The contemporary spectrum of multiple sclerosis misdiagnosis

A multicenter study

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ABSTRACT

Objective: To characterize patients misdiagnosed with multiple sclerosis (MS).

Methods: Neurologists at 4 academic MS centers submitted data on patients determined to have been misdiagnosed with MS.

Results: Of 110 misdiagnosed patients, 51 (46%) were classified as "definite" and 59 (54%) "probable" misdiagnoses according to study definitions. Alternate diagnoses included migraine alone or in combination with other diagnoses 24 (22%), fibromyalgia 16 (15%), nonspecific or nonlocalizing neurologic symptoms with abnormal MRI 13 (12%), conversion or psychogenic disorders 12 (11%), and neuromyelitis optica spectrum disorder 7 (6%). Duration of misdiagnosis was 10 years or longer in 36 (33%) and an earlier opportunity to make a correct diagnosis was identified for 79 patients (72%). Seventy-seven (70%) received disease-modifying therapy and 34 (31%) experienced unnecessary morbidity because of misdiagnosis. Four (4%) participated in a research study of an MS therapy. Leading factors contributing to misdiagnosis were consideration of symptoms atypical for demyelinating disease, lack of corroborative objective evidence of a CNS lesion as satisfying criteria for MS attacks, and overreliance on MRI abnormalities in patients with nonspecific neurologic symptoms.

Conclusions: Misdiagnosis of MS leads to unnecessary and potentially harmful risks to patients. Misinterpretation and misapplication of MS clinical and radiographic diagnostic criteria are important contemporary contributors to misdiagnosis. *Neurology*® 2016;87:1393–1399

GLOSSARY

IgG = immunoglobulin G; **MS** = multiple sclerosis; **NMOSD** = neuromyelitis optica spectrum disorder; **OCB** = oligoclonal band.

Multiple sclerosis (MS) remains a clinical diagnosis, as no specific biomarker for MS has been identified. Diagnosis relies on the appropriate interpretation of radiologic data in patients with the appropriate history and neurologic examination suggestive of demyelination. Despite well-validated diagnostic criteria,[1] misdiagnosis remains a problem that has significant implications for patients, their providers, and health care systems.[2–4]

In 2015, the Institute of Medicine described the need to study misdiagnosis as a "moral, professional, and public health imperative."[5,6] A recent study has suggested that medical error is the third leading cause of death in the United States.[7] Although misdiagnosis of MS is frequently acknowledged,[8,9] data concerning misdiagnosis typically originate from case reports, limiting generalizability and recommendable solutions. Few studies have reported characteristics of cohorts of patients mistakenly diagnosed with MS, the most recent published almost 20 years ago.[10–12] With the evolution of diagnostic criteria and the incorporation of imaging, the frequency and factors contributing to misdiagnosis of MS have likely changed. Prior studies may not reflect the current spectrum of, and contributors to, MS misdiagnosis. A survey of 122 MS specialists published in 2012 suggested that misdiagnosis of MS remains common, and most frequently

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migraine, psychiatric disease, and neuromyelitis optica spectrum disorders (NMOSDs) are mistaken for MS. Overreliance on MRI findings was hypothesized as contributing to misdiagnosis,[2] but conclusions from surveys are limited.

In this study, we assessed the clinical and radiographic characteristics of a large contemporary population of patients across 4 US-based academic medical centers who were determined by MS specialists to have been misdiagnosed with MS. The aim of this pilot study was to determine the contemporary spectrum of alternative diagnoses mistaken for MS and to understand the risks associated with these misdiagnoses. We subsequently assessed whether these diagnostic errors were avoidable by identifying problems arising from application of patient clinical and MRI data to current MS diagnostic criteria.

METHODS Twenty-three neurologists with subspecialty training and/or practice focus in MS on the staff of MS centers at the University of Vermont, Oregon Health & Science University, Washington University, and Mayo Clinic participated.

Patients were identified by participating neurologists during clinical evaluations either prospectively during the 13 months of the study or shortly before study initiation. Patients were classified as having "definite misdiagnosis" when an alternative diagnosis was definitively made based on clinical, laboratory, and neuroimaging evaluation and "probable misdiagnosis" when an alternative diagnosis was suspected and diagnostic criteria for MS were not met.

Only patients who were previously informed by another physician that they had a diagnosis of MS were included. Patients for whom MS was one of several diagnoses being considered, but who were not provided with a firm diagnosis, were excluded. Suspected or confirmed alternative diagnoses were recorded for each patient. Demographic, clinical, and radiographic data were also evaluated. Neurologists were asked to assess whether inappropriate application of clinical or radiographic MS diagnostic criteria contributed to misdiagnosis in each case.

A password-protected, web-based data entry form for the collection of individual patient characteristics was developed using REDCap, through collaboration among the lead investigators at each center (A.J.S., D.N.B., A.H.C., B.G.W.). The treating neurologist who established the MS misdiagnosis completed the patient data form. Data entry fields included no identifiable patient information. Although each institution was identifiable, no identifier linked specific neurologists at these institutions to their reports. Whether the participating provider or another provider made the initial misdiagnosis of MS was not surveyed.

Standard protocol approvals, registrations, and patient consents. The data entry form and the study were reviewed and approved by the institutional review boards at the University of Vermont, Oregon Health & Science University, Washington University, and Mayo Clinic. Data were collected from August 1, 2014, to September 1, 2015.

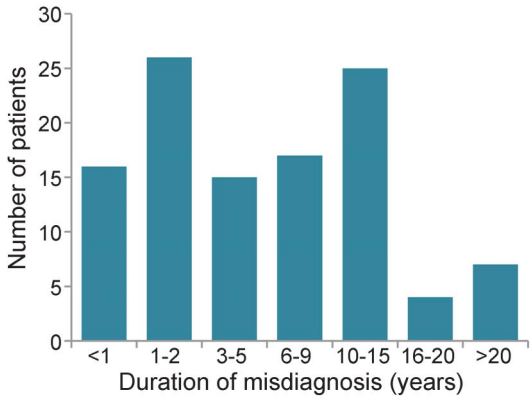
RESULTS **Demographic characteristics of misdiagnosed patients.** One-hundred ten patients incorrectly diagnosed with MS were identified, 61 (55%) from Mayo Clinic, 27 (25%) from University of Vermont, 12 (11%) from Washington University, and 10 (9%) from Oregon Health & Science University. Ninety-three (85%) were women and 17 (15%) were men. Mean age was 49 ± 11 years with a range from 21 to 77 years. Fifty-one patients (46%) were classified as "definite" and 59 (54%) as "probable" misdiagnoses. Figure 1 presents approximate duration of misdiagnosis in all 110 patients.

Neurologists informed 107 (97%) of the patients that their MS diagnosis was incorrect. In the remaining 3 patients (3%), neurologists intended to discuss misdiagnosis after further evaluation (1), the misdiagnosis discussion had occurred with another physician before their evaluation (1), and misdiagnosis was confirmed following postmortem evaluation (1). Misdiagnosis of MS was made by a neurologist with fellowship training or a practice focus in MS in 26 patients (24%), a neurologist without such training in 35 (32%), a nonneurologist in 3 (3%), and a physician with unknown training in the remaining 46 patients (42%).

Alternative diagnoses. The five most frequent alternative diagnoses reported by participating neurologists comprised 66% of the misdiagnosed patients (table 1), and included migraine alone or in combination with additional diagnoses, fibromyalgia, nonspecific or nonlocalizing neurologic symptoms with abnormal MRI, conversion or psychogenic disorder, and NMOSD. Fibromyalgia was reported significantly more often by Mayo Clinic neurologists than the other institutions ($p = 0.04$), but there were no other differences in the frequency of the other 4 most reported diagnoses among participating institutions.

Migraine alone or in combination with additional diagnoses was the most common alternative diagnosis in patients misdiagnosed with MS and was reported

Figure 1 Duration of misdiagnosis



The number of years patients had been misdiagnosed with multiple sclerosis.

Table 1 Diagnoses and syndromes mistaken for multiple sclerosis

	No. (%)
Migraine alone or in combination with other diagnoses	24 (22)
Fibromyalgia	16 (15)
Nonspecific or nonlocalizing neurologic symptoms with abnormal MRI	13 (12)
Conversion or psychogenic disorder	12 (11)
Neuromyelitis optica spectrum disorder	7 (6)
Clinically isolated syndrome	3 (3)
Neurodegenerative cerebellar syndrome	2 (2)
MRI changes caused by vascular disease	2 (2)
Parkinsonism with nonspecific white matter abnormalities	2 (2)
"Radiologically isolated syndrome"	2 (2)
Cervical spondylosis with myelopathy	2 (2)
Genetic leukodystrophy	2 (2)
Idiopathic transverse myelitis	2 (2)
Noninflammatory myelopathy	2 (2)
Nonspecific symptoms with positive CSF OCBs	2 (2)
Stroke, nonembolic	2 (2)
Anti-Ma2 paraneoplastic syndrome	1 (1)
Acute disseminated encephalomyelitis	1 (1)
Astrocytoma	1 (1)
Mitochondrial disorder	1 (1)
Neurosarcoidosis	1 (1)
Moyamoya disease	1 (1)
Hypertension and alcohol abuse	1 (1)
Neuropathy	1 (1)
Unclear diagnosis; complaints of paresthesias	1 (1)
Nonspecific or nonlocalizing neurologic symptoms with normal MRI	1 (1)
Viral meningoencephalitis with subsequent abnormal MRI and acute labyrinthitis	1 (1)
White matter lesions due to TNF-α inhibitor use for psoriasis	1 (1)
Behçet syndrome	1 (1)
CADASIL	1 (1)
Degenerative joint disease of lumbar spine	1 (1)

Abbreviations: CADASIL = cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; OCB = oligoclonal band; TNF-α = tumor necrosis factor α.

in 24 patients (22%). Additional diagnoses in combination with migraine included psychiatric disease (3), fibromyalgia (2), small vessel disease (2), acute labyrinthitis (1), spells of uncertain etiology (1), rheumatoid arthritis (1), vitamin B_{12} deficiency (1), and small fiber neuropathy (1). Neurologists also reported imaging abnormalities related to tobacco use, vitamin B_{12} deficiency, and small vessel ischemic disease in patients with migraine. In the patients with migraine, neurologists specified that migrainous symptoms mistaken for demyelinating attacks were incorrectly used to satisfy dissemination in time criteria. Presumed migraine-associated white matter lesions were often used to document dissemination in space imaging criteria.

In patients with a primary diagnosis of conversion or psychogenic disorder, additional diagnoses of migraine, diabetes mellitus, hypertension, tobacco use, and small vessel ischemic disease were noted to have contributed to abnormal imaging. In one case of nonspecific or nonlocalizing neurologic symptoms with abnormal MRI, a MRI contrast-enhancing vascular lesion resulted in an erroneous determination of dissemination in time. One case of conversion disorder and one case of fibromyalgia misdiagnosed as MS had normal imaging.

Of 7 patients with NMOSD, 5 were seropositive for anti–aquaporin-4 antibodies, one was seronegative, and serostatus for one was not reported. Six patients diagnosed with NMOSD had a history of optic neuritis, 6 had a history of a longitudinally extensive spinal cord lesion, and one had a history of "intractable vomiting or hiccoughs."

Exposure to immunomodulatory therapy. Seventy-seven patients (70%) had received one or more immunomodulatory therapies for MS (table 2). Twenty-six patients (24%) were exposed to 2 therapies, 6 (5%) to 3 therapies, 7 (6%) to 4 therapies, and 1 (1%) to 5 therapies. Figure 2 presents the approximate cumulative time of exposure to any combination of immunomodulatory therapy in 75 of the 77 patients. Exposure to methylprednisolone or prednisone was not recorded as part of the study.

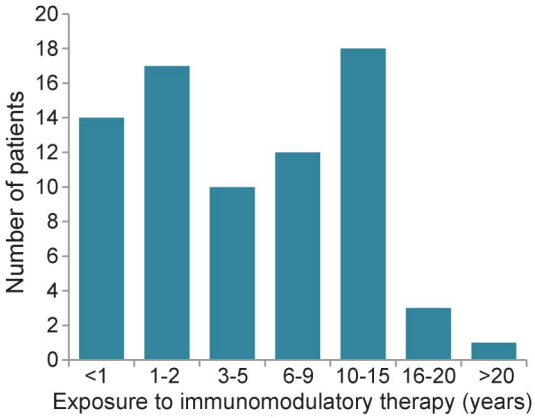
CSF evaluation. CSF was evaluated in 74 patients (67%) at the time of their initial misdiagnosis, and specific results were available for review in 52. Twenty-eight of 52 (54%) had negative results for

Table 2 Immunomodulatory therapies received by patients with misdiagnosis

	No. (%)
Interferon beta-1a or interferon beta-1b	58 (53)
Glatiramer acetate	44 (40)
Natalizumab	14 (13)
Dimethyl fumarate	7 (6)
Fingolimod	5 (5)
Teriflunomide	3 (3)
Mitoxantrone	2 (2)
Cyclophosphamide	1 (1)
IV immunoglobulin	1 (1)
Repository corticotropin injection	1 (1)
Unknown	1 (1)

Forty patients (36%) had received more than one therapy. Immunomodulatory therapy data were unavailable in 2 patients.

Figure 2 Cumulative exposure to immunomodulatory therapy



The cumulative number of years misdiagnosed patients had been exposed to any immunomodulatory therapy.

CSF oligoclonal bands (OCBs) and normal immunoglobulin G (IgG) index. Eight (15%) had negative OCBs with unknown IgG index results, 2 (4%) had normal IgG index with unknown OCB results, 6 (12%) had positive OCBs with unknown IgG index results, 1 (2%) had elevated IgG index with unknown OCB results, 2 (4%) had positive OCBs and normal IgG index, 1 (2%) had elevated IgG index and normal OCBs, and 4 (8%) had positive OCBs and elevated IgG index. Neurologists noted that in 8 of the patients where CSF was initially performed, an initial erroneous interpretation of the results contributed to misdiagnosis (i.e., OCBs were elevated both in serum and CSF). Potential differences between laboratories in CSF assay methods and positive result thresholds were not evaluated.

Contributors to misdiagnosis. Participating MS specialists were asked their opinion about the potential contribution to misdiagnosis from an inappropriate application of MS clinical and MRI diagnostic criteria for each patient. Inappropriate interpretation of symptoms as relapses, lack of objective demonstration that historical symptoms were demyelinating events, and misinterpretation of MRI were all identified as contributors to misdiagnosis (table 3).

Clinical trial exposure. Four patients (4%) participated in clinical trials for MS therapeutics. The diagnoses in these patients included nonspecific or nonlocalizing neurologic symptoms with abnormal MRI, moyamoya disease, migraine, and fibromyalgia, with spells and visual and urinary symptoms of uncertain etiology.

Missed opportunity and morbidity. Neurologists identified "clear evidence of an earlier missed opportunity to make a correct diagnosis" in 79 (72%) of misdiagnosed patients and that 34 (31%) experienced "unnecessary morbidity as a direct result of a misdiagnosis of MS." Morbidities included the following: risks associated with unnecessary immunomodulatory therapy exposure and treatment-related side effects (19), risks associated with unnecessary exposure to corticosteroids and related side effects (5) including psychosis in one patient, delay in treatment for cervical spondylosis (1), psychological harm including anxiety and depression (7), avoidable motor weakness (1), worsening of neuromyelitis spectrum disorder associated with interferon therapy (1), mesenchymal stem cell transplant (1), and death from fulminant neuromyelitis optica (1). Two morbidities were reported for 5 patients.

DISCUSSION In this study, we identified 110 patients incorrectly diagnosed with MS. A number of common diagnoses and syndromes were frequently mistaken for MS, and many patients had been misdiagnosed for a prolonged period of time. As a result, at least a third of all patients experienced morbidity and many more were

Table 3 Contributors to MS misdiagnosis

	Yes	No	Unknown
	n (%)	n (%)	n (%)
Inappropriate application to MS diagnostic criteria of neurologic symptoms atypical for a demyelinating attack	72 (65)	24 (22)	14 (13)
Inappropriate application to diagnostic criteria of a historical episode of neurologic dysfunction without corroborating objective evidence of a lesion (on neurologic examination, evoked potentials, or imaging)	53 (48)	38 (35)	19 (17)
Overreliance on the presence of MRI abnormalities meeting DIS to confirm a diagnosis of MS in a patient with "nonspecific neurologic symptoms"	66 (60)	28 (25)	16 (15)
Erroneous determination of juxtacortical or periventricular lesion location to fulfill DIS	36 (33)	43 (39)	31 (28)
Erroneous determination of DIT because of variability of MRI slice orientation (i.e., MRIs performed on different scanners leading to the appearance of new lesions)	13 (12)	64 (58)	33 (30)

Abbreviations: DIS = dissemination in space; DIT = dissemination in time; MS = multiple sclerosis.

likely exposed to unnecessary risk. Our study suggests that the misinterpretation and misapplication of MS clinical and radiographic diagnostic criteria are important contemporary contributors to misdiagnosis.

Approximately half of the patients in the study were classified as a "definite" misdiagnosis (in which an alternative confirmed diagnosis was made) while half were classified as a "probable" misdiagnosis (in which an alternative diagnosis was suspected and who did not satisfy diagnostic criteria for diagnosis of MS). However, participating neurologists were sufficiently confident to inform 97% of patients that they had been misdiagnosed. Migraine, fibromyalgia, nonspecific or nonlocalizing neurologic symptoms with abnormal MRI, conversion or psychogenic disorder, and NMOSD were the most frequently reported alternate diagnoses made among patients who had been misdiagnosed with MS and constituted two-thirds of the patients reported. These findings closely parallel the diagnoses reported to have been most frequently mistaken for MS in clinical practice by a large group of MS specialists in a 2012 survey.[2] Furthermore, previous data from 2 large cohort studies performed at MS tertiary care centers in 1984 and 2005 indicated that psychiatric disease and migraine were frequent final diagnoses in patients initially referred for evaluation for MS, suggesting the enduring potential for misdiagnosis in these disorders.[13,14]

With the exception of NMOSD, diagnoses frequently mistaken for MS in our study lack a specific biomarker and their correct identification relies instead on clinical and radiographic results and the clinician's acumen alone. Of note, 26 patients (24%) were misdiagnosed by neurologists with MS-focused practices, suggesting that this problem is not confined to nonspecialists. Prior authors have noted barriers to reexamining established diagnoses of MS,[4,8] and suggested a tendency for MS specialists, after seeing many atypical presentations of MS, to dismiss "red flags" as being within the spectrum of MS, rather than a clue to an alternative condition. Although the often-cited expansive differential diagnosis of MS includes red flags for a variety of rare disorders,[15] several of which were identified in this study, our data confirm that common disorders or syndromes account for misdiagnosis in most cases. This observation also suggests that an extensive serum laboratory evaluation may not always be helpful in the evaluation of suspect MS, as laboratory tests cannot confirm a diagnosis of fibromyalgia, migraine, or a psychogenic disorder and that overreliance on imaging abnormalities may contribute to misdiagnosis in such cases. However, our findings do not preclude the possibility that additional disorders known to mimic MS were identified through such testing and may have prevented misdiagnosis in those cases. A significant number of patients were misdiagnosed with MS despite the finding of normal CSF during their initial evaluation, perhaps a reflection of a relative higher weight given to interpretation of radiographic abnormalities in evaluation of patients for MS and the elimination of CSF consideration from the 2010 McDonald diagnostic criteria for relapsing-remitting MS.

Our data differ from prior studies. In the 1980s, 2 small studies[10,11] (including 33 and 10 patients) reported a higher number of neoplastic, infectious, or vascular disorders that were mistaken for MS, likely reflecting the lack of MRI availability at that time. In 1997, Charles Poser reported on 130 misdiagnosed patients he had evaluated.[12] His cohort contained 37% with "disseminated encephalomyelitis," 22% with chronic fatigue syndrome, 21% with "myelopathy," 4% with "posttraumatic syndrome," 4% with complicated migraine, and 4% with psychiatric disorders that were misdiagnosed as MS.[12] These diagnoses reflect referral patterns for a single well-known MS neurologist before the incorporation of MRI into MS diagnostic criteria in 2001.[16] MRI demonstration of dissemination in time by current criteria may have confirmed an MS diagnosis in a number of these patients. It is also possible that some of Poser's patients might have been subsequently diagnosed as NMOSD after this disorder was recognized as a pathologically distinct entity with a highly specific biomarker.

Many of the patients in our study carried a misdiagnosis for a lengthy period of time, including a third for 10 years or longer, and they were often exposed to unnecessary and potentially harmful treatments. More than two-thirds of the patients were exposed to immunomodulatory therapy, almost a third for 10 years or longer. Fourteen patients received natalizumab, a drug associated with progressive multifocal leukoencephalopathy. Four patients were exposed to investigational agents in a clinical trial for MS therapies. In addition to unnecessary exposure to these therapies, participating MS specialists indicated a number of morbidities experienced by patients in this study as a result of misdiagnosis, including one patient who died having a misdiagnosis of MS where appropriate therapies for NMOSD were not provided. Failure to treat the correct diagnosis was acknowledged as a contributor to morbidity in a number of patients. Although difficult to measure, the psychological harm associated with a misdiagnosis of MS and its subsequent reversal[3] was also noted in the study. Lastly, the financial risk to patients and our health care system as a consequence of expensive MS disease-modifying therapies,[17] imaging, and clinical care in these 110 patients alone was likely substantial.

Participating MS specialists identified "clear evidence of an earlier missed opportunity to make a correct diagnosis" in a majority (72%) of patients.

Most important, our study suggests that strict adherence to clinical and radiographic MS diagnostic criteria may have prevented misdiagnosis in many patients. Atypical symptoms for a demyelinating attack contributed to misdiagnosis in almost two-thirds of the patients. This observation likely reflects misunderstanding of what constitutes a "typical" demyelinating attack (i.e., optic neuritis, transverse myelitis, brainstem syndrome). MS diagnostic criteria were not rigorously validated in patients with atypical clinical presentations.[18] MRI criteria were also not developed to facilitate differentiation of MS from other conditions, such as migraine, associated with MRI white matter abnormalities, but to identify patients at high risk of MS after clinical presentations "typical for demyelination."[1] MRI abnormalities incorrectly attributed to MS in patients with nonspecific neurologic symptoms contributed to misdiagnosis in more than half of the patients in the study. MS diagnostic criteria also stipulate that corroborating objective findings must be sought in patients reporting historical episodes of neurologic dysfunction suggestive of demyelination before diagnosis is confirmed.[1] This frequently overlooked requirement[4,19,20] contributed to misdiagnosis in half of the patients in the study and corroboration of such reported symptoms through clinical, radiographic, or neurophysiologic evaluation providing evidence for a CNS lesion may have aided in diagnosis in these patients. Overreliance on the interpretation of MRI abnormalities in patients with atypical syndromes and unverified prior symptoms may be a significant cause of misdiagnosis.[2,18,21,22]

There are limitations to this study. Neurologists participating in the study may have been incorrect in their assessment of misdiagnosis in some cases. Given the lack of specific biomarkers for the disorders mistaken for MS identified in this study, it is possible that neurologists might disagree on their assessment of the correct clinical diagnosis in some cases. Selection and referral bias likely influenced patient characteristics. An estimate of the frequency of MS misdiagnosis would be desirable, but obtaining such an estimate would require a different study design. While contributors to misdiagnosis may be inferred from available patient records and the specific alternative diagnosis identified, in most instances, our neurologists did not participate in making the initial incorrect diagnosis of MS and thus their assessment of potential contributors to misdiagnosis may be considered speculative. Lastly, the assessment of some patients later in their disease course may have facilitated recognition of a misdiagnosis, and hindsight bias may have influenced opinions regarding earlier opportunity for a correct diagnosis.

MS is complex and can be challenging to diagnose. Some degree of diagnostic uncertainty is inevitable. Nevertheless, misdiagnosis of MS has significant consequences for patients. Although it may not be possible to eliminate diagnostic error completely, strict adherence and conservative application of MS clinical and corresponding radiographic diagnostic criteria and education concerning proper use of MS diagnostic criteria may prevent misdiagnosis. CSF analyses can be informative, although clinicians should understand that positive parameters for CNS inflammation are not specific for the diagnosis of MS. Serial clinical and radiographic monitoring may be prudent in patients with atypical clinical presentations and/or with nonspecific MRI abnormalities. Such observation over time may ultimately confirm a diagnosis of MS, or establish an alternative diagnosis. This approach may be difficult in light of emerging data supporting early initiation of disease-modifying therapy in patients with MS or at high risk of MS.[23–25] Continual vigilance for "red flags"[15,26,27] in patients with an existing diagnosis of MS remains important, especially in those with atypical clinical or radiographic features or lacking CSF markers of intrathecal IgG synthesis. Future MS diagnostic criteria should balance the need for prompt diagnosis and institution of therapy and the potential for misinterpretation or misapplication and the risks of misdiagnosis.

AUTHOR CONTRIBUTIONS

Andrew J. Solomon, MD: conceptualization and study design, analysis and interpretation of the data, and drafting of the manuscript for intellectual content. Dennis N. Bourdette, MD: conceptualization and study design, analysis and interpretation of the data, and drafting of the manuscript for intellectual content. Anne H. Cross, MD: conceptualization and study design, analysis and interpretation of the data, and drafting of the manuscript for intellectual content. Angela Applebee, MD: analysis and interpretation of the data, and drafting of the manuscript for intellectual content. Philip M. Skidd, MD: analysis and interpretation of the data, and drafting of the manuscript for intellectual content. Diantha B. Howard, MA: conceptualization and study design, analysis and interpretation of the data. Rebecca I. Spain, MD: analysis and interpretation of the data, and drafting of the manuscript for intellectual content. Michelle H. Cameron, MD: analysis and interpretation of the data, and drafting of the manuscript for intellectual content. Edward Kim, MD: analysis and interpretation of the data, and drafting of the manuscript for intellectual content. Michele K. Mass, MD: analysis and interpretation of the data, and drafting of the manuscript for intellectual content. Vijayshree Yadav, MD: analysis and interpretation of the data, and drafting of the manuscript for intellectual content. Ruth H. Whitham, MD: analysis and interpretation of the data, and drafting of the manuscript for intellectual content. Erin E. Longbrake, MD, PhD: analysis and interpretation of the data, and drafting of the manuscript for intellectual content. Robert T. Naismith, MD: analysis and interpretation of the data, and drafting of the manuscript for intellectual content. Gregory F. Wu, MD, PhD: analysis and interpretation of the data, and drafting of the manuscript for intellectual content. Becky J. Parks, MD: analysis and interpretation of the data, and drafting of the manuscript for intellectual content. Dean M. Wingerchuk, MD: analysis and interpretation of the data, and drafting of the manuscript for intellectual content. Brian L. Rabin, MD: analysis and interpretation of the data, and drafting of the manuscript for intellectual content. Michel Toledano, MD: analysis and interpretation of the data, and drafting of the manuscript for intellectual content. W. Oliver Tobin, MBBCh, PhD: analysis and interpretation of the data, and drafting of the manuscript for intellectual content. Orhun H. Kantarci, MD: analysis and interpretation of the data, and drafting of the manuscript for intellectual content. Jonathan L. Carter, MD: analysis and interpretation of the data, and drafting of the manuscript for intellectual content. B. Mark Keegan, MD: analysis and interpretation of the data, and drafting of the manuscript for

intellectual content. Brian G. Weinshenker, MD: conceptualization and study design, analysis and interpretation of the data, and drafting of the manuscript for intellectual content.

STUDY FUNDING

National Multiple Sclerosis Society PP2074. Anne H. Cross was supported in part by the Manny and Rosalyn Rosenthal–Dr. John L. Trotter MS Center Chair from the Barnes-Jewish Hospital Foundation.

DISCLOSURE

A. Solomon reports no disclosures relevant to the manuscript. D. Bourdette reports section editor *Current Neurology and Neuroscience*. A. Cross reports consulting for AbbVie, Biogen EMD Serono, Novartis, Mallinckrodt, Teva, Roche/Genentech, Genzyme/Sanofi; Scientific Advisory Board: Roche, Associate editor for *Annals of Clinical and Translational Neurology*; Research support: Biogen and Teva. A. Applebee, P. Skidd, and D. Howard report no disclosures relevant to the manuscript. R. Spain reports funding from the Conrad Hilton Foundation. M. Cameron reports consulting for Acorda therapeutics, MD consult, and ReWalk. E. Kim reports serving on advisory boards of Teva and Genzyme. M. Mass reports no disclosures relevant to the manuscript. V. Yadav reports consult for Biogen Idec and serving on an advisory board for Genentech. R. Whitham reports serving on a data safety monitoring board for a clinical trial sponsored by Chugai Pharmaceutical. E. Longbrake reports speaking and consulting for Genzyme. R. Naismith reports speaking for Acorda, Biogen, and Genzyme and consulting for Acorda, Alkermes, Biogen, EMD Serono, Genentech, Genzyme, Novartis, Pfizer, Questcor. G. Wu reports serving on an advisory board for Biogen Idec and speaking for Pfizer. B. Parks reports consulting for Biogen Idec and Novartis, serving on an advisory board, and holding stock or stock options greater than 5% of the company or greater than $10,000 in value (Regeneron). D. Wingerchuk reports serving on a clinical trial adjudication panel for MedImmune, research support from Alexion and TerumoBCT, and compensation for serving as editor in chief of *The Neurologist*. B. Rabin, M. Toledano, W. Oliver Tobin, and O. Kantarci report no disclosures relevant to the manuscript. J. Carter reports serving on the data safety and monitoring committee for Alder Pharmaceuticals, compensation for developing a drug treatment monograph for Omnicare/USciences, and research support from Roche, Sanofi, and Genzyme. B. Mark Keegan reports consulting for Novartis, Bionest, and Bristol-Myers Squibb and receives research support from Caridian BCT. B. Weinshenker reports data safety monitoring board membership for Novartis and Mitsubishi and MedImmune for adjudication committee membership. He reports for travel to attend an EMA conference supported by Alexion and royalties from RSR Ltd. and from Oxford University for patent for neuromyelitis optica IgG for diagnosis of neuromyelitis optica. Go to Neurology.org for full disclosures.

Received January 28, 2016. Accepted in final form June 9, 2016.

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