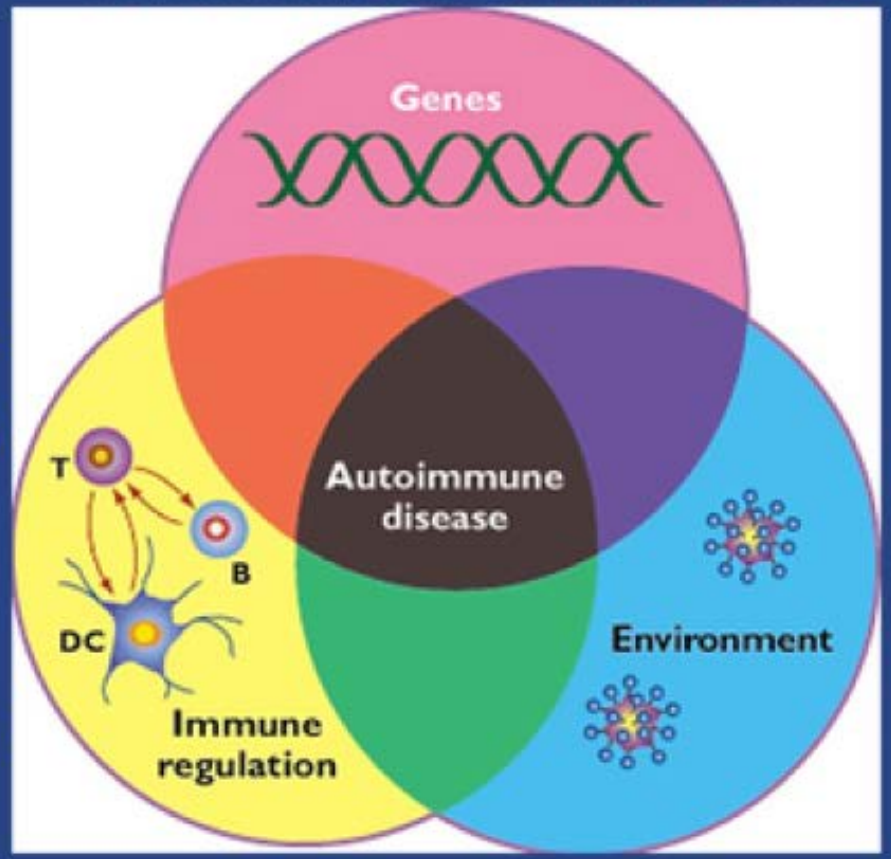
MS,
Laboratuar destekli
Klinik bir tanıdır

Münire Kılınç Toprak
Başkent Üniversitesi Nöroloji Bölümü

Etiology of MS

- Over >100 Immune Gene SNPs implicated in the risk of MS: HLADR2, IL-2rec, IL-7 rec

- Innate immune response (macrophages)
- Adaptive immune response
- (T and B lymphocytes)



- Viruses (EBV)
- Vitamin D
- Latitude
- Smoking
- Diet (salt)
- Gut Microbiome
- Obesity

SNP = single nucleotide polymorphisms.

Disease Mechanism: 3 Components

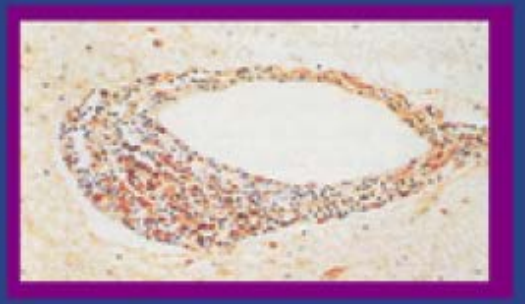
Inflammation

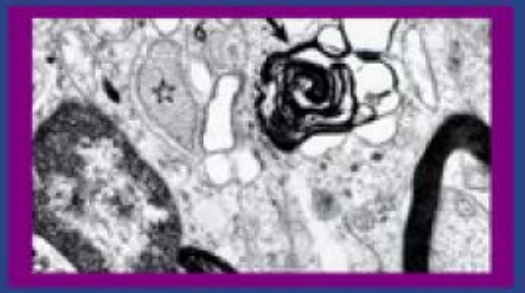
↓

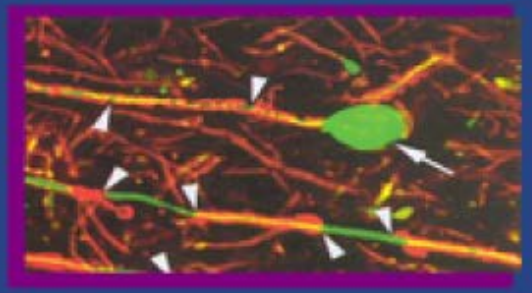
Demyelination

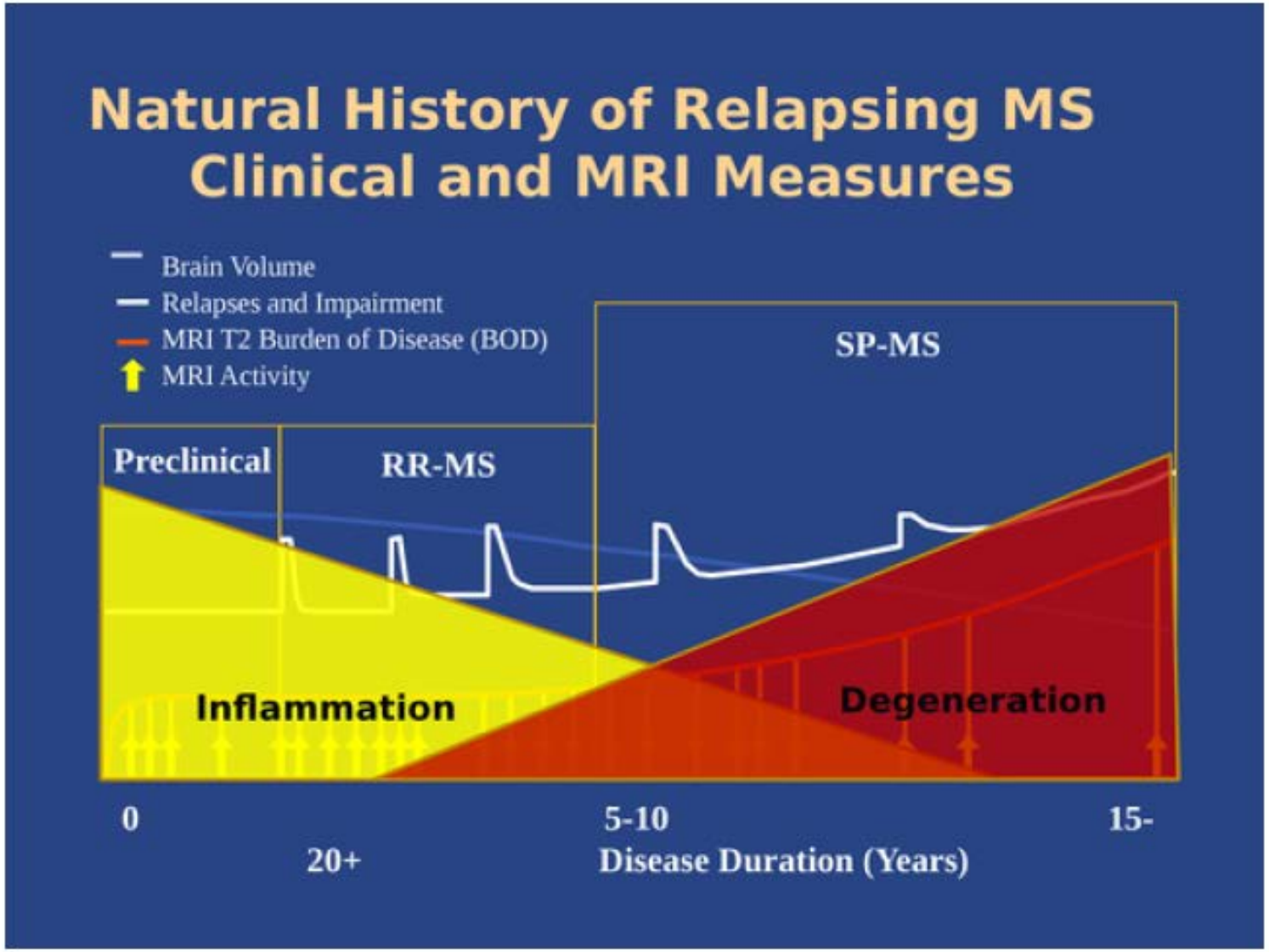
↓

Neuron Loss








Natural History of Relapsing MS
Clinical and MRI Measures
Brain Volume
Relapses and Impairment
MRI T2 Burden of Disease (BOD)
MRI Activity
Preclinical
RR-MS
SP-MS
Inflammation
Degeneration
0
20+
5-10
15-
Disease Duration (Years)

Relapses = Tip of the Iceberg

Suggestive and atypical features of multiple sclerosis

Features suggestive of multiple sclerosis
Relapses and remissions
Onset between ages 15 and 50 years
Optic neuritis
Lhermitte sign
Internuclear ophthalmoplegia
Fatigue
Heat sensitivity (Uhthoff phenomenon)
Features atypical for multiple sclerosis
Steady progression
Onset before age 10 or after age 50 years
Cortical deficits such as aphasia, apraxia, alexia, or neglect
Rigidity or sustained dystonia
Convulsions
Early dementia
Deficit developing within minutes

Manifestations of multiple sclerosis

Symptoms and signs	Total (percent)
Sensory in limbs	31
Visual loss	16
Motor (subacute)	9
Diplopia	7
Gait disturbance	5
Motor (acute)	4
Balance problems	3
Sensory in face	3
Lhermitte sign (electric shock-like sensations that run down the back and/or limbs upon flexion of the neck)	2
Vertigo	2
Bladder problems	1
Limb ataxia	1
Acute transverse myelopathy	1
Pain	<1
Other	3
Polysymptomatic onset	14

Curr Neurol Neurosci Rep (2015) 15: 57
DOI 10.1007/s11910-015-0576-7

DEMYELINATING DISORDERS (DN BOURDETTE AND M CAMERON, SECTION EDITORS)

A Clinical Approach to the Differential Diagnosis of Multiple Sclerosis

Michel Toledano[1] · Brian G. Weinshenker[1] · Andrew J. Solomon[2]

Step 1

Identify "Classic" Symptoms of MS

Painful ON, painless binocular diplopia, vertigo, paresis, myelopathic sensory loss (sensory level).

Step 2

Neurologic examination

Normal

Examination consistent with MS (e.g., APD, dyschromatopsia, INO, myelopathy, ataxia)

Examination consistent with another neurological disease

Step 3

MS Investigations

MRI brain, cervical, and thoracic spinal cord

CSF – specific oligoclonal bands and/or immunoglobulin (Ig)G index

Visual and somatosensory evoked potentials

Table 1 Clinical red flags and associated diagnosis

Clinical red flags	Possible diagnosis
General	
Hyperacute presentation	Ischemia, hemorrhage, seizure, and syncope
Fevers, weight loss, night sweats, alopecia, and synovitis	Infection, systemic vasculitis, systemic lupus, and erythematosus
Livedo reticularis, early trimester abortions, and thrombotic events	Antiphospholipid syndrome
Cerebral hemispheres	
Encephalopathy (alterations in awareness and coma)	ADEM, PRES, and infectious/autoimmune encephalitis
Hemianopsia and cortical blindness	Ischemic stroke, PRES, neoplasm, and PML
Insidious cognitive decline	Neurodegenerative, genetic leukoencephalopathy and leukodystrophy
Optic nerve	
Progressive optic nerve (ON)	Neoplasm, sarcoidosis, and LHON
Altitudinal deficit and monocular blindness	Ischemic optic neuropathy
Clinically serve or simultaneous bilateral ON	NMOSD and LHON
Neuroretinitis and uveitis	NMOSD
Spinal cord	
Anterior spinal syndrome	Ischemia
Complete transverse myelitis	NMOSD, idiopathic myelitis, and ADEM
Radiculitis	Infection, sarcoidosis, and carcinomatosis/lymphomatosis
Progressive spastic paraparesis	HTLV-1, HIV, cobalamin deficiency, PLS, CSM, and dAVF

Curr Neurol Neurosci Rep 2015 15: 57

Multiple sclerosis mimickers that may manifest with dissemination of lesions in space or dissemination in time or both

Hypoxic-ischemic vasculopathy	SVD, ARWMC, SAE, antiphospholipid syndrome, migraine, thromboembolic disease, vasculitis, CADASIL, CAA, Susac's syndrome
Inflammatory/ inflammatory autoimmune	Non-MS IIDD (e.g., ADEM, NMO, IMT), primary CNS vasculitis, Behçet, SLE, sarcoidosis, Wegener granulomatosis, Sjögren's disease, Susac's syndrome, celiac, IBD, CLIPPERS
Infectious	PML, HIV encephalopathy, HTLV, Lyme, Whipple, neurosyphilis, cysticercosis, toxoplasmosis
Toxic and metabolic	CPM, PRES, MB, Wernicke, vitamin B_{12} deficiency
Traumatic	DAI, radiotherapy
Tumoral	Glioma, metastasis, lymphoma, lymphomatoid granulomatosis
Hereditary/unknown	CADASIL, mitochondrial disorders, Fabry's disease and other leukodystrophies, Susac's syndrome

Handbook of Clinical Neurology, Vol. 122 (3rd series)

CONTEMPORARY ISSUES

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

Table 2 Patients misdiagnosed with multiple sclerosis

Characteristics	No. (%)
Evaluated a misdiagnosed patient within last year	
Yes	116 (95.1)
No	6 (4.9)
No. seen within last year	
1-2	30 (25.9)
3-5	46 (39.7)
6-10	20 (17.2)
≥10	20 (17.2)
Estimated on DMT	
0%	6 (5.2)
1-25%	35 (30.2)
26-50%	28 (24.1)
51-75%	17 (14.7)
≥75%	30 (25.9)

Figure 1 Suspected alternative diagnoses in patients misdiagnosed with multiple sclerosis (MS)

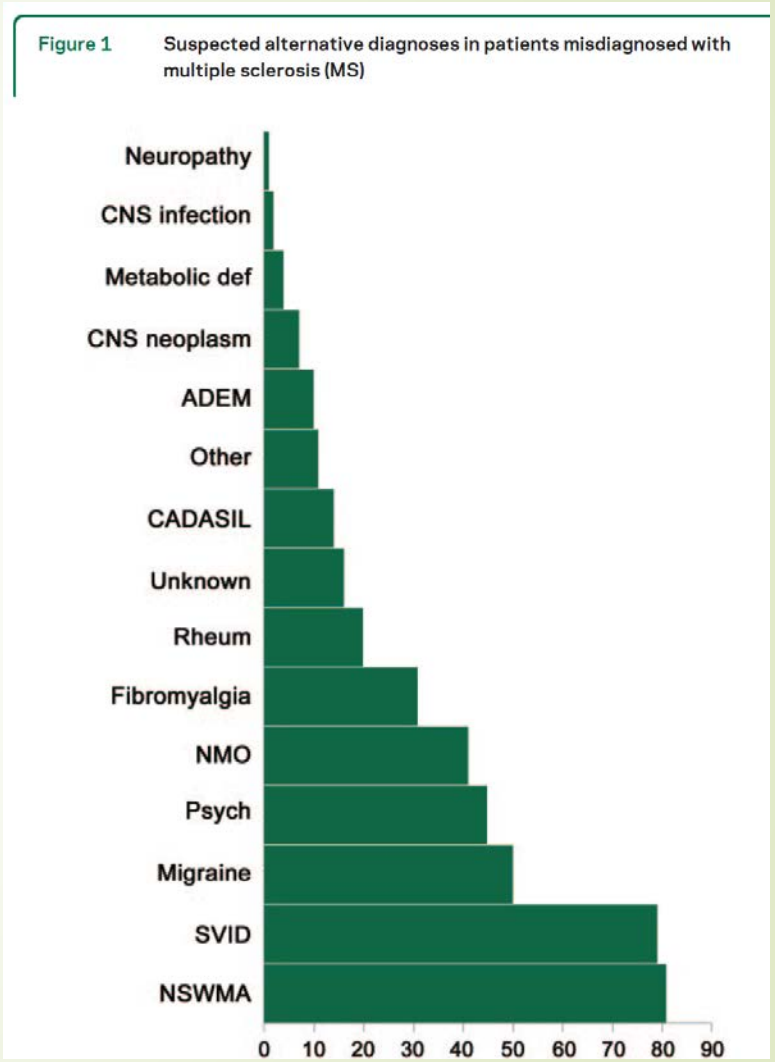


Figure 1 Duration of misdiagnosis

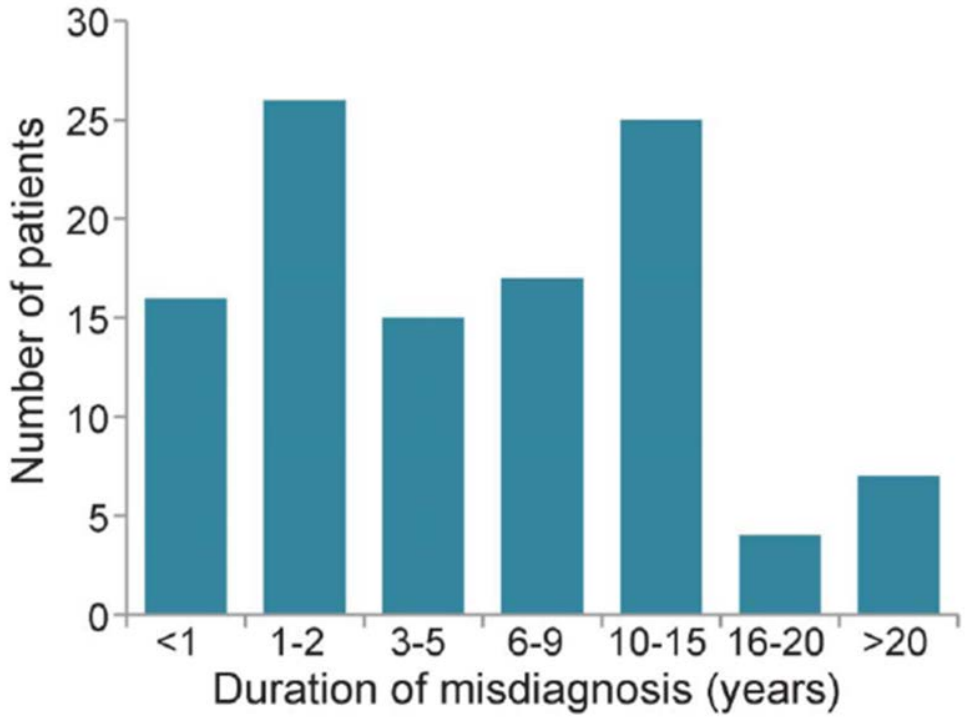
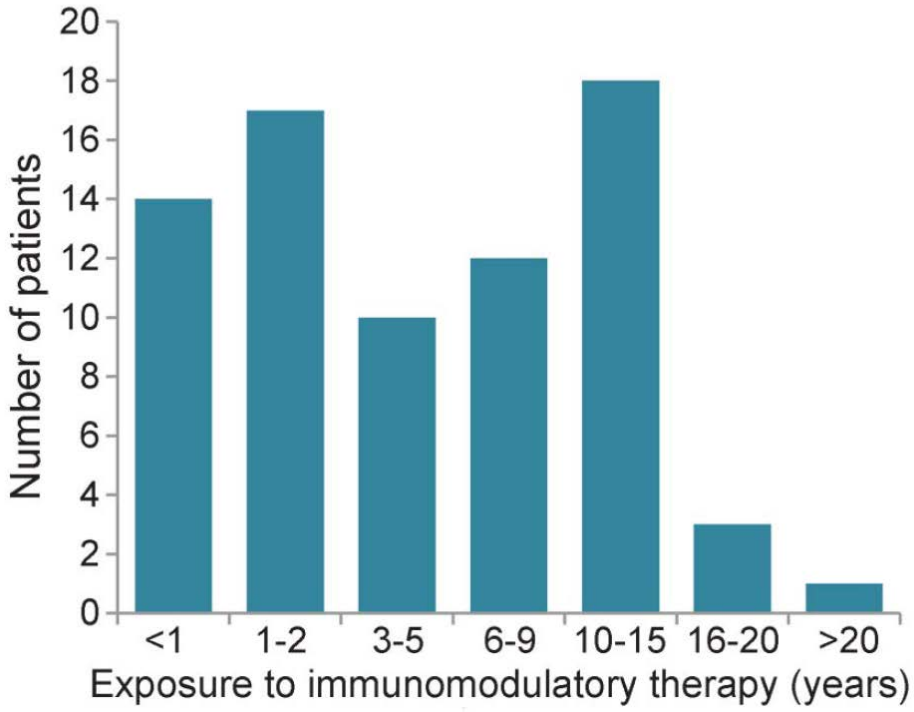


Figure 2 Cumulative exposure to immunomodulatory therapy



CONTEMPORARY ISSUES IN NEUROLOGIC PRACTICE

"Undiagnosing" multiple sclerosis

The challenge of misdiagnosis in MS

Andrew J. Solomon, MD
Eran P. Klein, MD, PhD
Dennis Bourdette, MD

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ABSTRACT

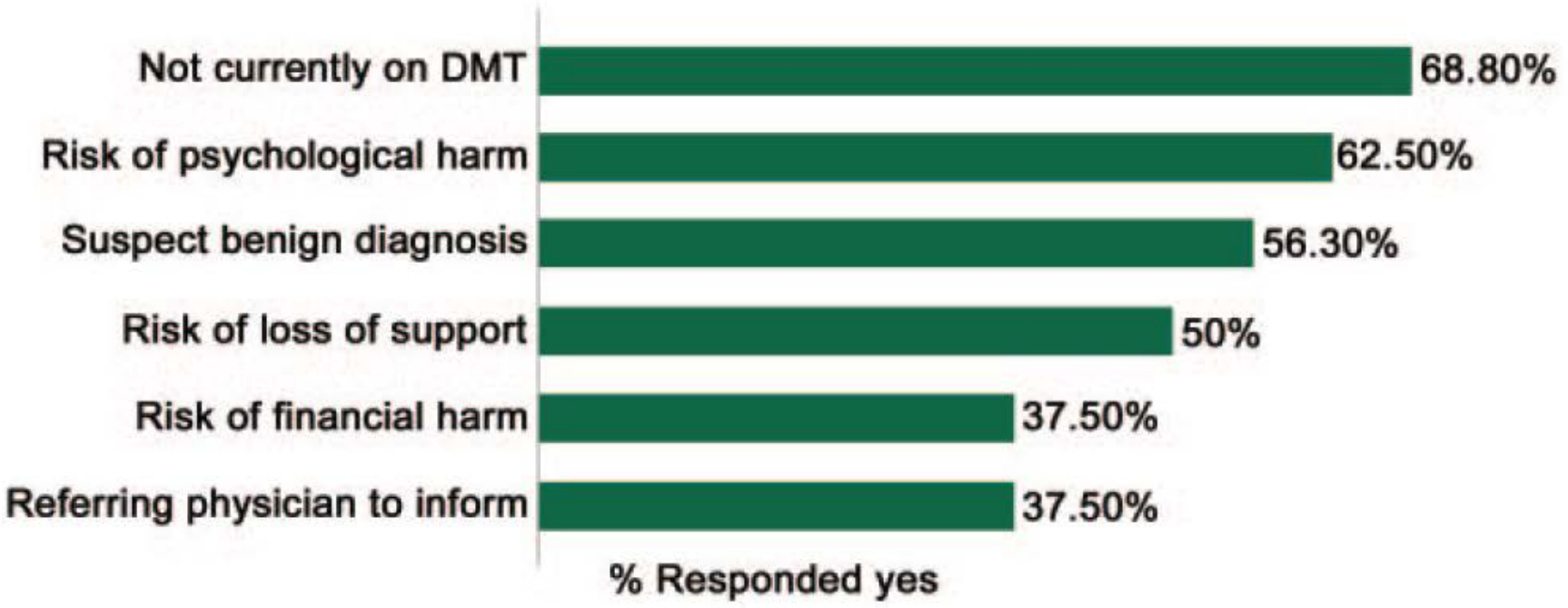
Objective: To describe the clinical characteristics of encounters with patients misdiagnosed with multiple sclerosis (MS).

Methods: A cross-sectional Internet-based physician survey of MS specialists was performed.

Results: The response rate for the survey was 50.4%. Of those who responded, the majority (95%) reported having evaluated 1 or more patients who had been diagnosed with MS, but who they strongly felt did not have MS, within the last year. The majority of respondents (>90%) also reported the use of disease-modifying therapy in a proportion of these patients. Most respondents (94%) found clinical encounters with these patients equally or more challenging than giving a new diagnosis of MS. Fourteen percent of respondents reported that they did not always inform such patients of their opinion that they did not have MS.

Conclusions: The misdiagnosis of MS is common and has significant consequences for patient care and health care system costs. Caring for a patient with a misdiagnosis of MS is challenging, and at times honest disclosure of a misdiagnosis represents an important ethical concern for neurologists. More data are needed on this patient population to improve diagnostic acumen and the care of these patients. *Neurology*® 2012;78:1986–1991

Figure 2 Reasons important to a decision not to inform of a misdiagnosis of multiple sclerosis (MS)



REVIEW Multiple Sclerosis 2008; 14: 1157–1174

Differential diagnosis of suspected multiple sclerosis: a consensus approach

DH Miller[1], BG Weinshenker[2], M Filippi[3], BL Banwell[4], JA Cohen[5], MS Freedman[6], SL Galetta[7], M Hutchinson[8], RT Johnson[9], L Kappos[10], J Kira[11], FD Lublin[12], HF McFarland[13], X Montalban[14], H Panitch[15], JR Richert[16], SC Reingold[16,17] and CH Polman[18]

Background and objectives Diagnosis of multiple sclerosis (MS) requires exclusion of diseases that could better explain the clinical and paraclinical findings. A systematic process for exclusion of alternative diagnoses has not been defined. An International Panel of MS experts developed consensus perspectives on MS differential diagnosis.

Methods Using available literature and consensus, we developed guidelines for MS differential diagnosis, focusing on exclusion of potential MS mimics, diagnosis of common initial isolated clinical syndromes, and differentiating between MS and non-MS idiopathic inflammatory demyelinating diseases.

Results We present recommendations for 1) clinical and paraclinical red flags suggesting alternative diagnoses to MS; 2) more precise definition of "clinically isolated syndromes" (CIS), often the first presentations of MS or its alternatives; 3) algorithms for diagnosis of three common CISs related to MS in the optic nerves, brainstem, and spinal cord; and 4) a classification scheme and diagnosis criteria for idiopathic inflammatory demyelinating disorders of the central nervous system.

Conclusions Differential diagnosis leading to MS or alternatives is complex and a strong evidence base is lacking. Consensus-determined guidelines provide a practical path for diagnosis and will be useful for the non-MS specialist neurologist. Recommendations are made for future research to validate and support these guidelines. Guidance on the differential diagnosis process when MS is under consideration will enhance diagnostic accuracy and precision. *Multiple Sclerosis* 2008; **14**: 1157–1174. http://msj.sagepub.com

- The group's initial mission statement was: to provide a data-driven and consensus-based diagnostic approach for patients who present with symptoms and objective clinical evidence suggesting CNS white matter disease;
- to include guidance for appropriate clinical, radiological, and/or laboratory tests that should be done to exclude alternative diagnoses,
- especially those that are amenable to appropriate treatment;
- and to develop a practical tool for neurologists to facilitate accurate diagnosis and to guide management and which will complement the McDonald Diagnostic Criteria

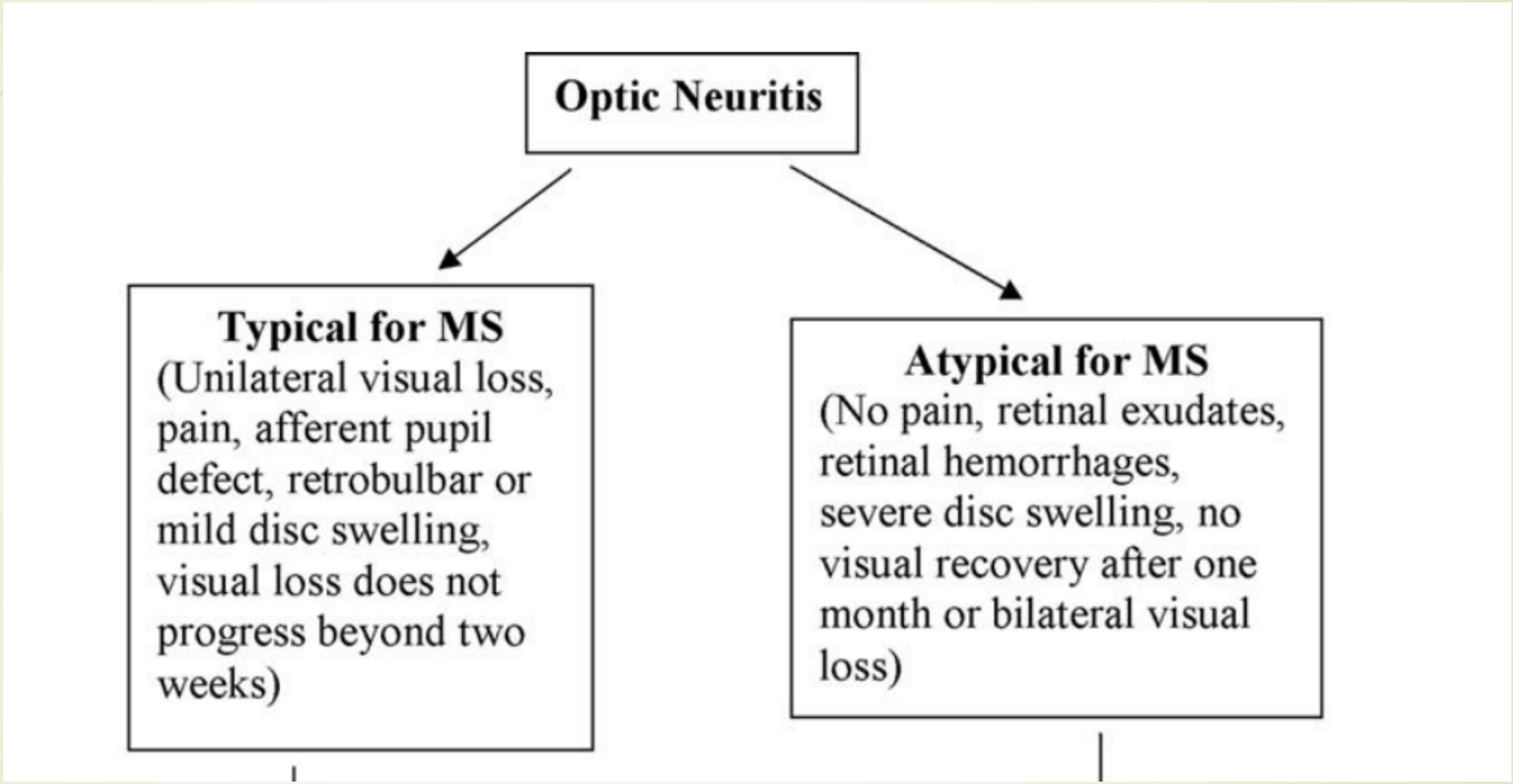
79 red flags were then classified into three groups according to the following criteria:

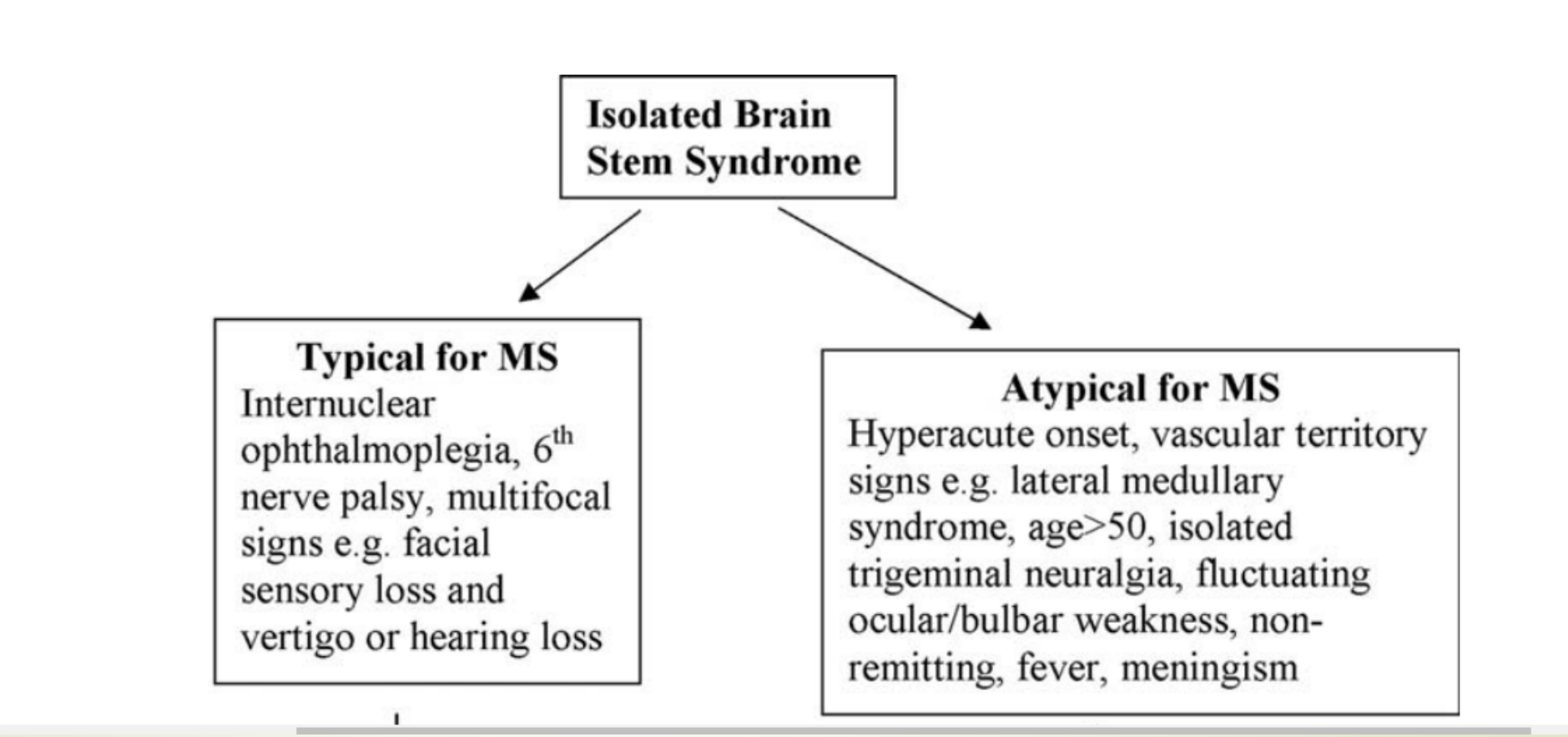
- Major red flags: total score ≥24 or total score of 23 and no more than one individual score of 3 (SD ≤ 0.41).
- Intermediate red flags, indicating a lack of agreement among the raters about the weighting: total score of ≥13 and ≤23 with more than one individual rating of 3 (SD ≥ 4.1).
- Minor red flags: total score ≤12 or total score of 13 with not more than one individual score of 3 (SD ≤ 0.41).

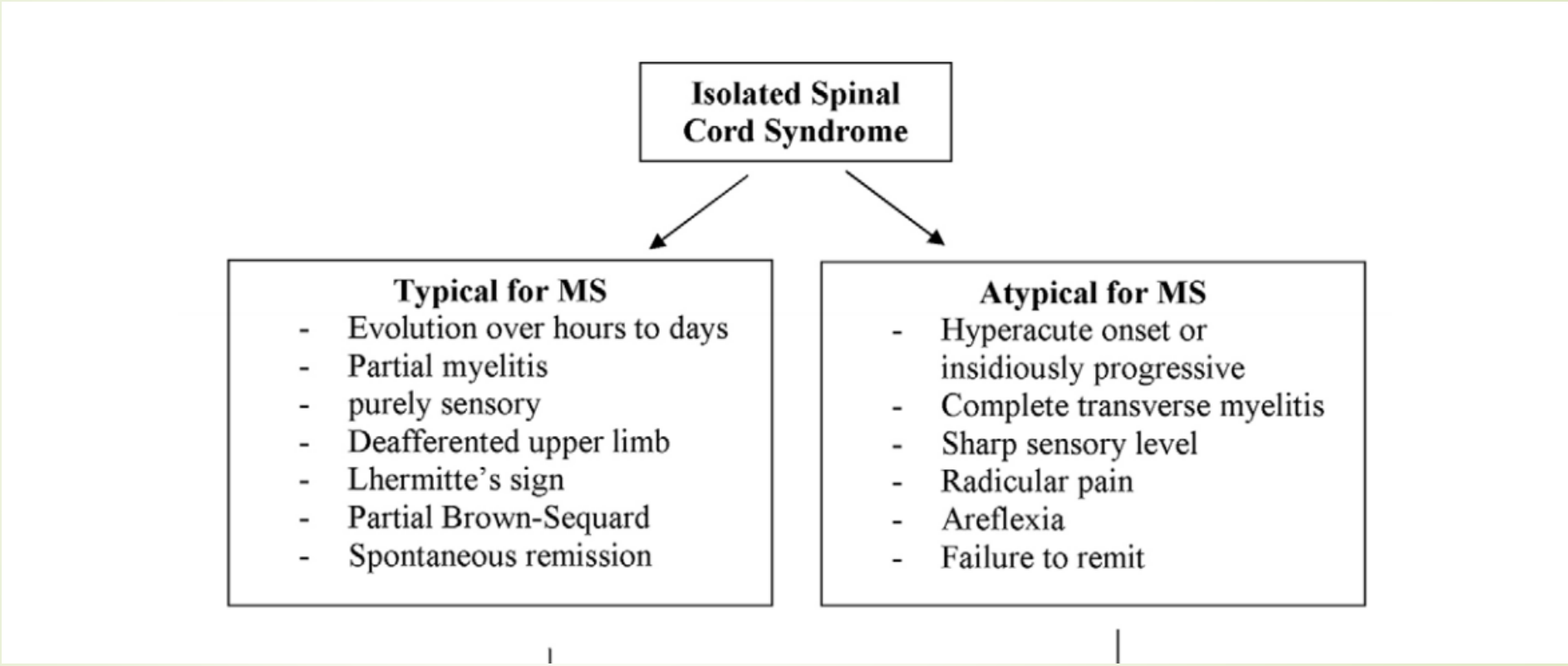
Table 3 CIS clinical features and likelihood of signaling an MS diagnosis

CIS features typically seen in MS	Less common CIS features which may be seen in MS	Atypical CIS features not expected in MS
Optic nerve		
Unilateral optic neuritis	Bilateral simultaneous optic neuritis	Progressive optic neuropathy
Pain on eye movement	No pain	Severe, continuous orbital pain
Partial and mainly central visual blurring	No light perception	Persistent complete loss of vision
Normal disc or mild disc swelling	Moderate to severe disc swelling with no hemorrhages	Neuroretinitis (optic disc swelling with macular star)
	Uveitis (mild, posterior)	Uveitis (severe, anterior)
Brain stem/cerebellum		
Bilateral internuclear ophthalmoplegia	Unilateral internuclear ophthalmoplegia, facial palsy, facial myokymia	Complete external ophthalmoplegia; vertical gaze palsies
Ataxia and multidirectional nystagmus	Deafness	Vascular territory syndrome, e.g., lateral medullary
Sixth nerve palsy	One-and-a-half syndrome	Third nerve palsy
Facial numbness	Trigeminal neuralgia	Progressive trigeminal sensory neuropathy
	Paroxysmal tonic spasms	Focal dystonia, torticollis
Spinal cord		
Partial myelopathy	Complete transverse myelitis	Anterior spinal artery territory lesion (sparing posterior columns only)
Lhermitte's symptom	Radiculopathy, areflexia	Cauda equina syndrome
Deafferented hand	Segmental loss of pain and temperature sensation	Sharp sensory level to all modalities and localized spinal pain
Numbness	Partial Brown-Sequard syndrome (sparing posterior columns)	Complete Brown-Sequard syndrome
Urinary urgency, incontinence, erectile dysfunction	Faecal incontinence	Acute urinary retention
Progressive spastic paraplegia (asymmetrical)	Progressive spastic paraplegia (symmetrical)	Progressive sensory ataxia (posterior columns)
Cerebral hemispheres		
Mild subcortical cognitive impairment	Epilepsy	Encephalopathy (obtundation, confusion, drowsiness)[a]
Hemiparesis	Hemianopia	Cortical blindness

[a]Although encephalopathy is required for ADEM, it may also be seen at presentation and/or during the course of MS.


Optic Neuritis
Typical for MS
(Unilateral visual loss, pain, afferent pupil defect, retrobulbar or mild disc swelling, visual loss does not progress beyond two weeks)
Atypical for MS
(No pain, retinal exudates, retinal hemorrhages, severe disc swelling, no visual recovery after one month or bilateral visual loss)


Isolated Brain Stem Syndrome
Typical for MS
Internuclear ophthalmoplegia, 6th nerve palsy, multifocal signs e.g. facial sensory loss and vertigo or hearing loss
Atypical for MS
Hyperacute onset, vascular territory signs e.g. lateral medullary syndrome, age>50, isolated trigeminal neuralgia, fluctuating ocular/bulbar weakness, non-remitting, fever, meningism


Isolated Spinal Cord Syndrome
Typical for MS
- Evolution over hours to days
- Partial myelitis
- purely sensory
- Deafferented upper limb
- Lhermitte's sign
- Partial Brown-Sequard
- Spontaneous remission
Atypical for MS
- Hyperacute onset or insidiously progressive
- Complete transverse myelitis
- Sharp sensory level
- Radicular pain
- Areflexia
- Failure to remit

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VIEWS & REVIEWS

Misdiagnosis of multiple sclerosis

Impact of the 2017 McDonald criteria on clinical practice

Andrew J. Solomon, MD, Robert T. Naismith, MD, and Anne H. Cross, MD

Neurology® 2019;00:1-8. doi:10.1212/WNL.0000000000006583

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Abstract

Misdiagnosis of multiple sclerosis (MS) (the incorrect assignment of a diagnosis of MS) remains a problem in contemporary clinical practice. Studies indicate that misdiagnosed patients are often exposed to prolonged unnecessary health care risks and morbidity. The recently published 2017 revision of the McDonald criteria for the diagnosis of MS provides an opportunity to consider the effect of these revisions on the problem of MS misdiagnosis. The 2017 McDonald criteria include several new recommendations to reduce potential for mis-

RELATED ARTICLE

Editorial
Misdiagnosis of multiple sclerosis: If you have a hammer, everything looks like a nail?

Page XXX

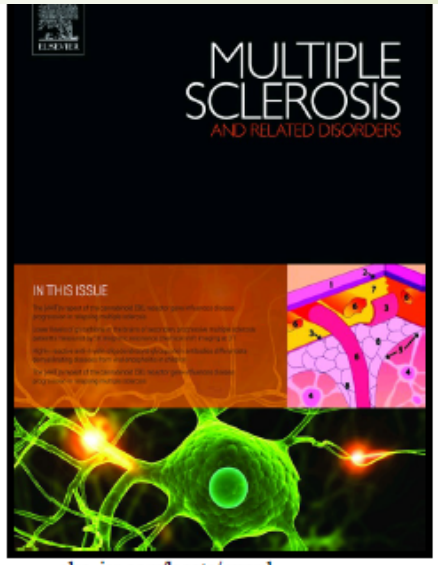
- The 2017 McDonald criteria outline the measures to fulfill these elements.
- The risk for misdiagnosis is higher when these 4 principles are incompletely satisfied.
- All versions of the McDonald criteria have required “no better explanation” for the clinical picture before making a diagnosis of MS.
- However, the converse of this statement does not apply; when the possibility of MS cannot be excluded, the diagnosis should not be made prematurely.
- Rather, the patient should be followed until there is sufficient evidence to support the diagnosis

Table 1 Clinical syndromes typical and atypical for multiple sclerosis (MS)–related demyelination

Typical for MS	Atypical for MS
Unilateral optic neuritis, mild and with partial or full recovery	Bilateral optic neuritis; severe optic neuritis; poor recovery from optic neuritis
Diplopia due to internuclear ophthalmoplegia	Headache, with or without diplopia or visual obscuration
Facial sensory loss or trigeminal neuralgia in young patient	Acute or subacute cognitive impairment
Cerebellar syndromes that include ataxia and nystagmus	Dizziness or vertigo without brainstem or cerebellar findings
Sensory impairment or motor weakness localizing to the spinal cord, with partial or full recovery	Sensory loss in extremities without a clear CNS pattern
	Complete transverse myelopathy

Clinically Isolated Syndromes or Clinically Isolated Patients? A Patient and Clinician Perspective on the Utility of CIS as a Diagnosis

Teresa Leahy, Mohammed Elseed, Timothy J Counihan



www.elsevier.com/locate/msard

PII: S2211-0348(17)30198-0
DOI: http://dx.doi.org/10.1016/j.msard.2017.08.015

Methods

The study uses a qualitative descriptive design involving both a semi-structured interview of patients with CIS as well as a short questionnaire sent to practising clinicians in the Republic of Ireland. Narrative data was coded onto themes.

Results

Thirty CIS patients were interviewed. The majority of patients understood the term "CIS" but not the link between CIS and MS. Two themes were identified: emotional reactions following CIS diagnosis; and terminology and communication. Confusion and anxiety among patients due to inconsistent communication of CIS was identified. Of the thirty-three clinicians surveyed, only thirty-nine per cent found the term "CIS" clinically useful. Eighteen per cent of clinicians diagnosed MS from the CIS case vignette provided.

Conclusion

In the diagnosis of a first demyelinating event, use of the term "CIS" is confusing to patients and inconsistent among clinicians. We suggest that the term "CIS" be abandoned in favour of terminology that reflects both its pathogenesis and inherent risk of subsequent MS.

KEYWORDS: CIS; MS; Qualitative; Terminology; Communication

Relief:

- *"Probably a relief..... I wasn't upset or anything..... at least we knew what it was and we could start treating it or doing whatever they need to do with it. So that was a relief to me." (Participant 15).*
- *"To be honest when it was clinically isolated that is better than labelling me with something I suppose I didn't have.... and even now I don't feel any seriousness about it as of yet. (Participant 26).*
- *"Initially I was delighted it wasn't called MS just from the one episode.." (Participant 22).*

Shock:

- *"Well I was kinda shocked... he [the doctor] said I have CIS I don't have MS..so I am lucky in that sense I don't have MS". (Participant 11).*
- *"I got a shock but he said it nicely and very kind when he said it. He also used the*

Health Care Professional Communication

- *"The first time when I heard anything when one of the nurses [ward nurse] came back to me with the results that it wasn't MS. And if my jaw could hit floor it would have … because it [MS] hadn't been mentioned". (Participant 12).*
- *"It was only when I was in the hospital two random doctors that I hadn't had before [medical students] examined me all over … it was a Friday afternoon….. they said something that led me to look up the internet and because I knew I wouldn't see anyone until the Monday and I couldn't help myself and I did …. They used those words and used that language and that was the first time to be honest that I thought that this could be something serious". (Participant 14).*
- *"Poked and prodded for 3 days …….. coming round all asking the same questions….. and when you don't know what is wrong with you and they coming in and no one can give you an answer.. but they are tapping you on the knee and checking your reflexes and you going like… someone up there is saying there is a guinea pig down there". (Participant 27)*
- *"I knew something was going to show… I was then told I had demyelination over the phone by the GP and I thought what the hell? What's wrong? Is this bad? What does it mean? And she is off the phone before you can ask. She asked to see me the next day so I was left from 6pm to 11 am the following morning of what the hell?". (Participant 23).*
- *".....when I meet the nurse supporting me for the drug I am on. She sees me as an MS patient. Doctors and staff are talking to me as not yet hopefully not ever having MS. So there is confusion in there in all are saying different things. The literature. I read something and I have to realise this is related but different (MS and CIS) so it is confusing. So getting straight in my head. Who am I talking to… what am I reading and what state am I at". (Participant 18).*
- *"One doctor said in October you have MS another doctor today CIS but subjectively he said you could say mild MS… but for me as far as I am concerned I have CIS but she [MS Nurse] was really good in settling things down". (Participant 26).*

Documentation and Media Communication

- *"… google it didn't explain demyelination at that point [angry tone] and that it was required that I would need to see a neurologist.. so I had to probe her what it meant*

The Abyss

James D. Weisfeld-Adams, M.B., Ch.B.

I sat at the kitchen table at my in-laws' home in Florida, collating a list of everything I owned. My precise, microscopic handwriting suddenly resembled the scrawl of a 6-year-old. It was 2006, and we were preparing to ship all our belongings from England to New York, where I'd been accepted into a pediatrics residency program at a major teaching hospital. This move represented the culmination of years of preparation for living indefinitely overseas. We had arrived in Florida only 2 weeks earlier; for my wife, it was a homecoming after 4 years of living as a foreigner in Britain.

Now, suddenly, I couldn't write. I felt like an amputee retraining myself to write with my nondominant hand. My right hand had a peculiar tremor at rest, a vague heaviness waxed and waned in my right arm and leg, and my pupils were unmistakably asymmetric. Nagging uneasiness turned to panic. Being 27 years old and healthy, I hadn't arranged for additional health insurance to cover me before my new appointment, and without the convenience of affordable diagnostic testing options, I indulged in some free-form speculative self-diagnosis. My basic neuroanatomical knowledge suggested that the distribution — involvement of the arm and the leg on the same side — meant that there was a good chance that the problem

MULTIPLE SCLEROSIS JOURNAL | MSJ

Original Research Paper

School performance as a marker of cognitive decline prior to diagnosis of multiple sclerosis

Multiple Sclerosis Journal

1–8

DOI: 10.1177/1352458514554054

Vladimiro Sinay, Manuel Perez Akly, Gisela Zanga, Celina Ciardi and Juan M Racosta

Abstract

Background: For many years, cognitive impairment has been established as a well-known symptom of multiple sclerosis. Moreover, we know that it was present even at the beginning of the disease.

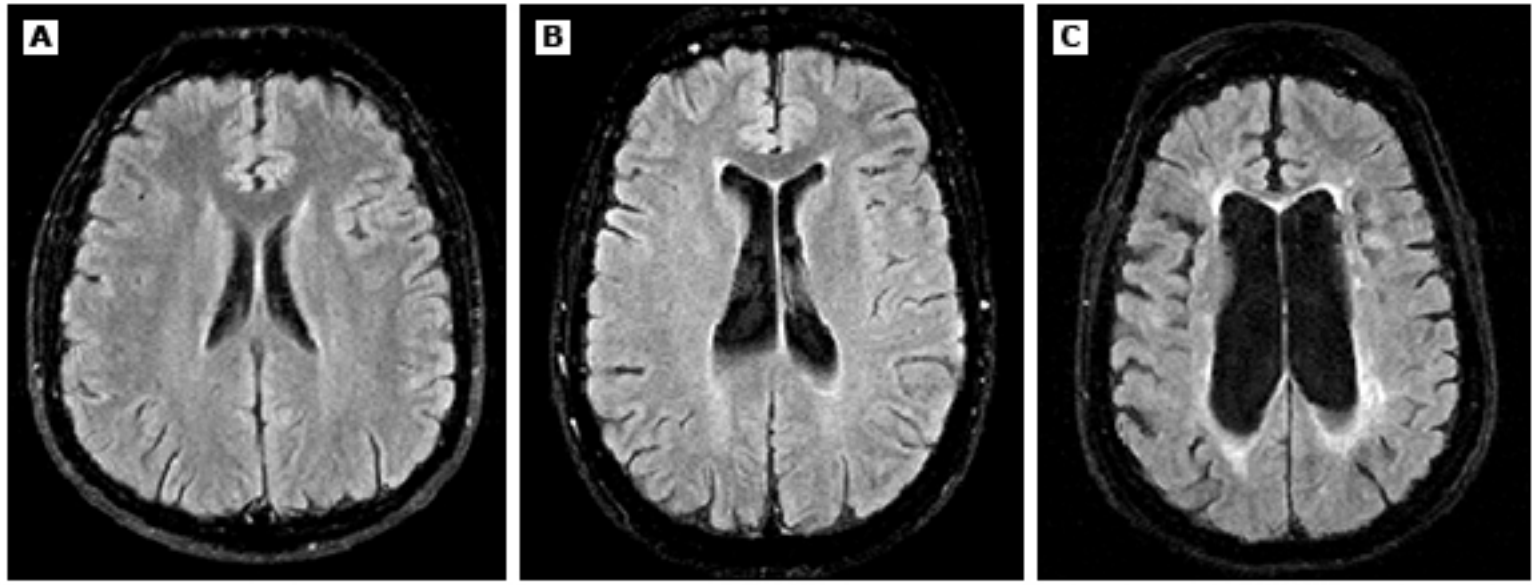
Objective: In this case-control study, we decided to evaluate whether there is an impairment of cognitive functions even before onset in those patients who will eventually suffer from multiple sclerosis.

Methods: We evaluated the overall school performance, and particularly school performance in math and language in a group of patients who would later develop the disease and we compared our findings with a control group.

Results: We found that school performance was poorer in subjects who were to become patients. And we found that the later the start of the first symptom, the better the qualifications.

Conclusion: Testing a premorbid cognitive deficit by a validated indirect evaluation method allowed us to verify that there was evidence of neurological compromise even before a clinical diagnosis or the completion of the first magnetic resonance imaging in patients who would then suffer from multiple sclerosis.

Brain atrophy in multiple sclerosis on MRI



These brain MRI images were acquired over the course of seven years from a single untreated patient with multiple sclerosis, and show progression of generalized brain atrophy from the first scan (left panel) to the most recent (right panel).

MRI: magnetic resonance imaging.

Table 1. Baseline characteristics for cases and controls for demographic data and school performance.

Variable	*Cases=75*	*Controls=75*	*p*
Sex (% women)	73.8	65.2	0.32
Age (mean, SD)	40.1 (11.1)	33.5 (10.1)	0.2
Socio economical status			
Low (%)	8	9.3	0.5
Middle (%)	68	60	
High (%)	24	30	
Type of school			
Private (%)	34.7	46.7	0.092
Public (%)	65.3	53.3	
Comorbidities			
Asthma (%)	6.7	2.7	0.22
Epilepsy (%)	1.3	4	0.31
Diabetes mellitus (%)	0	1.3	0.5
Psychiatric illness (%)	2.7	2.7	0.69
Drug abuse (%)	4	1.3	0.31
School performance			
School drop (%)	6.7	4	0.467
Repetition rate (%)	12	6	0.48
Average 5th year (SD)	7.1 (1.5)	7.8 (1.3)	0.003
Average 4th year (SD)	6.4 (2.1)	7.6 (2)	0.001
Average 3rd year (SD)	7.1 (1.7)	7.8 (1.8)	0.012
Mathematics 5th year (SD)	6.5 (1.8)	7.5 (1.7)	0.011
Mathematics 4th year (SD)	6.3 (2.2)	7.4 (2.1)	0.002
Mathematics 3rd year (SD)	6.8 (2.3)	7.6 (2.1)	0.026
Literature 5th year (SD)	6.7 (1.8)	7.6 (1.5)	0.013
Literature 4th year (SD)	6.5 (2.2)	7.6 (1.9)	0.003
Literature 3rd year (SD)	6.8 (2.1)	7.9 (2.1)	0.001

SD: standard deviation.

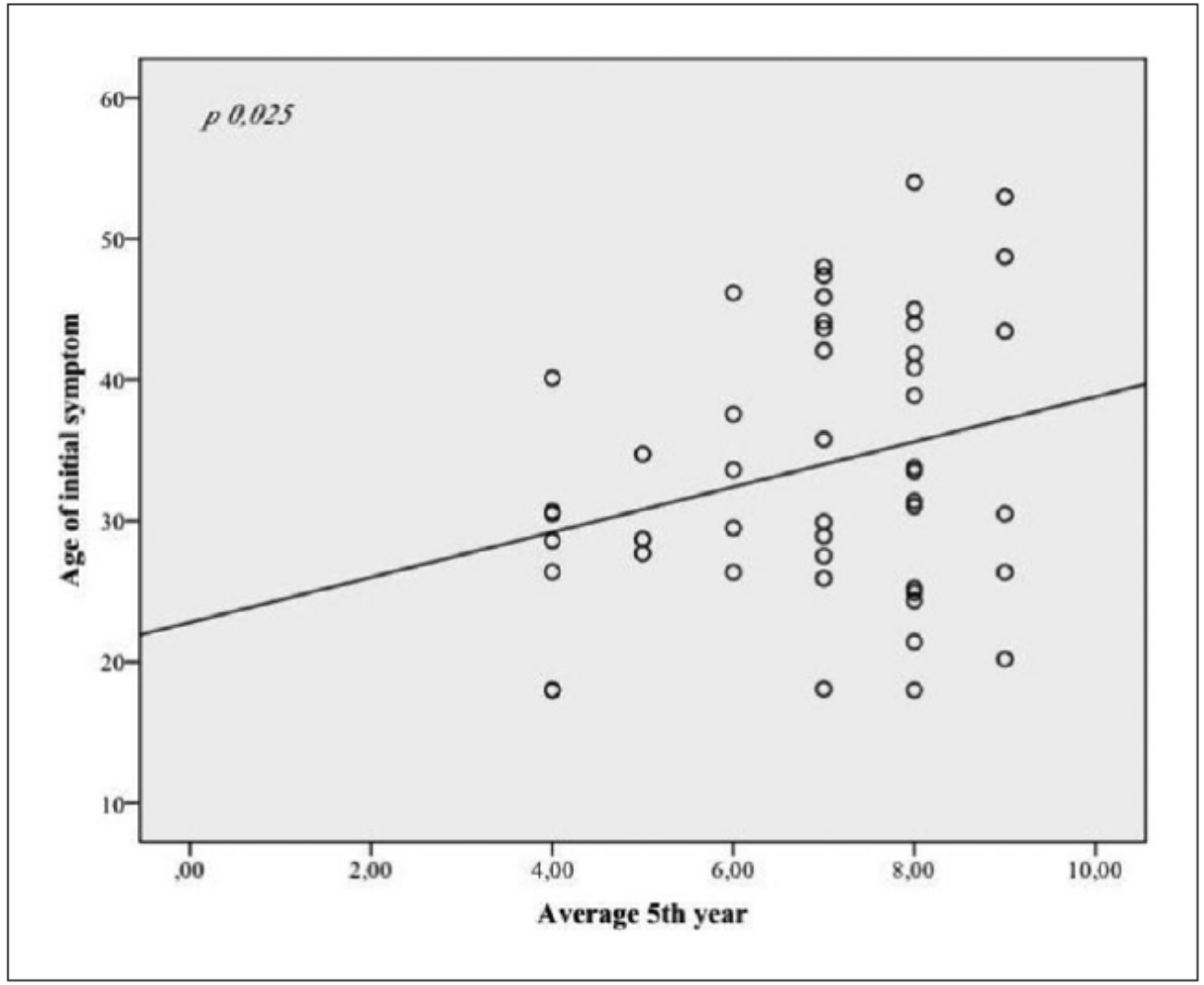


Figure 1. Direct relationship between grade point average of the last school year and how long the patients take to initiate disease.

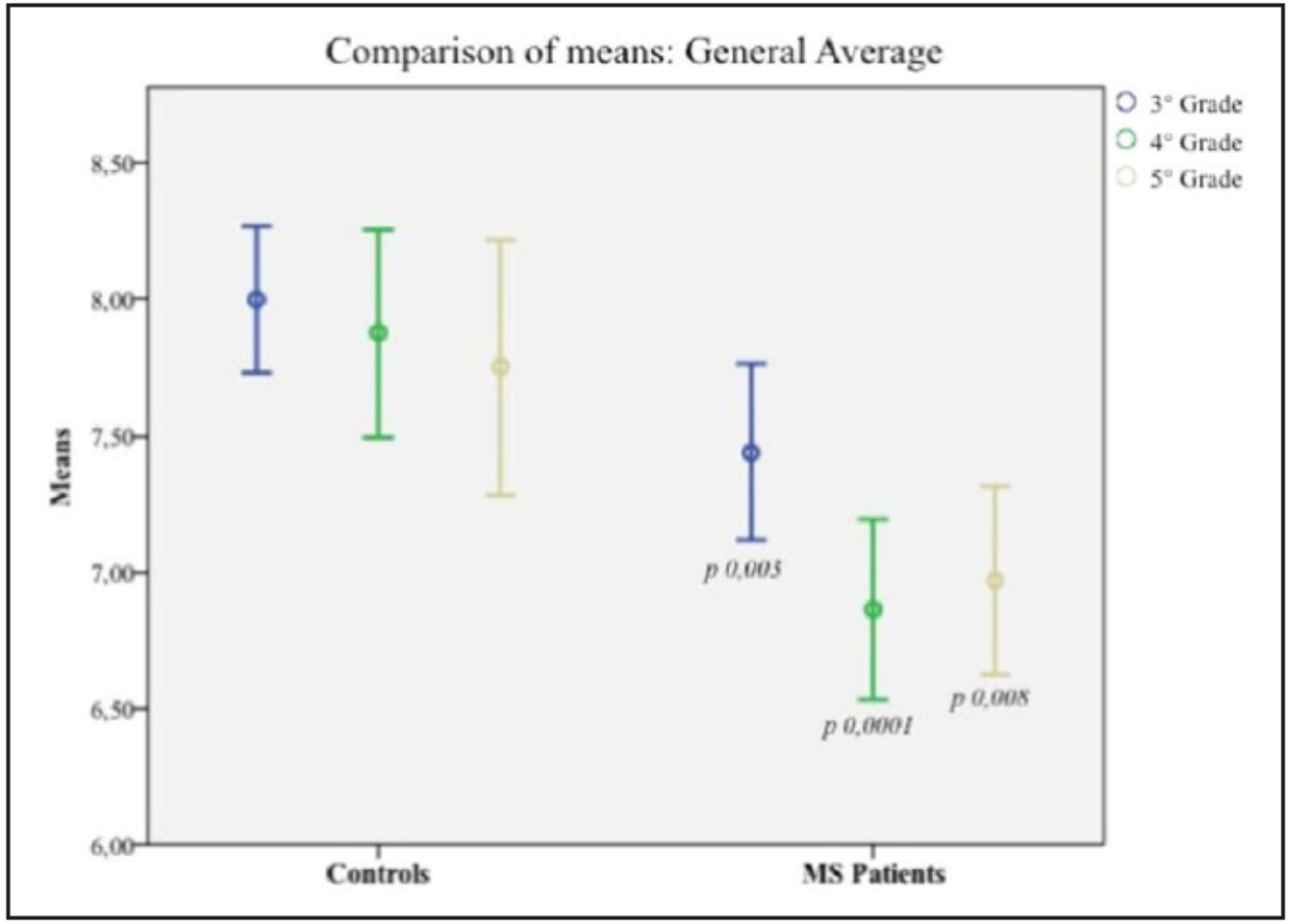


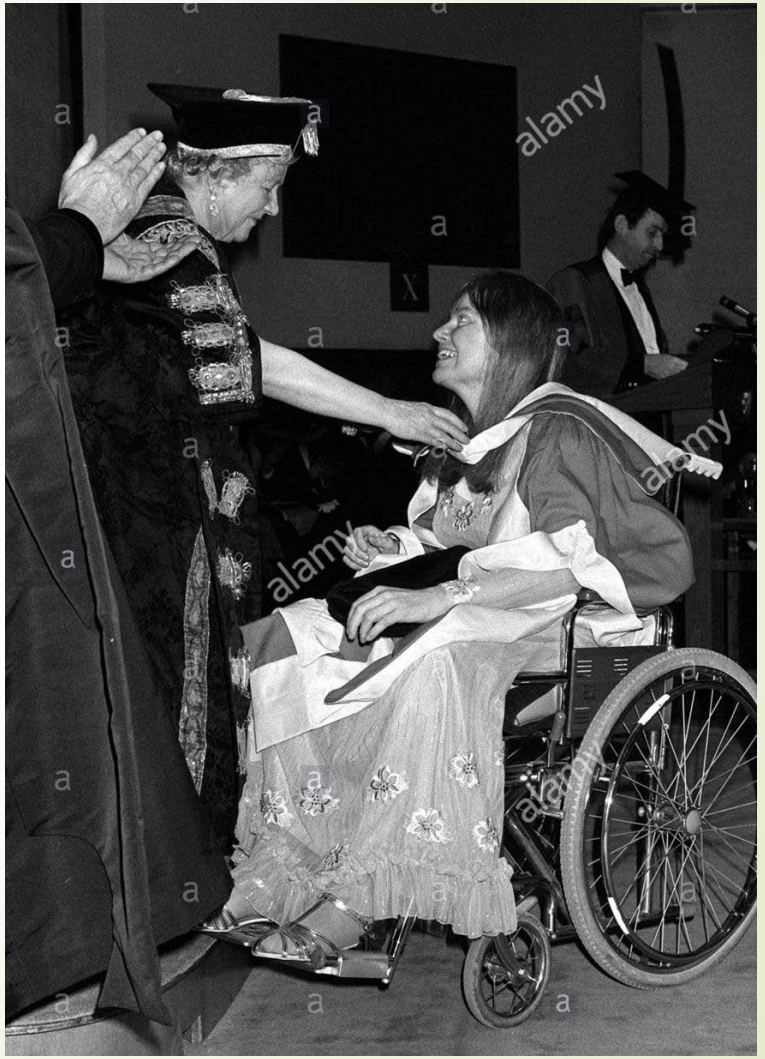
Figure 2. Comparison of overall averages of the last three years of schooling of future multiple sclerosis (MS) patients and controls.

of cognitive impairment in multiple sclerosis and other diseases. Three potential determinants were proposed: education, cognitively stimulating leisure time activities at middle age and lifetime socioeconomic status.[21,22] Strong associations have been found between reserve and cognitively stimulating activities at the age of 40 years, suggesting that cognitive activity during middle age is especially important to cognitive reserve. After formal education ends, work and leisure cognitive activities provide ongoing mental exercise and stimulation critical to further developing and maintaining reserve.[23,24] Occupational attainment has also been described as a marker of cognitive reserve in multiple sclerosis.[25] All these variables have an influence after finishing school. However, at 18, who are still building their reserve and at the time of evaluation it was similar since the patients and controls are paired by education level. After completing high school, educational and employment activities are separated in each individual and cognitive reserve differences are multiple sclerosis.

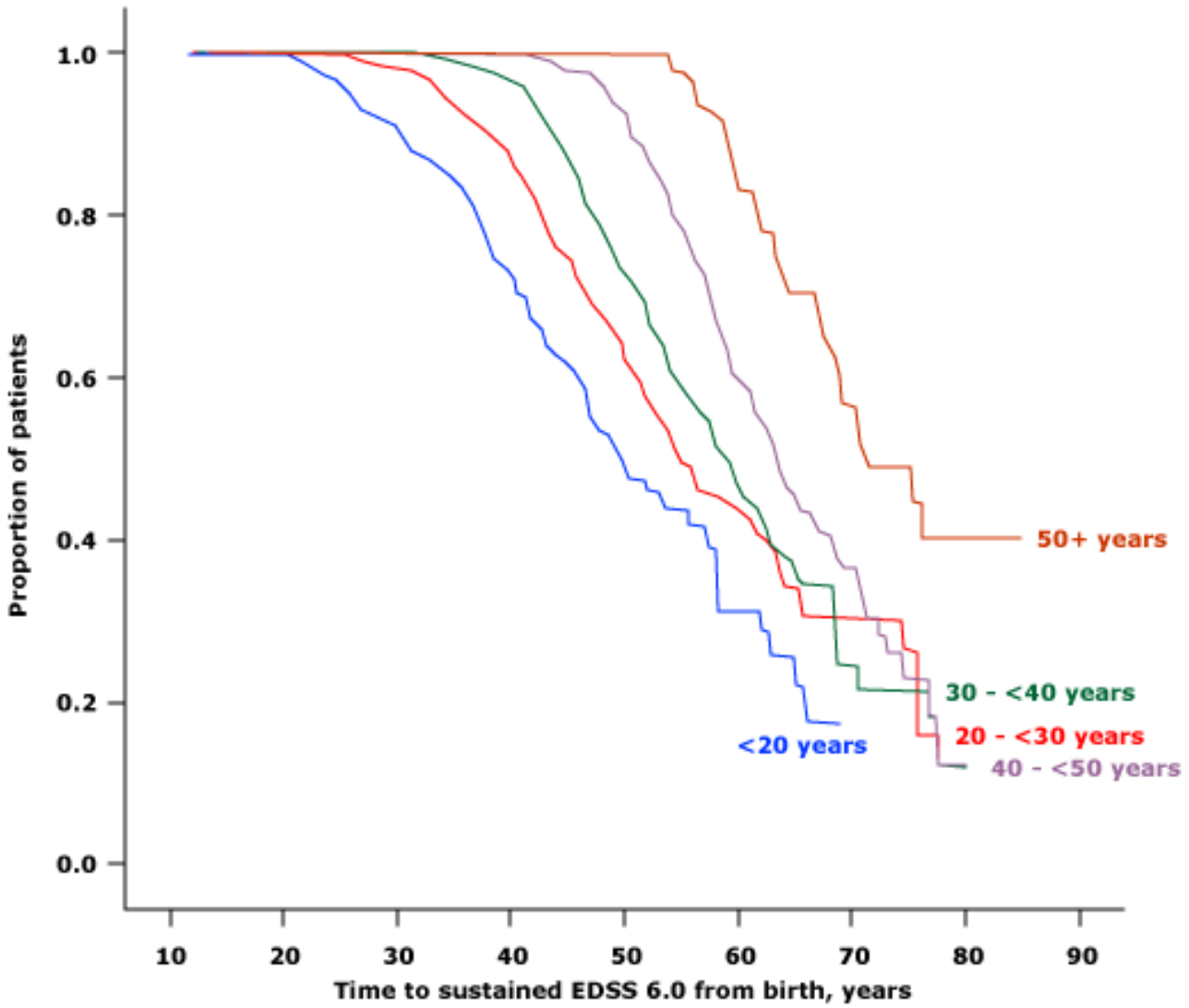
We actually know that future multiple sclerosis patients have worse school performance as compared with control paired subjects but the present work poses many unanswered questions for further studies. The first one is whether mild cognitive impairment should be taken into account to support the diagnosis of multiple sclerosis in a proper magnetic resonance image context since our study shows this symptom so early in the disease. Furthermore, in regions with a high prevalence of multiple sclerosis, those young students with academic difficulties should be evaluated not only by teachers, educational psychologists and social workers as it is usually done, but also by neurologists. Perhaps they should perform an image to rule out an unexpected finding. And our final question: Will we have to face a "cognitively isolated syndrome (CoIS)" as the very beginning of multiple sclerosis in the future?

Further studies will help to answer these questions.

Jacline Du Prey



Time to sustained disability (use of a cane) with multiple sclerosis



Hastalık başlangıcındaki belirtiler ve sıklıkları	
Bir yada daha fazla ekstremitede güçsüzlük	%35
Optik nörit	%20
Parestezi	%20
Diplopi	%10
Vertigo	%5
Mesane problemleri	%5
Diğer	<5

Ayırıcı Tanıda Optik Nörit Özellikleri		
MS Tipik	MS'de Nadir	MS için Atipik
Unilateral ON	Bilateral ON	Progressif ON
Ağrı	Ağrısız	Şiddetli, devamlı orbital ağrı
Parsiyel-santral görme bulanıklığı	Işık algısı yok	Kalıcı tam görme kaybı
Normal disk veya hafif ödemli disk	Hemorajisiz orta-ağır disk ödemi	Nöroretinit
	Üveit (Ilımlı, posterior)	Üveit (ağır, ön)

Ayırıcı Tanıda Beyinsapı-Serebellum Bulguları

MS için Tipik	MS'de Nadir	MS için Atipik
- Bilateral İNO - Ataksi - Farklı yönlere nistagmus - 6.KS paralizisi - Fasial uyuşukluk	- Unilateral İNO - Fasial paralizi - Fasial myokimi - Sağırlık - 1.5 sendromu - Trigeminal nevralji - Paroksismal tonik spazm	- Tam external oftalmopleji - Vertikal bakış paralizisi - Vasküler alan sendromları - 3.KS paralizisi - Progressif trigeminal nöropati - Fokal distoni, tortikollis

Ayırıcı Tanıda Spinal Kord Bulguları

MS için Tipik	MS'de Nadir	MS için Atipik
Parsiyel Myelopati	Transvers myelit	A. spinal arter sendr.
Lhermitte	Radikülopati, arefleksi	Kauda equina sendromu
Deafferente el	Segmental ısı ve	Tüm duyularda keskin düzey ve
Uyuşma	ağrı kaybı	lokalize spinal ağrı
Üriner urgency	Parsiyel Brown-	Brown-Sequard sendromu
İnkontinans	Sequard Sendromu	Akut üriner retansiyon
Erektil disfonk.	Fekal inkontinans	Progressif sensoryal ataksi
Asimetrik progresif	Simetrik progressif	
Spastik paraparezi	Spastik parapleji	

Ayırıcı Tanıda Serebral Hemisfer Bulguları		
MS için Tipik	MS'de Nadir	MS için Atipik
- Hafif subkortikal kognitif bozulma - Hemiparezi	- Epilepsi - Hemianopi	Ensefalopati Kortikal körlük