS A total of 44 patients were identified (41 female; median age = 38.5, range: 16.2–67.1).

Table 2 Summary of the clinical and radiologic data for patients with suspected asymptomatic demyelinating disease

Age at initial baseline scan, y	44
Median	38.5
Range	16.2–67.1
Gender	F: 41 (93%); M: 3 (7%)
Ethnicity	White (39), African American (2), Asian/Pacific Islander (1), Hispanic (2)
Structural neuroimaging studies	
CT Head	6
Brain MRI	112 (+CE: 21)
Cervical spine MRI	37 (+CE: 5)
Thoracic spine MRI	16 (+CE: 2)
Contrast enhancement on baseline MRI	Yes: 10 (24%); no: 31 (76%)
MRI dissemination in time from RIS, y	Yes: 24 (59%); no: 17 (41%)
Median	2.7
Range	0.1–26.0
Clinical and paraclinical data	
CSF analysis	27 (+OCB or >0.7 IgG index: 18 [67%])
Time to first clinical event, y	10 (F: 9; M: 1)
Median	5.4
Range	1.1–9.8
Optic nerve	4
Brainstem	1
Spinal cord (sensory/motor)	5
Exposure to disease modifying therapy	Yes: 7 (12%); no: 52 (88%)

+CE = presence of contrast enhancement; +OCB = presence of oligoclonal bands not present in the periphery; RIS = radiologically isolated syndrome.

Brain MRI studies were performed for the following reasons: migraine headache (17), craniocerebral trauma (4), stereotypical vertigo with head tilt (Type I Chiari malformation) (1), curiosity (4), spells of uncertain etiology (4), galactorrhea (2), otic complaints (ear pain with air travel) (1), amenorrhea (1), angioedema (1), hypersomnolence (1), panic attacks (2), lacunar syndrome (1), low back pain (2), screening for familial aneurysms (1) or as part of a protocol for experimental melanoma treatment (1), and asymptomatic quadrantanopsia detected by routine, formal visual field testing (1).

The clinical and radiologic features of the study cohort are described in table 2.

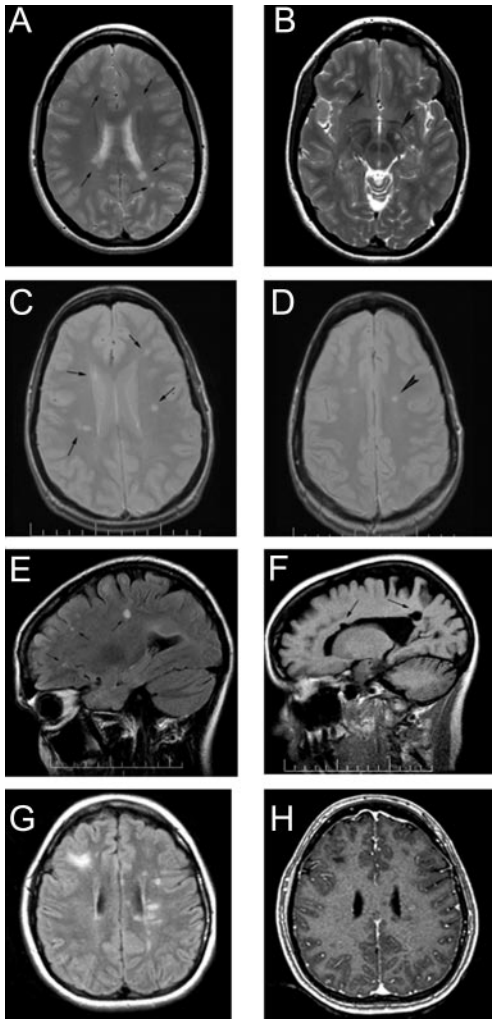
The structural neuroimaging studies acquired from our study cohort included 6 head CT evaluations and 165 MRI studies (112 brain, 37 cervical, and 16 thoracic). Contrast enhancement was observed in 28 MRI studies (21 brain [15 unique patients (1–6 foci)]; 5 cervical [4 unique patients (1–2 foci)]; 2 thoracic [2 unique patients]);10 (24%) of 41 who had gadolinium administered on the first scan had one or more enhancing lesions. All patients met Barkhof criteria for dissemination in space on baseline brain MRI scans. Longitudinal imaging data were acquired for 41 patients following the identification of the incidental foci; 28 patients were imaged three or more times. Individual patients had a range of 1–10 MRI studies. In this group, the median follow-up time between the initial baseline scan revealing incidental T2 foci to the most recent follow-up study was 2.7 years (range: 0.1–26.0). Radiologic progression (presence of new T2 foci, gadolinium enhancement, or enlargement of pre-existing lesions) on longitudinal MRI was identified in 59% (24/41) of patients. Figure 1 illustrates cross-sectional and longitudinal MR images from select RIS cases.

Upon initial presentation for clinical evaluation at our center, seven patients had already been prescribed disease-modifying therapy for MS despite the lack of symptoms consistent with the disease. Neurologic examinations at the time of the initial MRI scan were normal in nearly all cases (with the exception of the patient presenting with a cerebrovascular accident, and two with asymmetric reflexes). Lumbar punctures were performed in 27 of 44 patients and CSF profiles (evaluated at different laboratories) were suggestive of MS in 67% (18/27) of these cases (IgG index $\geq$0.7 or $\geq$2 unique oligoclonal bands not observed in the periphery). Of the CSF+ cases, 11 (61%) experienced radiologic progression and 8 (44%) developed clinical symptomatology. Thirty percent (10/30) of the cohort, in whom longitudinal clinical follow-up data were acquired in our Center, have converted to either CIS or CDMS.[8] The median time to the first clinically defining event (CIS) was 5.4 years (range: 1.1–9.8).

Figure 2 illustrates the Kaplan-Meier curves for both clinical and radiologic endpoints. Age at RIS onset, gender, ethnicity, and abnormal CSF were not significant predictors for the development of future clinical events or further radiologic progression in the Cox regression model. There were more patients who had new radiologic abnormalities than new symptoms consistent with demyelination. The presence of contrast-enhancing lesions on the initial MRI signifying RIS constituted a significant factor in increasing the risk of dissemination in time on subsequent brain MRI scans (HR = 3.4, 95% CI [1.3, 8.7], $p = 0.01$).

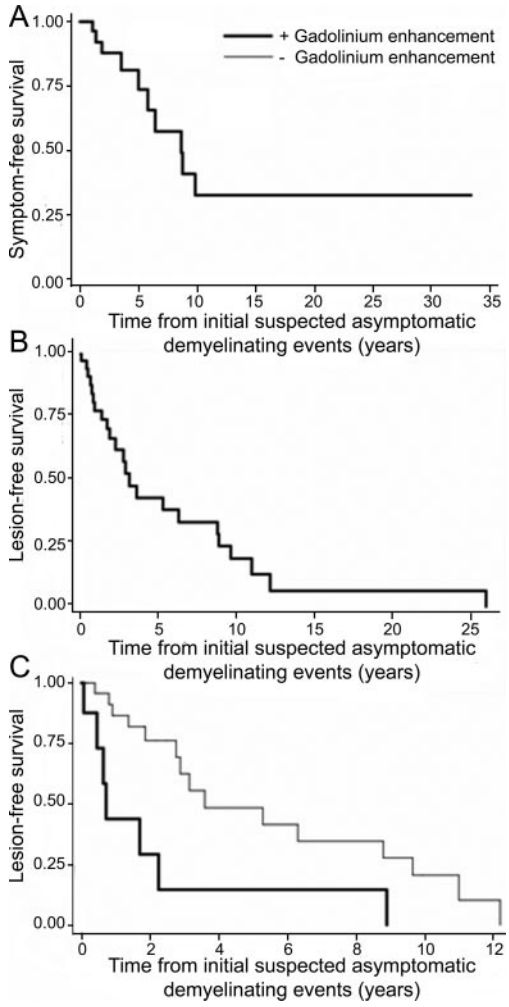
DISCUSSION In this natural history study of patients with incidentally identified MRI abnormalities highly suggestive of demyelinating disease, we demonstrated that patients with RIS are at increased risk of developing clinical symptoms of MS or experiencing radiologic progression.

Figure 1 Cross-sectional and longitudinal MR images from select RIS cases



(A) Axial 3.0 T proton density image demonstrating a juxtacortical and multiple, ovoid, periventricular foci of T2 prolongation (arrows). (B) Axial 3.0 T T2-weighted image 1 year later revealing new areas of T2 prolongation (arrowheads) involving the deep white matter and midbrain. A total of four new foci of T2 prolongation (>3 mm) were identified (all new lesions not shown). (C) Axial 3.0 T proton density image demonstrating multiple regions of T2 prolongation involving the periventricular and deep white matter (arrows). Chiari Type I malformation identified following clinical presentation along with incidental white matter changes. (D) Repeat axial 3.0 T proton density MR image at 1.5 years demonstrating a new focus (>3 mm) of T2 prolongation (arrowhead). (E) Sagittal 1.5 T T1-weighted image revealing two regions of T1 hypointensity adjacent to the corpus callosum. A reduction in total brain volume, outside the upper limits of normal for age, is seen. (F) Sagittal 1.5 T FLAIR image demonstrating multiple areas of hyperintensity extending in a Dawson's finger pattern. Despite the high lesion load, the patient currently remains asymptomatic and exhibits a normal neurologic examination. (G) Axial 1.5 T, post contrast T1-weighted image (H) from the same patient with a periventricular gadolinium-enhancing lesion in the left hemisphere. A total of three contrast-enhancing lesions (all not shown) were present in this study and discordant with clinical symptomatology. T = Tesla; FLAIR = fluid-attenuated inversion recovery.

Figure 2 Kaplan-Meier curves for clinical and radiologic endpoints



Kaplan-Meier curves for patients with endpoints including (A) time to first clinical event and (B) time to first new T2-weighted focus on subsequent brain MRI studies. The presence of contrast-enhancing lesions on the initial MRI was associated with an increased risk of dissemination in time on repeat imaging of the brain (C) (HR = 3.4, 95% CI [1.3, 8.7], $p = 0.01$).

In postmortem studies, the prevalence of clinically silent demyelinating disease is approximately 0.1%.[9-11] The data from these studies, however, were collected in the pre-MRI era; in addition, the clinical information on these patients was incomplete.[9-11] Noninvasive, structural neuroimaging studies of the brain have provided premorbid data in more recent years. An MRI investigation of 2,783 asymptomatic individuals revealed incidental white matter abnormalities suggestive of MS in 23 patients (0.83%).[12] This prevalence, however, is likely not uniform across individuals and requires stratification, as patients with a family history for MS may be at higher risk of asymptomatic demyelinating pathology. An investigation of 48 clinically discordant twins demonstrated abnormalities on MRI typical for MS in

13% (2/15) monozygotic and 9% (3/33) dizygotic asymptomatic twins.[13] In a study of 240 asymptomatic first-degree relatives of sporadic (n = 152) and familial MS (n = 88) cases, 3.9% and 10.2% of cases met Barkhof criteria for dissemination in space.[14] Interestingly, of the 56 healthy volunteers studied, 9 (16.1%) had abnormal signals in the white matter not meeting temporal-spatial dissemination criteria. We observed three patients in the RIS cohort with a significant family history for MS; two with MS recently identified in first-degree relatives. These data suggest that the incidence of RIS in asymptomatic first-degree family members may meet or exceed the lifetime risk for the development of MS in those with a significant family history.[15] A limitation of these investigations and ours is the lack of results from other diagnostic studies (i.e., neuropsychiatric testing) that may detect the presence of clinical deficits not appreciated on routine neurologic evaluation.

There are limited published data regarding the natural history of patients with subclinical demyelinating pathology on MRI; however, the existing baseline lesion load appears to have prognostic relevance. In a cohort of 30 patients with unexpected MS, 25 (83%) demonstrated progression on imaging criteria alone within the first 2 years; clinical symptoms occurred in 11 (37%) patients within 5 years.[16]

In our series, the median time to CIS was 5.4 years (range: 1.1–9.8). Radiologic progression (new T2 foci, enhancing, or enlarging lesions) occurred in 59% of cases over a median time period of 2.7 years. Patients with baseline MRI scans demonstrating gadolinium-enhancing lesions exhibited a substantial (HR = 3.4) increase in risk of developing new lesions on subsequent MRI scans compared to those who did not have enhancement. As previously described, this risk of enhancement may be related to the existing burden of disease.[17] The presence of gadolinium-enhancing lesions in the study of MS was identified as a predictor of radiologic progression,[18] subsequent clinical relapses,[19,20] and as the most predictive MRI parameter in predicting conversion to CDMS[21] by Poser criteria,[22] affirming the importance of this finding in RIS. The observed shorter time to radiologic progression compared to clinical progression may reflect the highly sensitive nature of MRI technology and previous observations that the development of new MS plaques outnumbers the occurrence of new relapses.[16,18]

The MR images obtained in our clinical cohort were not ascertained using standardized research protocols and therefore reflect what physicians are faced with in daily clinical practice. Given the methodologic differences (i.e., slice thickness, spacing between slices) used in the acquisition of images and varying signal-to-noise ratios and magnet field strengths, lesion numbers or volumes could not be accurately calculated in our study. A prospective study is currently underway, utilizing a standardized, high-resolution imaging protocol at 3.0 T. This will allow for the accurate determination of lesion volumes along with regional and global brain atrophy measures.

To date, this is the largest RIS cohort reported in the literature and therefore offers a unique opportunity to provide further insight into the biology and natural history of MS. Of the available cases, none has subsequently been identified as having another disease entity other than MS. Currently, routine clinical follow-up and neuroimaging surveillance serve as the standards by which these patients are followed. Asymptomatic white matter changes fulfilling Barkhof criteria for dissemination in space not better accounted by another medical condition appear to place individuals at risk for subsequent, clinically evident demyelinating symptoms. However, these data should not be generally applied in those cases with nonspecific brain MRI anomalies, leukoaraiosis, or those who fail to meet validated dissemination in space criteria. We specifically targeted individuals who exhibited radiologic features highly suggestive of demyelinating disease by geographic location criteria as well as morphologic features. At the moment, it is unclear if RIS cases represent presymptomatic or benign MS, or another disease process not immediately apparent. Therefore, caution should be utilized with respect to recommended treatment interventions to patients with RIS as a better explanation, other than demyelinating disease, may ultimately prove to be responsible for the incidental radiologic changes observed. Overall, it appears apparent based on the ranges of conversion from RIS to CIS that heterogeneity exists, much like in MS, in the clinical evolution of these cases.

Our study highlights the importance of existing lesions suggestive of demyelinating disease and gadolinium enhancement on the baseline scan regardless of the absence or presence of clinical symptoms. Although additional investigations will be necessary to fully understand the risk of conversion to CIS and MS and the rate of pathophysiologic expression based on genetic susceptibility, it appears that RIS may be a precursor to MS. Considerably more research is needed on a larger cohort to confirm these findings and to fully understand the natural history of RIS and conversion to CIS or CDMS, in addition to the impact of clinical implications and recommendations regarding treatment, as outcomes are currently uncertain.

Received June 17, 2008. Accepted in final form August 19, 2008.

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Announcement of Winner

2009 Resident and Fellow Section Writing Award

Neurology® is delighted to announce that **Megan Alcauskas, MD**, a resident at Mount Sinai Hospital in New York City, is the recipient of the first Annual Resident and Fellow Section Writing Award. The Resident and Fellow Section editorial team gave the award for the article "Right Brain: Reading, writing, and reflecting: Making a case for narrative medicine in neurology" (*Neurology*® 2008;70:891–894), which was co-authored by Rita Charon, MD, PhD.

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