Asymptomatic spinal cord lesions predict disease progression in radiologically isolated syndrome

D.T. Okuda, MD
E.M. Mowry, MD, MCR
B.A.C. Cree, MD, PhD,
MCR
E.C. Crabtree, MD
D.S. Goodin, MD
E. Waubant, MD, PhD
D. Pelletier, MD

Address correspondence and reprint requests to Dr. Darin T. Okuda, Barrow Neurological Institute, Department of Neurology, BNI Multiple Sclerosis Center, 500 West Thomas Road, Suite 300, Phoenix, AZ 85013
darin.okuda@chw.edu

ABSTRACT

Background: Technological advancements in neuroimaging and the increased use of these diagnostic modalities are responsible for the discovery of incidentally identified anomalies within the CNS. In addition to the identification of unanticipated brain MRI abnormalities suggestive of demyelinating disease in patients undergoing neuroimaging for a medical reason other than evaluation for multiple sclerosis (MS), asymptomatic spinal cord lesions are periodically identified.

Objective: To determine if asymptomatic spinal cord lesions are associated with clinical progression in subjects with radiologically isolated syndrome (RIS).

Methods: A retrospective review of RIS cases at the University of California, San Francisco Multiple Sclerosis Center was performed. The presence of asymptomatic cervical spinal cord MRI lesions was analyzed as a potential predictor for clinical progression.

Results: Twenty-five of 71 subjects with RIS possessed findings within the cervical spine that were highly suggestive of demyelinating disease. Of these subjects, 21 (84%) progressed clinically to clinically isolated syndrome ($n = 19$) or primary progressive multiple sclerosis ($n = 2$) over a median time of 1.6 years from the date of RIS identification (interquartile range 0.8–3.8). The sensitivity, specificity, and positive predictive value of an asymptomatic spinal cord lesion for subsequent development of either a first demyelinating attack or primary progressive MS were 87.5%, 91.5%, and 84%, respectively. The odds ratio of clinical progression was 75.3 (95% confidence interval 16.1–350.0, $p < 0.0001$). This association remained significant after adjusting for potential confounders.

Conclusion: These findings suggest that the presence of asymptomatic spinal cord lesions place subjects with RIS at substantial risk for clinical conversion to either an acute or progressive event, a risk that is independent of brain lesions on MRI. *Neurology*® 2011;76:686–692

GLOSSARY

CI = confidence interval; **CIS** = clinically isolated syndrome; **IQR** = interquartile range; **MS** = multiple sclerosis; **OR** = odds ratio; **PPMS** = primary progressive multiple sclerosis; **RIS** = radiologically isolated syndrome; **ROC** = receiver operating characteristic; **UCSF** = University of California, San Francisco.

Imaging of the CNS has provided fundamental knowledge regarding the association between structural elements and function in relation to disease. Incidentally observed findings have been an inevitable consequence of the discovery and implementation of medical noninvasive imaging. Unanticipated intracranial anomalies may be nonspecific, indicative of distinct pathology (e.g., brain infarction, vascular malformations, or intracranial tumors),^{1,2} or may be highly suspicious for demyelinating disease based on the morphology and geographic distribution of the lesions within the brain parenchyma.^{3–5}

Existing literature suggests that there is a spectrum of asymptomatic demyelination, extending from the premortem to the postmortem period.^{6–8} Further expanding upon the phenotype of at-risk individuals, the term radiologically isolated syndrome (RIS)⁹ was recently proposed to describe asymptomatic individuals who possess radiologic abnormalities highly suggestive of multiple sclerosis (MS).

In addition to the identification of brain MRI abnormalities suggestive of demyelinating disease, asymptomatic spinal cord lesions are periodically identified—either during the course

Editorial, page 680

e-Pub ahead of print on January 26, 2011, at www.neurology.org.

From the Department of Neurology, UCSF Multiple Sclerosis Center, University of California, San Francisco, San Francisco.

Disclosure: Author disclosures are provided at the end of the article.

(A) Sagittal T2-weighted MRI of the cervical spine demonstrating a focus of high signal abnormality at C2. (B) Postcontrast T1-weighted image acquired during the same evaluation revealing an area of enhancement and parenchymal swelling at C2. (C) Axial T2-weighted MRI of the same lesion revealing a posterolateral predominance.

of the medical query, or as the initial focus of incidentally observed abnormality prior to brain imaging. The relationship between asymptomatic spinal cord lesions and clinical outcomes, and the frequency and potential relevance to disease progression in subjects with RIS, are unknown. The principal aim of this investigation was to determine if asymptomatic spinal cord lesions are associated with clinical progression in subjects with RIS.

METHODS Study participants. The cohort was ascertained through a retrospective analysis of individuals at the University of California, San Francisco (UCSF) Multiple Sclerosis Center who fulfilled previously described criteria for RIS.⁹ Subjects meeting RIS criteria were invited to have their clinical and radiologic data evaluated. In all cases, data from a detailed clinical history, comprehensive neurologic evaluation, serologic studies, and imaging studies were available for review.

Standard protocol approvals, registrations, and patient consents. The research protocol was approved by the UCSF Committee on Human Research, and informed consent was obtained from all participants.

Structural neuroimaging. All patients included had previously undergone one or more MRI studies of the brain that established the diagnosis of RIS using nonuniform protocols at magnetic field strengths of 1.5 T or 3.0 T. These scans were performed at multiple academic and community institutions, yielding MRI studies containing images with varying slice thicknesses and gaps between acquired images. For purposes of this study, we included patients who also had cervical spine imaging conducted prior to the development of clinical symptoms or signs consistent with relapsing or progressive MS. In select cases ($n = 17$), imaging of the thoracic spine was also performed. All examinations included T1- and T2-weighted spin-echo sequences in multiple planes of view (axial, coronal, and sagittal) with and without the administration of gadolinium. Gadolinium was administered in all MRI studies of the cervical spine.

In all cases, incidental MRI abnormalities within the brain or spinal cord were identified by a neuroradiologist on the initial examination and subsequently reviewed by at least 2 MS specialists (D.O., D.P.) who were blinded to the formal reading. A qualitative and quantitative (i.e., number of T2 foci, presence or absence of gadolinium enhancement) analysis of the available brain and cervical spine imaging studies was performed on all study participants.

Brain MRI lesion load from the initial available scan for RIS cases was classified into 3 categories based on the number of lesions measuring $\geq 3 \text{ mm}^2$: 1) <5 T2 foci, 2) 5–10 T2 foci, and 3) >10 T2 foci. Cervical spine imaging studies containing anomalies highly suggestive for demyelinating disease were deemed significant if the following criteria were met: 1) focal or multifocal involvement of the spinal cord parenchyma with ovoid, well-circumscribed lesions; 2) noncontiguous lesions involving ≤ 2 spinal segments; 3) imaging anomalies observed on more than one MRI sequence or plane; and 4) imaging anomalies not consistent with a vascular malformation (figure). Scans were excluded if a structural defect (i.e., protruding disc) or other medical condition could better account for the parenchymal signal changes within the cervical spinal cord.

Statistical analysis. Medians with interquartile ranges (IQR) (25th–75th percentiles) were used to summarize the demographic, clinical, and radiologic data.

The performance of the presence of a cervical spine lesion in predicting clinical progression was determined with true positives (subjects with RIS with an abnormal cervical spine MRI study with clinical progression to either clinically isolated syndrome [CIS] or primary progressive MS [PPMS]), false positives (subjects with RIS with an abnormal cervical spine MRI study with no clinical progression), true negatives (subjects with RIS with no cervical spine lesions and no clinical progression), and false negatives (subjects with RIS with no cervical spine lesions but developing clinical progression) used in determining the sensitivity (true positives/true positives + false negatives), specificity (true negatives/true negatives + false positives), and positive predictive value (true positives/true positives + false positives) with corresponding 95% confidence intervals (CI). The receiver operating characteristic (ROC) area [(sensitivity + specificity)/2] and likelihood ratios ($\pm$) were also determined. A 2-tailed Fisher

exact test was used for analysis of the contingency tables with odds ratios (ORs), 95% CI, and *p* values calculated.

The presence of asymptomatic cervical spinal cord lesions was the primary predictor in a logistic regression model in which the outcome was defined as clinical progression to either CIS or PPMS.¹⁰ Covariates that were considered for the multivariate models included age at the time of first RIS scan, race/ethnicity, gender, presence of brain contrast-enhancing lesions, family history of MS, presence of brainstem or posterior fossa lesions, exposure to disease-modifying therapy, length of clinical follow-up, and the brain MRI lesion load score. The effect of accounting for differences in length of clinical follow-up times and the duration between the first and last structural neuroimaging study acquired for a given subject prior to the development of CIS was also assessed. These covariates were screened in a univariate model; those that appeared to be meaningful were included in the multivariate logistic regression model, generating ORs and 95% CI and *p* values. A *p* value ≤ 0.05 was considered significant. Statistical analyses were performed using Stata/SE 10.0 (Stata Corporation, College Station, TX).

RESULTS A total of 102 individuals meeting criteria for RIS were identified. Longitudinal clinical data were available on 93 subjects. Cervical spine MRI scans acquired prior to the development of the first clinical event in subjects with RIS were available in 71 of these cases. Thoracic MRI scans were acquired on 17 subjects. Some subjects with RIS were excluded from this analysis due to either the lack of a cervical spine MRI study (*n* = 17) or a cervical imaging study acquired after the onset of clinical symptoms (*n* = 5). The demographics of the excluded subjects without presymptomatic cervical spine MRI studies were not significantly different from the study cohort (data not shown). Table 1 summarizes the demographic data of the study cohort.

The reasons for brain MRI were highly varied (table 1). The majority of the cases underwent brain MRI for evaluation of headache. A brain MRI scan was the initial neuroimaging study acquired with the exception of 3 cases in which CT imaging of the head was performed following a traumatic event, revealing brain parenchymal anomalies prior to the acquisition of brain MRI sequences. Cervical spinal cord imaging was acquired on one patient prior to the brain MRI during the evaluation of a congenital cervical rib. Overall, the reasons for acquiring a cervical spine MRI evaluation were nonuniform, with data acquired at the discretion of the referring physician or MS specialist providing longitudinal care. Cervical spine MRI scans were acquired shortly after RIS identification (median time 0.34 years [IQR 0.0–7.8]) during the medical workup for demyelinating disease, or as a baseline measure of disease during longitudinal care.

Cervical spinal cord anomalies highly suggestive of demyelination were discovered on imaging prior to clinical progression in 25 (35%) of the 71 subjects.

Table 1 Demographics of subjects with RIS with cervical spine MRI

Cohort (<i>n</i> = 71)	Values
Median age, y (interquartile range)	37.9 (20.9–61.7)
Female, <i>n</i> (%)	56 (78.9)
Race/ethnicity, <i>n</i> (%)	
White	60 (84.5)
African American	2 (2.8)
Asian/Pacific Islander	2 (2.8)
Middle Eastern	3 (4.2)
Hispanic	2 (2.8)
Mixed	2 (2.8)
Reasons for MRI, <i>n</i> (%)	
Headache	24 (33.8)
Trauma/fall	6 (8.5)
Vascular events	5 (7.0)
Spell	4 (5.6)
Research control	3 (4.2)
Anxiety/panic attack	3 (4.2)
Syncope	3 (4.2)
Dysmenorrhea/amenorrhea	2 (2.8)
MS family history or twin with MS	2 (2.8)
Orthostasis	2 (2.8)
Back pain	2 (2.8)
Galactorrhea	2 (2.8)
Medical screen	2 (2.8)
Abdominal pain	1 (1.4)
Cervical rib evaluation	1 (1.4)
Curiosity	1 (1.4)
Dizziness (1 min)	1 (1.4)
Ear popping with air travel	1 (1.4)
Hypersomnolence	1 (1.4)
Hypertension	1 (1.4)
Loss of smell	1 (1.4)
Aneurysm screen (polycystic kidney)	1 (1.4)
Tumor screen	1 (1.4)
Dry eyes	1 (1.4)
Exposure to DMT, <i>n</i> (%)	7 (9.9)

Abbreviations: DMT = disease-modifying therapy; MS = multiple sclerosis; RIS = radiologically isolated syndrome.

Gadolinium-enhancing lesions were observed in 6 cases. Of the thoracic MRI studies performed, 6 of 17 demonstrated abnormalities suggestive of demyelination (5 of the 6 cases with concomitant cervical spine lesions). Clinical progression to a diagnosis of CIS or PPMS was observed in 21 of these 25 subjects (84%) over a median time of 1.6 years (IQR 0.8–3.8). This clinical conversion time was reduced to 1 year (IQR 0.25–3.55) when evaluating the time in-

terval from the cervical spine imaging study to the first clinical event. The most common clinical event for these subjects was localized to the spinal cord, long tract motor, or long tract sensory pathways (n = 15) followed by involvement of the brainstem (n = 4) and optic nerve (n = 2). Prior to the development of the initial neurologic event, no focal deficits were identified on the neurologic examination. Of the subjects who progressed clinically, 2 demonstrated a progressive subtype and subsequently met criteria for PPMS.

Clinical progression to an acute event was observed in 3 (brainstem [n = 2], optic nerve [n = 1]) of the 46 subjects who did not possess an abnormality within the cervical spinal cord. Table 2 summa-

Table 2 Summary of clinical and radiologic characteristics of subjects with RIS with MRI cervical spine data

	Values
Abnormal cervical spine MRI, n	25
Median follow-up time, y (IQR) ^a	3.3 (1.3-4.8)
Clinical progression (CIS or PPMS), n (%)	21 (84)
Time from RIS to CIS or PPMS, y, median (IQR)	1.6 (0.8-3.8)
Time from cervical MRI scan to CIS or PPMS, y, median (IQR)	1.0 (0.3-3.6)
Clinical events	
Optic nerve	2
Spinal cord or long tract sensory or motor symptoms	15
Brainstem	4
Demyelinating subtypes	
CIS	19
PPMS	2
Normal cervical spine MRI, n	46
Median follow-up time, y (IQR) ^a	2.7 (1.0-3.5)
Clinical progression (CIS or PPMS), n (%)	3 (7)
Time from RIS to CIS or PPMS, y, median (range: min-max)	1.9 (1.0-9.8)
Time from cervical MRI scan to CIS or PPMS, y, median (range: min-max)	1.9 (1.0-2.0)
Clinical events	
Optic nerve	1
Spinal cord or long tract sensory or motor symptoms	0
Brainstem	2
Demyelinating subtypes	
CIS	3
PPMS	0

Abbreviations: CIS = clinically isolated syndrome; IQR = interquartile range; PPMS = primary progressive multiple sclerosis; RIS = radiologically isolated syndrome.

^a Follow-up time between the initial baseline RIS MRI to most recent clinical visit.

Table 3 Predictive utility of an asymptomatic spinal cord lesion for clinical conversion to clinically isolated syndrome or primary progressive MS

	Point estimate	95% CI (min-max)
Sensitivity	87.5%	67.6-97.3
Specificity	91.5%	79.6-97.6
ROC area	0.895	0.816-0.974
PPV	84.0%	63.9-95.5
Likelihood ratio (+)	10.30	3.98-26.60
Likelihood ratio (-)	0.14	0.05-0.40
Odds ratio ^a	75.3	16.1-350.0

Abbreviations: CI = confidence interval; PPV = positive predictive value; ROC = receiver operating characteristic.

^a $p < 0.0001$, Fisher exact test (2-tailed).

rizes the clinical outcomes from subjects with RIS with cervical spine MRI data.

Of the subjects with RIS with cervical spine lesions who progressed clinically, 19% were referred to our Center after the first clinical episode. Of the 3 individuals who progressed clinically but lacked involvement of the cervical spine, all subjects developed an initial event while being actively followed in our Center.

The diagnostic predictive value of an asymptomatic spinal cord lesion in subjects with RIS for development of the first clinical relapse or progression to a diagnosis of PPMS was determined with a sensitivity of 87.5% (95% CI 67.6-97.3), specificity of 91.5% (79.6-97.6), and positive predictive value of 84.0%. A substantial increase in the odds of clinical progression was observed (OR 75.3 [16.1-350.0]; $p < 0.0001$, 2-tailed Fisher exact test) in those subjects with RIS who possessed one or more lesions within the cervical spine (table 3).

Next, a multivariate regression model was used to assess the relative influences of several baseline covariates on the clinical outcome (table 4). In the multivariate logistic regression model, a substantial increase in the odds of clinical progression was observed when abnormalities typical for MS were present within the cervical spinal cord (OR 128.0, 95% CI 13.0-1256.5, $p < 0.0001$), whereas the presence of a lesion within the brainstem or posterior fossa involvement was moderate (OR 9.2 [1.1-75.2], $p = 0.04$). The association of age with progression also appeared to be important; for every 10-year increase in age, the odds of converting clinically were reduced (OR 0.38 [0.15-0.97]; $p = 0.04$).

PPMS subtypes were identified in a total of 3 cases; however, only 2 (61-year-old man and 66-year-old woman) were incorporated into the data analysis. The third case involved a 41-year-old man,

Table 4 Multivariate logistic regression model evaluating the impact of significant covariates on clinical conversion to CIS or PPMS

Outcome: clinical progression (conversion to CIS or PPMS)	Odds ratio	95% CI (min-max)	p Value
Presence of cervical spine lesion	128.0	13.0-1,256.5	<0.0001
Presence of a brainstem/posterior fossa lesion	9.18	1.12-75.10	0.038
Age at RIS presentation (per 10-y age increase)	0.38	0.15-0.97	0.043
Brain contrast enhancement ever	1.37	0.20-9.34	0.763
Brain MRI lesion load (5-10 lesions)	2.14	0.18-25.13	0.547
Brain MRI lesion load (>10 lesions)	1.12	0.11-11.82	0.915

Abbreviations: CI = confidence interval; CIS = clinically isolated syndrome; PPMS = primary progressive MS; RIS = radiologically isolated syndrome.

initially imaged (brain scan) following a spell who subsequently developed progressive unilateral leg weakness persisting over 12 months approximately 2 years after RIS identification. A spinal cord MRI scan was acquired after the report of progressive leg weakness revealing 3 nonenhancing foci throughout the cervical spine. His case was removed from the data analysis because the cervical imaging study was acquired after the onset of a clinical symptom. In both PPMS cases, formal criteria for PPMS were met.¹⁰ When a sensitivity analysis was performed with progressive subtypes removed, no significant changes in the outcomes were observed.

DISCUSSION This study found a significant relationship between unanticipated radiologic anomalies within the cervical spinal cord of patients with RIS with clinical progression. Our results suggest that those asymptomatic individuals who possess abnormal foci within the brain and cervical spinal cord, in comparison to the brain alone, are at high risk for developing acute or progressive clinical symptoms. Importantly, this risk is independent of brain lesion load.

The reason for the acquisition of a cervical spine MRI study varied widely between subjects. We believe that cervical spine imaging studies were obtained in some RIS cases to support the diagnosis of demyelinating disease or to establish a baseline measure of involvement. If cervical spine imaging studies were performed in the setting of a perceived equivocal brain MRI study for demyelination, a bias toward the null hypothesis of finding no effect would be expected. The fact that such a strong association was still observed with our data affirms the importance of this predictor for defining risk.

Based on our observations about the high predictive value of asymptomatic spinal cord lesions, it is now our Center's practice to acquire a cervical spine MRI study for all RIS cases. The sensitivity, specificity, and positive predictive value compare favorably

to proposed MS diagnostic criteria¹⁰⁻¹² that utilize radiologic evidence for dissemination in space and time following a single clinical event. The clinical utility of these criteria apply principally to assigning risk for further disease activity in CIS cases. Subjects with RIS with an asymptomatic cervical cord lesion may possess a comparable risk profile for conversion to MS similar to CIS. In addition, subjects with RIS without cervical spinal cord lesions may have a risk of disease progression comparable to CIS cases lacking brain lesions as only 7% of these subjects progressed clinically. This comparison underscores the importance in assessing disease progression and potential value in defining risk of clinical progression in asymptomatic cohorts.

Historically, the spinal cord has been regarded as a tightly networked, condensed structure containing well-organized and eloquent afferent and efferent sensorimotor pathways, with little capacity for compensatory mechanisms following injury in comparison to the brain. Thus, it would be reasonable to theorize that the presence of a spinal cord lesion would be associated with a clinically apparent physical examination finding or symptom, yet no such deficits were identified at the time spinal cord lesions were identified in our cohort. The current literature supports this as asymptomatic spinal cord lesions have been identified by clinicians unexpectedly,^{3,4,11,13} in the evaluation of suspected MS cases,¹⁴ in CIS,^{15,16} and in established MS cases.¹⁷ Despite this commonality in spatial involvement between demyelinating subtypes extending from asymptomatic to established cases of MS, the correlation between MS spinal cord lesions and clinical disability remains poor,^{17,18} affirming the intrinsic variability in the clinical expression of MS lesions.

The lack of overt subjective clinical symptoms reported by subjects with RIS or objective findings on neurologic examination suggests that the spinal cord may possess adept compensatory mechanisms for recovery. Alternatively, a critical mass in the degree of axonal loss may need to be reached before significant clinical findings are experienced. Previous data identified that axonal loss within the spinal cord in patients with MS are tract and fiber size specific, with smaller fibers measuring $<3 \mu\text{m}^2$ being more susceptible to demyelinating injury.¹⁹ Other factors that may explain why the cervical spine anomalies preceded distinct clinical events by nearly 2 years in our study include lesion site, axonal remyelination, or degree of recovery.²⁰

Interestingly, both acute and progressive demyelinating subtypes were identified as potential outcomes for subjects with RIS. Whether a similar prevalence for PPMS exists among those RIS cases

that ultimately convert clinically is unknown. Thus far, only a single case of subclinical PPMS has been described, with a progressive phenotype observed 9 years after the identification of brain anomalies suspicious for MS observed while serving as a healthy control subject.²¹

The results from this study underscore the value of assessing the structural integrity of the cervical spine in addition to the brain in demyelinating disease. However, the identification of MS foci by MRI may be biased due to differences in the timing and frequency of scanning along with MRI magnet field strengths and supporting software affecting image quality. Ideally, the use of a standardized imaging protocol and imaging data that encompass the entire central neuraxis would be highly valuable in assessing the extent of disease as demyelinating foci may occur in other spinal regions. The individual contribution of clinically discordant spinal cord lesions is currently unknown but represents an important data point not only in our understanding of MS, but also in relation to disability outcome measures.

This work suggests that a prospective study to understand the natural history of RIS is needed, incorporating a comprehensive array of clinical outcomes, standardized neuroimaging protocols, and molecular biomarkers to extend these data. These findings also affirm the importance of the inclusion of spinal cord imaging in the assessment and management of RIS cases. Subjects with RIS with spinal cord lesions may represent the group at highest risk for disease progression and, therefore, an ideal group in whom to study the effect of an immune-modulating therapeutic in clinical MS prevention. Large prospective studies of RIS with and without cervical lesions need to be performed to determine the actual risk of conversion to MS, in addition to searching for differing biological mechanisms that explain why some demyelinating cases appear to remain clinically silent for life, only to first appear unexpectedly at autopsy.⁶

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Darin T. Okuda and Dr. Bruce A.C. Cree.

DISCLOSURE

Dr. Okuda has received funding for travel or speaker honoraria from the National MS Society and MS Association of America; and receives research support from Pfizer Inc. and EMD Serono, Inc. Dr. Mowry receives research support from the National MS Society and the NIH. Dr. Cree has served as a consultant for Biogen Idec, Elan Corporation, and Teva Pharmaceutical Industries Ltd.; and receives research support from BioMS Medical, EMD Serono, Inc., Genentech Inc., the NIH, and the National MS Society. Dr. Crabtree serves as a consultant or on speakers' bureaus for Bayer Schering Pharma, Biogen Idec, Teva Pharmaceutical Industries Ltd., and EMD Serono, Inc. Dr. Goodin has served on scientific advisory boards and served as a consultant for Bayer Schering Pharma and Merck Serono; has received funding for travel or speaker honoraria from Bayer Schering Pharma, Teva Pharmaceutical Industries Ltd., and

Merck Serono; serves as Editor-in-Chief for the *International MS Journal*; has received research support from Bayer Schering Pharma and Novartis; and has served as an expert witness in medico-legal cases. Dr. Waubant serves on scientific advisory boards for the NIH and Actelion Pharmaceuticals Ltd.; has received free drugs for ongoing trials from Pfizer Inc., Sanofi-Aventis, and Biogen Idec; served as a one-time ad hoc consultant from Artielle ImmunoTherapeutics, Inc.; and receives research support from the National MS Society, The Immune Tolerance Network, and the Nancy Davis Foundation. Dr. Pelletier serves as a consultant for Biogen Idec, Bayer Schering Pharma, Genentech, Inc., and SYNARC Inc.; serves on speakers' bureaus for Biogen Idec and Teva Pharmaceutical Industries Ltd.; and receives research support from Biogen Idec, the NIH, and the National MS Society.

Received June 13, 2010. Accepted in final form September 27, 2010.

REFERENCES

1. Vernooij MW, Ikram MA, Tanghe HL, et al. Incidental findings on brain MRI in the general population. *N Engl J Med* 2007;357:1821–1828.
2. Bryan RN, Wells SW, Miller TJ, et al. Infarctlike lesions in the brain: prevalence and anatomic characteristics at MR imaging of the elderly: data from the Cardiovascular Health Study. *Radiology* 1997;202:47–54.
3. Lebrun C, Bensa C, Debouverie M, et al. Unexpected multiple sclerosis: follow-up of 30 patients with magnetic resonance imaging and clinical conversion profile. *J Neurol Neurosurg Psychiatry* 2008;79:195–198.
4. Siva A, Saip S, Altintas A, Jacob A, Keegan BM, Kantarci OH. Multiple sclerosis risk in radiologically uncovered asymptomatic possible inflammatory-demyelinating disease. *Mult Scler* 2009;15:918–927.
5. Lebrun C, Bensa C, Debouverie M, 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;66:841–846.
6. Georgi W. [Multiple sclerosis: anatomopathological findings of multiple sclerosis in diseases not clinically diagnosed.] *Schweiz Med Wochenschr* 1961;91:605–607.
7. De Stefano N, Cocco E, Lai M, et al. Imaging brain damage in first-degree relatives of sporadic and familial multiple sclerosis. *Ann Neurol* 2006;59:634–639.
8. Lyoo IK, Seol HY, Byun HS, Renshaw PF. Unsuspected multiple sclerosis in patients with psychiatric disorders: a magnetic resonance imaging study. *J Neuropsychiatry Clin Neurosci* 1996;8:54–59.
9. Okuda DT, Mowry EM, Beheshtian A, et al. Incidental MRI anomalies suggestive of multiple sclerosis: the radiologically isolated syndrome. *Neurology* 2009;72:800–805.
10. Polman CH, Reingold SC, Edan G, et al. Diagnostic criteria for multiple sclerosis: 2005 revisions to the “McDonald Criteria.” *Ann Neurol* 2005;58:840–846.
11. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol* 2001;50:121–127.
12. Swanton JK, Rovira A, Tintore M, et al. MRI criteria for multiple sclerosis in patients presenting with clinically isolated syndromes: a multicentre retrospective study. *Lancet Neurol* 2007;6:677–686.
13. Barkhof F, Scheltens P, Kamphorst W. Pre-and post-mortem MR imaging of unsuspected multiple sclerosis in a patient with Alzheimer's disease. *J Neurol Sci* 1993;117:175–178.

14. Lycklama a Nijeholt GJ, Uitdehaag BM, Bergers E, Castelijns JA, Polman CH, Barkhof F. Spinal cord magnetic resonance imaging in suspected multiple sclerosis. *Eur Radiol* 2000;10:368–376.
15. Brex PA, Leary SM, O’Riordan JI, et al. Measurement of spinal cord area in clinically isolated syndromes suggestive of multiple sclerosis. *J Neurol Neurosurg Psychiatry* 2001;70:544–547.
16. O’Riordan JI, Losseff NA, Phatouros C, et al. Asymptomatic spinal cord lesions in clinically isolated optic nerve, brain stem, and spinal cord syndromes suggestive of demyelination. *J Neurol Neurosurg Psychiatry* 1998;64:353–357.
17. Nijeholt GJ, van Walderveen MA, Castelijns JA, et al. Brain and spinal cord abnormalities in multiple sclerosis. Correlation between MRI parameters, clinical subtypes and symptoms. *Brain* 1998;121:687–697.
18. Trop I, Bourgouin PM, Lapierre Y, et al. Multiple sclerosis of the spinal cord: diagnosis and follow-up with contrast-enhanced MR and correlation with clinical activity. *AJNR Am J Neuroradiol* 1998;19:1025–1033.
19. DeLuca GC, Ebers GC, Esiri MM. Axonal loss in multiple sclerosis: a pathological survey of the corticospinal and sensory tracts. *Brain* 2004;127:1009–1018.
20. Mews I, Bergmann M, Bunkowski S, Gullotta F, Bruck W. Oligodendrocyte and axon pathology in clinically silent multiple sclerosis lesions. *Mult Scler* 1998;4:55–62.
21. McDonnell GV, Cabrera-Gomez J, Calne DB, Li DK, Oger J. Clinical presentation of primary progressive multiple sclerosis 10 years after the incidental finding of typical magnetic resonance imaging brain lesions: the subclinical stage of primary progressive multiple sclerosis may last 10 years. *Mult Scler* 2003;9:204–209.

The AAN Provides a New Resource for Your Patients

Written by Ronald DeVere, MD, Director of the Taste and Smell Disorders Clinic in Austin, Texas and Marjorie Calvert, Food Consultant at the clinic, *Navigating Smell and Taste Disorders* includes causes, treatment options, and 36 recipes and additional tips that will make food appealing again. “More than 200,000 people visit doctors each year for smell and taste problems, which often are the first sign of neurologic disorders, such as Alzheimer’s disease, Parkinson’s disease, head injury, or multiple sclerosis,” said DeVere.

“An enlightening guide. . . this patient-oriented approach should be hailed as a groundbreaking book. It is highly recommended for any patients suffering from these often undiagnosed and untreated disorders and the relatives who help care for them.”

—Alan R. Hirsch, MD, neurological director at the Smell and Taste Treatment and Research Foundation in Chicago

Invite your patients to visit www.aan.com/view/smellandtaste for more information about this invaluable resource. Available from all major booksellers.