Differential diagnosis of suspected multiple sclerosis: considerations in minority ethnic people in North America, Northern Europe, and Australasia

Lilyana Amezcua, MD[1*] Dalia Rotstein, MD[2,3] Afsaneh Shirani, MD[4] Professor Olga Ciccarelli, MD[5,6] Professor Daniel Ontaneda, MD, PhD[7] Melinda Magyari, MD, PhD[8] Professor Victor Rivera, MD[9], Dorlan Kimbrough, MD[10], Professor Ruth Dobson, MD[11], Professor Bruce Taylor, PhD[12], Mitzi Williams, MD[13], Professor Ruth Ann Marrie, MD, PhD[14] Professor Brenda Banwell, MD[15], Professor Bernhard Hemmer, MD[16], Professor Scott D. Newsome, DO[17], Professor Jeffrey A Cohen, MD[7] Professor Andrew J. Solomon, MD[18], Professor Walter Royal, Walter, III, MD[19]

Affiliations:

[1]*Corresponding author** University of Southern California (USC), Keck School of Medicine, Department of Neurology, Los Angeles, California, USA, lamezcua@usc.edu

[2]Division of Neurology, Department of Medicine, University of Toronto, Canada

[3] St. Michael's Hospital-Unity Health Toronto, Ontario, Canada

[4]Department of Neurological Sciences, University of Nebraska Medical Center, Omaha, Nebraska, USA

[5] Queen Square MS Centre, UCL Institute of Neurology, Faculty of Brain Sciences, London, UK

[6] NIHR University College London Hospitals Biomedical Research Centre

[7] Mellen Center for Multiple Sclerosis, Cleveland Clinic, Cleveland, Ohio, USA

[8] Danish Multiple Sclerosis Center and The Danish Multiple Sclerosis Registry, Department of Neurology, Copenhagen University Hospital – Rigshospitalet, Denmark

[9]Department of Neurology, Baylor College of Medicine, One Baylor Plaza, Houston, Texas, USA

of Neurology,

[10] Department of Neurology, Duke University Medical Center, Durham, North Carolina, USA.

[11]Preventive Neurology Unit, Wolfson Institute of Population Health, Queen Mary University, London, UK

[12]BVT Menzies Institute for Medical Research University of Tasmania, Australia

[13]Joi Life Wellness MS Center, Smyrna, Georgia, USA, Morehouse School of Medicine, Atlanta, GA

[14] Departments of Internal Medicine and Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada

[15], Department of Neurology, University of Pennsylvania, Division of Child Neurology, Department of Pediatrics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

[16], Department of Neurology, Klinikum rechts der Isar, Medical Faculty, Technische Universität München, Germany and Munich Cluster for Systems Neurology, Germany

[17], Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA

[18] Department of Neurological Sciences, Larner College of Medicine at the University of Vermont. University Health Center. Burlington, Vermont, USA.

[19] Department of Neurobiology & Neuroscience Institute, Morehouse School of Medicine. Atlanta, Georgia, USA.

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Authors' Contributions:

Lilyana Amezcua: manuscript conceptualization, methodology, literature search, figure and table development, writing – original draft, writing – review and editing.

Dalia Rotstein: manuscript conceptualization, review, revision, and editing.

Afsaneh Shirani: manuscript conceptualization, review, revision, and editing.

Olga Ciccarelli: manuscript conceptualization, review, revision, and editing.

Daniel Ontaneda: manuscript conceptualization, review, revision, and editing.

Melinda Magyari: manuscript conceptualization, review, revision, and editing.

Victor Rivera: manuscript conceptualization, review, revision, and editing.

Dorlan Kimbrough: manuscript conceptualization, review, revision, and editing.

Ruth Dobson: manuscript conceptualization, review, revision, and editing.

Bruce Taylor: manuscript conceptualization, review, revision, and editing.

Mitzi Williams: manuscript conceptualization, review, revision, and editing.

Ruth Ann Marrie: manuscript conceptualization, review, revision, and editing.

Brenda Banwell: Manuscript review and editing.

Bernhard Hemmer: manuscript conceptualization, review, revision, and editing.

Scott D. Newsome: manuscript conceptualization, review, revision, and editing.

Jeffrey A Cohen: manuscript conceptualization, review, revision, and editing.

Andrew J. Solomon: manuscript conceptualization, review, revision, and editing.

Professor Walter Royal, III: manuscript conceptualization, review, revision, and editing.

Abstract

The diagnosis of suspected multiple sclerosis (MS) in North America, Northern Europe, and Australasia have focused mostly on White populations. People from minority ethnic and racial backgrounds in high-prevalence regions of MS are more often found to be affected by social determinants of health (SDOH) compared to White people. SDOH are the circumstances in which people are born, live, and work that impact health status and disease risk. A better understanding of changing demographics, the clinical characteristics of people from minority ethnic or racial backgrounds, and the social challenges they face in diagnostic delays might facilitate more equitable clinical approaches when considering a diagnosis of MS. Differential diagnoses such as neuromyelitis optica, systemic lupus erythematous, neurosarcoidosis, infectious etiologies, and comorbidities must be considered in the differential. The diagnosis of MS in people from a minority ethnic or racial background requires a comprehensive approach that considers the complex interplay of immigration, diagnostic inequity, and SDOH.

Introduction

Diagnosing multiple sclerosis (MS) includes evaluating a clinical history, neurological examination, imaging review, and excluding alternative diagnoses.(1) The 2023 consensus approach to MS (2) delineates red flags that consider alternative diagnoses. However, MS differential diagnoses have mostly been derived from White European and North American cohorts.(1) Since 2013, countries with high MS prevalence as defined by the World Atlas of MS (101 or higher per 100,000 people)(3) have seen an increase in MS in people from minority ethnic or racial backgrounds (Panel 1). Higher than previously recognized estimates are reported in Black people in the United Kingdom (UK)(4) and United States (US),(5, 6) Hispanic people(6, 7) and other US racial groups,(6) and Middle Eastern and North African (MENA) people in Canada(8). These changing demographics of MS likely reflect the ethnic migration over time to these countries and the non-medical factors that are known to play a fundamental role in who has access to healthcare. (Social Determinants of Health; SDOH; Panel 1). For example, economic stability, health care access and quality, education, social and community context, and neighborhood living can impact the diagnostic process of any disease, including MS. Race is a social construct and in the US, Black people with MS have greater health disparities and inequities including lower education and socioeconomic status, higher morbidity, and premature death.(9, 10) The intersection of race and ethnicity and SDOH in the diagnosis of MS is poorly understood and likely contributes to the substantial morbidity and mortality differences reported. The goal of this review, prepared by the Multiple Sclerosis Differential Diagnosis Consortium subcommittee, is to highlight the expected clinical and social challenges complicating the MS differential diagnostic workup in people from minority ethnic or racial backgrounds (Panel 1, Glossary of Terms), historically underrepresented in MS research and from high MS prevalence regions in North America, Northern Europe, and Australasia (see Appendix 1, page 32).

Prevalence and Incidence of MS in People from a Minority Ethnic or Racial Background in North America, Northern Europe, and Australasia

Estimates of the number of cases of MS in the US vary geographically and, likely, by the proportion of the ethnic and racial group(s) within that area.(5) Recently, a national US population-based cohort using private, military, and public (Medicaid and Medicare) administrative health claims datasets estimated that the prevalence of MS per 100,000 US adults (based on cumulative prevalence from 2008-2010) was highest in White people (374.8 per 100,000; 95% confidence interval [CI] 373.8-375.8), followed by Black people (298.4 per 100,000; 95% CI 296.4-300.5), Asian or Pacific Islander or Native Hawaiian, Native American or Alaska Native, and multiracial people combined (197.7 per 100,000; 95% CI 195.6-199.9), and Hispanic people (161.2 per 100,000; 95% CI 159.8-162.5; **Figure 1A**).(6) Prevalence estimates for Hispanic people in the US, however, are much higher than for Hispanic people in Puerto Rico (95.3 per 100,000)(7) and Mexico (7.5-30 per 100,0000(11), with whom most Hispanic people in the US (61.6% of 61.2 million Hispanic people) ethnically identify.(12) The sharp decline in MS prevalence noted in Black persons age 55 and older compared to White people in the US, might be attributed to differences in mortality rates compared to White people (9) as incidence and longevity influence prevalence. Notably, the significant overall increase in US MS prevalence in Black people in the last 20-30 years (6) alerts us that this is a population at risk of MS and likely affects the predictive value of currently recommended approaches for diagnosing MS.

In Canada, a substantially increased risk of MS is observed in certain immigrant groups and second-generation immigrants relative to their forebears (8). MENA immigrants are reported to have a greater risk (hazard ratio 1.22, 95% CI 1.06-1.40) than immigrants from Europe, Russia, Australia, New Zealand, and the US. (8) Incidence of MS in people with ethnic origins from East Asia (such as Japan) or Southeast Asia living in Canada has doubled (1986-2010) from 1.04 per 100,000 to 2.02 per 100,000 for females.(13) Japanese Canadian-born and Japanese immigrants are reported to have a considerably higher risk than the age and sex-standardized incidence in Japan (age and sex-adjusted, 0.99 per 100,000).(14) This higher risk is likewise true for the risk of MS in Iranian immigrants to Canada.(15) The crude prevalence of MS in the immigrant Iranian population in British Columbia, Canada (287 per 100,000, year 2006)(15) is also greater than the overall prevalence of MS reported in Iran (100 per 100,000; pooled estimates for 1989-2018; **Figure 1B**).(16) Greater

environmental risk factors, improved diagnostic algorithms, and access to care in MS in the new host country could be responsible.

Indigenous populations are reported to have significantly lower MS incidence and prevalence than White people in the US and Canada, (17) which could reflect underreporting or underdiagnosis. An increase in the incidence and prevalence of MS in indigenous peoples in North America is reported over the last 30 years (1980-2011) despite the underrepresentation in research and lack of high-quality studies(17). Although the incidence and prevalence of MS among First Nations Canadians are lower than in non-First Nations Canadians, they are still among the highest in the world. (**Figure 1B**).(17, 18)

Prevalence estimates for MS among indigenous groups such as Australian First Nations people (0.00 95%CI 0.00–0.95) and Asian people (further breakdown of Asian background not available) living in Australia suggest a very low prevalence (1.53 per 100,000 95% CI 0.19–2.88) compared to people in Australia who identify as white European (75.2 per 100,000 95% CI 71.0–79.3).(19) An increase in MS prevalence in the indigenous Māori people within New Zealand is also reported over time,(20) with recent estimates of 15.9 per 100,000 (95%CI 12.6–19.2); this remains much lower than that reported for people of self-reported white European background (103.4 per 100,000; 95%CI 99.5–107.3; **Figure 1C**).(19) An underestimation of MS prevalence among indigenous people as a result of health disadvantages and discrimination is possible.(21)

MS is more often diagnosed among Black people and South Asian people living in the UK compared to populations in Africa and South Asia.(4) Studies in East London(4) report an overall age-standardized prevalence of MS of 111 per 100,000, with 180, 74, and 29 per 100,000 for White, Black, and South Asian populations, respectively (**Figure 1D**). A higher prevalence is also observed for MENA first-generation descendants in France than in their native countries.(22) Improved health service delivery and greater access to neurologists in France is likely given the inequitable access to health services and deficiency in the health workforce reported in MENA countries.(23) Population-based studies in Scandinavian countries have also

demonstrated that MS risk is higher in people who migrate to regions with documented high MS risk compared to lower latitude countries and increases with duration of residence in the new country. (8, 24) This observation may be due to changes in environmental exposures, improved diagnosis in the new host country, and better healthcare access. Lower prevalence MS regions are more likely to have fragmented healthcare systems and poor quality care.(25) In second-generation immigrants from Iran or Afghanistan to Denmark, Norway, and Sweden, MS risk approached and sometimes exceeded that of the general Danish white population.(24, 26, 27) In a large nationwide cohort from Denmark, second-generation immigrants from Pakistan, had a 28% higher risk of MS (relative risk=1.28;95%CI:1.06–1.56) compared with Danish people whose parents had both been born in Denmark whereas Danish-born participants with one foreign and one Danish-born parent had MS risks similar to ethnic Danes.(24)

Hence, the age of immigration might contribute to the risk of developing MS or being diagnosed with MS even with migration in adulthood, although the effect appears greater with migration in childhood or adolescence.(8, 24) Environmental factors such as Epstein-Barr virus seropositivity is shown to increase with distance from the equator(28). Diet changes, obesity and vitamin D and sunlight exposures are also potential contributors to changes in incidence with migration. Efforts are needed to understand these changing demographics and how they may affect the differential workup of MS.

Clinical and Paraclinical Characteristics of MS in People from Minority Ethnic or Racial Backgrounds

The clinical demyelinating syndromes such as optic neuritis, myelitis, and brainstem syndromes do not significantly differ in people from minority ethnic or racial backgrounds.(29) However, the proportion of people with the various clinical demyelinating syndromes, disease subtypes (relapsing versus progressive), and disability progression do differ. Age of onset, humoral response, and lesion load on MRI also differ and can confound the diagnostic process due to specialist healthcare services, and public and healthcare provider assumptions.

People from minority ethnic or racial backgrounds clinical disease onset is at a younger age (i.e., Black, Asian, and Middle Eastern as a combined group 28.6 years vs. White 32.8 years, p=0.001 for a UK cohort,(30) Hispanic 28.5 years vs. White 32.6 years in a US cohort, p<0.05(31)). A younger age of onset has also been reported for First Nations Canadians compared to non-First Nations participants.(18) This younger age of onset may be responsible for the variations in presentation and disease severity noted compared to White people. Whether younger age is related to other disease characteristics is unclear. Greater Native American and Black genetic ancestry are reported to be associated with younger age of onset compared to greater European ancestry in a US Hispanic adult cohort with MS.(32)

Optic neuritis is a common manifestation of MS, affecting approximately 20% of patients in White-dominant cohorts. Cross-sectional and retrospective cohort studies suggest that the frequency of optic neuritis as a presenting syndrome varies by race and ethnicity.(29, 33) Hispanic people in the US who are eventually diagnosed with MS are two times more likely to present with optic neuritis than White people matched for age and gender (n=94 in each group, 42.6% vs. 25.5%; odds ratio [OR] 2.16, 95% CI 1.10-2.53).(33) Optic neuritis is also a common presentation in Black people in the US and often is more severe than in White people, as reflected by the severity of visual impairment at MS presentation and follow-up and the degree of retinal nerve fiber layer (RNFL) and ganglion cell inner plexiform layer (GCIPL) thinning.(31, 34, 35),(36, 37) In a longitudinal study of RNFL (-1.1% versus -0.8%: p=0.02; adjusted for age at baseline, sex, disease duration and history of optic neuritis) and GCIPL (-0.7%/year versus -0.4%/year: p=0.01) atrophy rates over a mean of 4.5 years were faster in African American (n=116) compared to White (n=116) people with MS. (38) Whether delayed diagnosis or misdiagnosis of neuromyelitis optica spectrum disorder (NMOSD) cases before the advent of the 2015 diagnostic criteria occurred is not clear. Black people are at a higher risk for retinal and other ocular diseases (e.g, glaucoma and diabetic retinopathy) which need to be considered in optic neuritis (**Table 1)**.

Transverse myelitis at onset is reported to be more common in Black (n=105/375, 28% vs. 77/427,18% in White people; p=0.001)(39) and Hispanic populations in the US (n=30/119, 25% vs. 10/76, 13.1% in White

people; p=0.07).(31) Motor and sensory deficits can be more severe and symmetric and are more likely to be accompanied by urinary dysfunction in these populations. Consistent with these clinical observations, Black people in the US with MS exhibit greater atrophy in the upper cervical cord compared to White people with MS ($p<0.0001$), suggesting greater relapse-associated tissue injury and neurodegeneration.(40) Additional signs and symptoms to be considered in people from a minority ethnic or racial background are presented in **Table 2**.

General differences in the severity of symptoms between populations are reported. A cross-sectional assessment from a patient-reported North American registry reported a higher burden of mobility, dexterity, vision, fatigue, cognition, bladder function, sensory function, spasticity, pain, dizziness, depression, and anxiety symptoms among Black and Hispanic people compared to White people (n=2,622; self-identified as 66.4% White, 21.7% African American and 11.9% Hispanic).(41) US Hispanic patients also demonstrated worse self-reported symptom scores than White and Black patients, particularly in pain, cognition, depression, and anxiety (adjusted for age and sex but not disease duration).(41) In a large MS center network (n=7,430), Black people with MS in the US had significantly worse neurological quality scores for fatigue (1.83 points, 95%CI 0.37–3.29), depression (2.98 points, 95%CI 1.77–4.19), and anxiety (2.43 points,95% CI 1.01–3.85) when employment was used as the predictor in those disabled or unemployed. (42) Within US White people, similar trends were found for disabled and unemployed patients which underscores SDOH's strong influence on health outcomes.(42)

Greater disease severity at diagnosis, including greater frequency of multifocal involvement at initial clinical presentation and higher Expanded Disability Status Scale (EDSS) scores at diagnosis and 5-year follow-up, are reported for US Black people with MS which could reflect inadequate treatment compared to White people.(35, 39) Faster clinical progression and poorer clinical outcomes, including shorter median time from diagnosis to needing a cane (16 years vs. 22 years; $p < 0.0001$) or wheelchair (30 years vs. 38 years; $p=0.05$) are reported in the US for Black people compared to White people potentially underscoring differences in care treatment and other socioeconomic factors as diagnostic delay was not found.(35) A higher proportion of progressive forms of MS is more often reported for Black people in the US. A multi-ethnic retrospective, observational cohort

study of US people with MS using electronic health records (n=3,286/1,058,102) found primary progressive MS (10.0% vs. 0.0–4.0%) and secondary progressive MS (6.0% vs. 0.0–2.0%) to be more common in Black people with MS compared to White people.(43) A prior US study reported 6.8% (n=46/673) of Black compared to 4.6% (n=33/717) of White people with MS to have primary progressive MS, with secondary progressive MS being more common in Black than White people with MS (n=182/673, 27.0% vs. 155/717, 21.6%, respectively).(44) However, primary progressive MS was less commonly observed in a multi-ethnic cohort of Afro-Caribbean, Asian, and Middle Eastern people compared to White people from a UK regional disease registry (4.8% vs. 11.6%, respectively, p=0.03).(30)

Greater disease severity and faster progression are reported in migrants to Europe (South Asia and Black populations), (22, 30, 33) the US (Hispanics), (45) and Canada (Asians) compared to White people.(15, 46) First-generation migrants from Morocco, Algeria, or Tunisia to France have a higher risk of ambulatory disability compared to White people in France.(22) Hispanic people with MS immigrating to the US are observed to be three times more likely to have a worse ambulatory disability compared to those born in the US.(45, 47) People from Asia, MENA, or South and Central America who immigrated to Norway with MS had an increased disease severity compared with Norwegians and immigrants from Europe, North America and Australia.(48)

Racial and ethnic differences in paraclinical investigations important in the diagnostic criteria and differential diagnosis of MS are also observed. This includes CSF variations, which their presence can substitute for the dissemination in time criterion.(1) A meta-analysis found that 87.7% (n=10,746/12,253) of White people with MS have CSF-OCBs.(49) The frequency of CSF-OCBs in people from minority ethnic or racial backgrounds is less clear. A lower prevalence of CSF-OCBs has been reported for Korean people and Brazilian Black people with MS.(50, 51) Higher IgG index and synthesis rate are reported for US Black people with MS indicating a more active intrathecal immune response compared to White people (IgG index: Mean 1.35±SD 0.62 vs.

1.05±0.55; p=0.001, and IgG synthesis rates: 13.55 vs 8.20 mg/day; p=0.01) respectively.(52) The frequency of CSF-OCB was also higher for US Black people compared to White people, (n=55/66, 87.3% vs. 95/132, 74.2%; p=0.04). Additionally, circulating antibody-secreting cell frequencies are reported to be significantly elevated in Black and Hispanic people with MS compared to White people with MS in the US (on treatment n=54, 1.17% vs. 0.72%, p=0.05 or untreated n=20, 6.56% vs. 2.1%, p=0.04, respectively).(53) More pronounced brain tissue damage compared to White people with MS is reported among Black people in the US.(38, 54) This includes higher numbers of brain MRI T2 lesions and lower whole brain and gray matter brain volumes, including thalamic and cortical volumes.(54) However, significant group differences were found in healthcare access where Black people were more likely to have public insurance (i.e., Medicaid), be disabled, or unemployed compared to White people in the US which could have impacted the time to diagnosis and treatment.

Differential Diagnosis:

CNS Disorders and Systemic Conditions with CNS Involvement

Important disorders to exclude in people from a minority ethnic or racial background include NMOSD, myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD), systemic lupus erythematosus (SLE), and neurosarcoidosis. Certain disorders such as NMOSD disproportionately affect Black people and can obscure the diagnosis of MS. Nevertheless, to help arrive at a more accurate diagnosis(2) it is important to recognize that they share clinical syndromes with MS (e.g., ON, transverse myelitis (TM)), but can vary by ethnicity even within Europe.(55, 56) NMOSD is a rare, severe, antibody-mediated CNS disorder characterized by optic neuritis (often longitudinally extensive and involving the posterior aspect of the optic nerve and chiasm), area postrema syndrome, and longitudinally extensive myelitis.(57) Aquaporin-4 antibody can be found in most cases.(57) The incidence and prevalence of NMOSD among White populations are <1/million and ~1/100,000, respectively. Among East Asian people, the prevalence is higher at ~3.5/100,000 population, while the prevalence in Black people in Martinique may be up to 10/100,00 depending on geography.(58) Specifically, Black people appeared to be at higher risk (13/100,000) compared to White people (4.0/100,000) when examined in Olmsted County, Minnesota, US.(59) More severe attacks, defined as an EDSS score of ≥6.0 at the

nadir of the attack, or an increase of ≥0.5 points if the patient had a baseline EDSS score of ≥6.0 at onset, are reported for Black people (58%; n=53/92) compared to Asian (46%; n=140/304) and White (38%; n=79/207, p=0.005) people.(60) In addition, cerebral attacks (such as encephalopathy, seizures, and decreased mental status) and brain MRI abnormalities (e.g., higher lesion loads) develop more frequently in Asian and Black people (US and Europe combined) with NMOSD,(60) underscoring the importance of thorough history taking and neuroimaging. In addition, the proportion of MS to NMOSD in clinical practice varies, primarily due to the wide disparities in MS prevalence across the globe rather than that of NMOSD. Hence, a clinical presentation with bilateral simultaneous or sequential optic neuritis, or longitudinally extensive optic neuritis or myelitis should prompt testing for aquaporin-4 autoantibody, preferably using a cell-based assay. MOGAD is an antibody-mediated demyelinating disorder of the CNS characterized by attacks of immune-mediated demyelination predominantly targeting the optic nerves, brain, and spinal cord. Thus far, no specific racial or ethnic differences have been reported.(10) Nevertheless, careful assessment of MOG antibody titers, spinal cord (e.g., distal cord), and optic nerve (e.g., optic nerve sheath and anterior optic nerve) as seen via MRI, and evaluation for MOGAD criteria(61) is important given the overlap with MS syndromes.

Systemic lupus erythematosus (SLE) is a chronic, systemic autoimmune disease with a higher prevalence among people from minority ethnic and racial backgrounds. In US registries, age-standardized incidence and prevalence of SLE are estimated to be higher among Black (15.5 per 100,000 person-years; 241.0 per 100,000 persons), Asian/Pacific islanders (4.1 per 100,000 person-years; 90.5 per 100,000 persons), and Hispanic populations (4.2 per 100,000 person-years; 94.7 per 100,000 persons) relative to White populations (2.8 per 100,000 person-years; 55.2 per 100,000 persons).(62) In the UK, the prevalence of SLE is estimated at 517.51 (398.54 to 660.84 per 100,000) for Black people from the Caribbean islands, 193.09 (140.84 to 258.37 per 100,000) in Indian people, and 134.53 (128.21 to 141.08 per 100,000) in White people.(63) Nevertheless, an increase in the prevalence of neurological manifestations of SLE is reported in US Black people compared to White people,(64) potentially complicating the MS diagnostic process because of the shared neurological manifestations with MS (e.g., myelitis). The distinction is important because the underlying immune

mechanisms and disease-modifying therapies differ from those in MS. If the clinical history (e.g., hematologic, mucocutaneous, serosal, arthritic) or laboratory evaluation (e.g., elevated anti-nuclear antibody titer) raises concern for SLE, neurologists should consider the 2019 European League Against Rheumatism/American College of Rheumatology diagnostic criteria to search for other features and refer to a rheumatologist.(65)

Sarcoidosis is an immune-mediated inflammatory condition characterized by non-caseating granulomas. The incidence and prevalence of sarcoidosis vary by ethnicity and geography.(66) Incidence and prevalence estimates are higher in Black people in the US (Northeast) and the UK compared to White people, with the highest prevalence reported at 2,000 per 100,000 from a race-specific registry in the US (US Black Women's Health Study Cohort).(66-68) US Black people are more likely to experience multiorgan involvement, particularly pulmonary involvement.(67) About 5%-10% have neurosarcoidosis and about 10%–20% do not have identifiable systemic involvement.(69) Diagnosing neurosarcoidosis involves excluding other causes and discerning clinical and radiological patterns suggestive of leptomeningeal and pachymeningeal enhancement. (69, 70)

Comorbid Conditions

A history of comorbidities may confound or delay the diagnosis MS.(71) They are often chronic, associated with a range of poor health outcomes, and are resource-intensive. (71, 72)

In the US, vascular comorbidities such as hypertension and diabetes disproportionally affect people from minority ethnic and racial backgrounds(71, 73). Black people have a higher prevalence of vascular comorbidities compared to White people in the US; this is also true of immigrants in Canada who develop MS compared to other immigrants.(74-76) Hispanic people with MS in the US, independent of the age of immigration, have more vascular risk factors, such as diabetes, hypertension, stroke, coronary artery disease, and hypercholesterolemia (n=11/67, 16% in late immigrants and 5/35, 14% in early immigrants) compared to US-born people (n=8/202, 4%).(45) Hence, special attention should be paid to evaluating comorbidities and

neuroimaging (e.g., MRI). Lesions in vascular watershed areas favor a vascular etiology versus characteristic Dawson's fingers, ovoid lesions, corpus callosum lesions, and short-segment spinal cord lesions, which favor MS. In addition, ophthalmic findings such as retinal haemorrhage, exudates, and macular abnormalities may accompany vascular comorbidities (**Table 1**). Shared mechanisms that underlie the coexistence of two or more conditions (i.e., direct causation, shared risk factors) may inform future treatments or preventive strategies.

Infections and Immigration

Infections endemic to the country of origin of individuals who have newly immigrated to high-risk MS regions, are also important to consider in North America, Northern Europe, and Australasia. Atypical features such as fever, seizures, and meningoencephalitis may indicate an infectious etiology. Travel history should consider maps of endemic regions and outbreaks, tropical/subtropical countries, insect bites, animal exposure, eating undercooked meat, drinking contaminated water, extensive soil exposure, and unprotected intercourse which can help with early identification of foreign-based-associated infections **(Table 3)** and are expanded by Solomon et al.(2). People from minority ethnic and racial backgrounds immigrating from tropical regions and developing countries, parasitic infections such as cerebral malaria, neuro-schistosomiasis, and neurocysticercosis should be excluded.(77) Immigrants from Latin America and the Caribbean are particularly at risk of human T-lymphotropic virus type 1 infection, Chagas disease, chikungunya infection, dengue fever, and zika virus infection, among other infections.(78) With increasing global migration patterns, infections in the differential diagnosis of MS must be considered.(2)

Diagnostic Inequity and Social Determinants of Health

Diagnostic inequity represents the lack of a fair and just chance to experience the benefits of diagnostic excellence.(79) It results from diagnostic errors, that is, the failure to establish an accurate and timely explanation of a patient's health problem as defined by the National Academy of Medicine (**Figure 2**). Errors are widespread and global, affecting 10%-15% of people in every setting investigated, and are often associated with substantial patient harm; this includes permanent disability and increased mortality.(80, 81) Medical errors

often reflect healthcare system complexities and vulnerability. In 2020, medication or treatment errors were experienced by 13.1% of patients in Australia, 12.6% of patients in the USA, 11% of patients in the UK, and 10.4% of patients in Canada.(82) The heterogeneous clinical and imaging manifestations of MS and extensive differentials, heighten the risk of diagnostic errors and misapplication of the McDonald Criteria to diagnose MS (1) (83-85) (Panel 2).

SDOH can impact the diagnostic process of any disease but are less accounted for in MS studies (**Figure 2**).(10) Data support that Black and Hispanic people in the US with neurological conditions are 30% and 40% (respectively) less likely to access specialty care compared to White people, and Black people have higher utilization of emergency department care as well.(86) Delays in MS diagnosis have been reported for US Black and Hispanic people (1.2 years vs. 0.3 years for White people).(31, 87, 88) Both younger(89) and older age at presentation, lower education level, and motor symptoms at onset are associated with longer diagnostic delays in MS.(90) Prior work has overlooked other SDOH that could reflect physician-related insufficient experience, knowledge or bias, or be system-based (e.g., unavailability or delays in paraclinical and diagnostic tools).(91) A qualitative study of US Black females reported that healthcare providers harbored skepticism and were reluctant to consider a diagnosis of MS.(88) Language use and cultural differences in symptomatic expression and idioms of distress were found in as many as 57% of Hispanic people with MS in the US(92) which could augment diagnostic inaccuracies.

Immigrant status has been linked to diagnostic delays in MS(15, 45) and greater ambulatory disability.(31) In the Iranian immigrant population of British Columbia, Canada, the median time from onset to diagnosis was significantly greater for those who developed MS in Iran than those developing MS in Canada (5 years vs. 1 year, respectively).(15) Whether these observations are due to a lack of specialty care in the country of origin or greater difficulty for immigrants accessing the Iranian healthcare system compared to the Canadian universal healthcare system is unclear as SDOH were unaccounted. The Iranian healthcare system covers about 70% of its population but is reported to have limited access to high-quality medical equipment.(93) Foreign-born or

recent immigrants had a higher risk of adverse outcomes soon after MS diagnosis, including hospitalization, disability accrual, and mortality.(22, 45, 94, 95)

The inclusion of children and youth into the McDonald criteria(1) has facilitated the diagnosis of MS for patients aged <19 years. However, pediatric-onset MS (POMS) is rare, and worldwide, access to expert care is limited.(96) Furthermore, between 20.6%-30.2% of POMS patients self-identify as Black or Hispanic in the US, and 39% have one or both foreign-born parents.(97) Compared to adult MS, the POMS community has limited access to educational materials, research funding, treatment (e.g., fingolimod in the US) and clinical trial prioritization (Panel 3). (98, 99)

Conclusion and Future Directions

In high-prevalence MS regions, MS has often been overlooked in people from minority ethnic or racial backgrounds.(43) The increased severity of disease observed in these populations may partly reflect diagnostic delays, errors, and other sequelae of SDOH. Clinical presentations indicative of MS should be evaluated using sequential strategies, as proposed by Solomon et al.(2) irrespective of race and ethnicity. To mitigate diagnostic inequity and decrease subsequent disease burden, education, outreach, and research about the barriers that hinder access are needed (Panel 3). As neurology healthcare providers, we must be aware of the evolving literature and actively address our biases to strive for a more timely and accurate diagnosis of MS in all people.

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Panel 1: Glossary of Terms

People from minority ethnic or racial backgrounds: We defined ethnic and racial people in a country who do not identify as White people, are generally at risk of poorer health and healthcare outcomes, and who have been historically underrepresented in MS research.

White people: People of European ancestry who do not identify as Hispanic and have historically been termed Caucasian.

Hispanic, Latino or Latina, Latinx, and Latine people: These terms are used interchangeably to describe people who come from or have family roots coming from countries in Latin America and the Caribbean in the US. Hispanic is a common term used in United States-based studies.

Black people: A person having origins in any of the black racial groups of Africa.

African American people: People who are born in the United States and have African ancestry. The term is used interchangeably with Black people.

Indigenous populations or people: Original inhabitants such as indigenous people to North America (i.e., Native American, or American Indian), Canada (e.g., First Nations people), Australia (e.g., Aboriginal), and New Zealand (e.g., Māori people).

Asian people: A broad category that can include numerous countries of origin (e.g., Cambodia, China, India, Japan, Korea, Malaysia, Afghanistan, Pakistan, the Philippine Islands, Thailand, Vietnam, and others) and geographical regions (e.g., East Asia, South Asia, Southeast Asia).

Middle Eastern and North African people (MENA): A distinct ethnic category that allows for different racial identifications of people who have origins in Algeria, Bahrain, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Libya, Morocco, Oman, Qatar, Saudi Arabia, Syria, Tunisia, United Arab Emirates, and Yemen. In the United States, people from Iran are currently not categorized under MENA (categorized as White people) but are expected to be included under MENA in the 2030 US census.

Immigrant: A person who moves away from their place of usual residence, for a variety of reasons. This includes forced immigration as a result of enslavement or political and economic instability.

Diagnostic Inequity: Lack of a fair and just chance to experience the benefits of diagnostic excellence.

Diagnostic Error: Failure to establish an accurate and timely explanation of a patient's health problem; this includes diagnostic delays, wrong diagnosis, and misdiagnosis.

Social Determinants of Health: Environmental and social conditions where people are born, live, and age that affect a wide range of health outcomes. They can be grouped into economic stability, education, health care access and quality, neighborhood and built environment, and social and community context (Figure 2).

Panel 2: Misapplication of the McDonald Diagnostic Criteria for Multiple Sclerosis

The original development of the McDonald criteria and subsequent revisions were primarily based on data from White adult populations with a typical clinically demyelinating syndrome and age <50 years.(1) The formal inclusion of children and youth into the McDonald criteria(1) has also facilitated the diagnosis of MS for patients aged <19 years.

Factors that increase the risk of misapplication and misdiagnosis
Misdiagnosis of MS in White people is estimated at 20% (83, 84) and people of minority ethnic or racial backgrounds could be at greater vulnerability due to:

- Misinterpretation of paraclinical and imaging studies.
- Failure to exclude other conditions that mimic MS.
- Physician-related insufficient experience, knowledge, personal bias, or system-based factors.

The current McDonald Criteria can be applied to minority ethnic and racial populations.

The McDonald Criteria have been applied widely to diverse people in various countries (e.g., Asia, Canada, Italy, the Netherlands, Spain, the Middle East, and Latin America).(1)(85) Thus far, the available data provide no evidence that the McDonald criteria cannot be used in people from a minority ethnic or racial background.

Panel 3: Future Directions and Research Priorities

Clinical Care

- Include social determinants of health, immigration, travel, and infectious exposures in the clinical history-taking process.

- Enhance coordination of care for immigrants and other high-risk populations with MS.

Education and Outreach

- Develop provider, patient, and community outreach programs to advance health knowledge about MS in people of minority ethnic and racial backgrounds.

- Provide cultural competency training to healthcare providers to minimize diagnostic delays.

- Work to implement and disseminate system-wide access policies that improve healthcare delivery across diverse systems such as universal healthcare systems, safety net institutions and local hospitals.

- Use findings to educate policymakers about the populations at most risk of health disparities.

Research

- Ensure adequate representation of people of minority ethnic and racial backgrounds in future interventional and observational studies.

- Examine the changing demographics of MS and how they may affect the differential workup of MS.

- Collect and analyze multilevel data related to social determinants of health and integrate them into clinical diagnostic algorithms.

- Develop interventions that consider the clinical and paraclinical variations of disease presentation, including comorbidities, in people of minority ethnic and racial backgrounds.

- Design feasible clinical trials for pediatric-onset MS to address the significant gap in treatment access and to provide critical safety data for children and youth with MS.

- Develop research plans that integrate investigators representative of culturally and linguistically diverse communities.

Table 1: Presentation of Optic Neuritis in People from a Minority Ethnic or Racial Background with Multiple Sclerosis

	Typical features for MS-ON (2)	**Additional features that might be more common in with MS-ON in MEPs***
Clinical	•Unilateral •Mild-moderate visual loss •Central scotoma •Normal or mildly swollen optic disc •Responsive to corticosteroids with good recovery	•Haemorrhages, exudates, and/or macular abnormalities due to high risk of vascular comorbidities •Visual acuity to be worse in African American people compared to White people (36) •Less response to corticosteroids •Poor recovery
MRI	•Short-segment optic nerve T2-hyperintensity +/- gadolinium enhancement •Asymptomatic T2-hyperintense ovoid well-demarcated brain or spinal cord lesions typical of MS	no data available
VEP	•Prolonged P100 latency with only mild to moderate amplitude reduction •Sub-clinical involvement of the fellow eye	no data available
OCT	•Acute pRNFL swelling, followed by temporal quadrant predominant pRNFL thinning •Early GCIPL thinning •Sub-clinical pRNFL and mGCIPL thinning in the fellow eye	•More pronounced pRNFL thinning in African American people compared to White people (36)(37) •More pronounced mGCIPL thinning in Black people compared to White people(38)
CSF	•Positive oligoclonal bands •High IgG index	•Higher Ig G index and synthesis rate (in general-not specific to myelitis) in Black people compared to White people (52)

VEP: visual evoked potentials, OCT: optical coherence tomography; pRNFL: peripapillary retinal nerve fiber layer; mGCIPL: macular ganglion cell-inner plexiform layer, *These additional features might have several contributing factors, including delayed recognition, eg because of differences in access to diagnostic services. However, the absence of these additional features does not exclude optic neuritis.

Table 2: Approach to Myelitis in People from a Minority Ethnic or Racial Background with Multiple Sclerosis

	Typical features for MS (2)	**Additional features that may be seen in patients with MS in MEPs***
Clinical	•Young adult •Sensory predominant •Mild motor deficit, asymmetric •Urinary urgency or incomplete emptying	•Transverse myelitis defined as motor, sensory and including urinary dysfunction reported more frequently reported in African American (39) and Hispanic people (31) • Black patients and immigrants are more likely to have vascular comorbidities compared to White patients with MS (71-75) which can increase peripheral nervous system findings •Greater multifocal involvement at presentation in Black people compared to White people (39)
MRI Spine	•Multiple short segment T2-hyperintense lesions •Lesions reaching the spinal cord surface: asymmetric dorsal/lateral column •Cervical cord more frequently involved than thoracic cord •Enhancement: focal with or without ring; transient (<3 months)	•Pseudo longitudinally extensive lesions due to coalescence of multiple lesions •Disproportionate medullary and cervical degeneration in Black people compared to White people (40)
MRI Brain	•Typical MS T2 lesions in infratentorial, juxtacortical, and periventricular locations •Well demarcated	•higher T2 lesion volumes, as well as borderline lower whole and nuclear thalamic volumes and cortical grey matter observed in Black people compared to White people (38) •lower baseline thalamic volume measures correlating with a higher median baseline Expanded Disability Severity Scale in Hispanic people compared to White people(33)
CSF	•Positive oligoclonal bands •WBC <50 cells/µL	•Higher Ig G index and synthesis rate (in general-not specific to myelitis) in Black people compared to White people (52)

*These additional features might have several contributing factors, including delayed recognition, eg because of differences in access to diagnostic services. However, the absence of these additional features does not exclude myelitis.

Table 3: Important Infectious Exposures to Consider in the Differential Work-up of Multiple Sclerosis in People from a Minority Ethnic or Racial Background. (2)(77-78)

Exposure Scenario*	Infections	Neurological Manifestations
Northern hemisphere including the United States, Europe, and parts of Asia	Lyme	Cranial neuritis (most often facial nerve palsy), meningitis, and radiculoneuritis
Southern Japan, the Caribbean region, areas of South America, tropical Africa and the Middle East, Australia, and Melanesia	HTLV-1	Myelopathy, encephalopathy, and myositis
Mediterranean basin, Middle East, Central Asia, China, the Indian subcontinent, sub-Saharan Africa, and parts of Mexico and Central and South America	Brucellosis	Encephalitis, meningoencephalitis, radiculitis, myelitis, peripheral and cranial neuropathies, subarachnoid hemorrhage, and psychiatric manifestations
Africa, Russia, Eastern Europe, Asia, Latin America, and the Caribbean	Tuberculosis	Meningitis, tuberculoma, spinal arachnoiditis
Central and South America, sub-Saharan Africa, India, and Asia	Cysticercosis	Chronic epilepsy, encephalopathy, blindness, headaches
Africa South of the Sahara and in parts of Oceania such as Papua New Guinea	Malaria	Seizures, encephalopathy, cerebral vasculitis
Tropical and sub-tropical areas, in communities that are resource-limited	Schistosomiasis	Seizures, encephalopathy, cerebral vasculitis, cerebellar syndrome
Continental Latin America	Chagas	Meningoencephalitis, stroke, autonomic nervous system dysfunction
Africa, Southeast Asia, the Indian subcontinent, the Pacific Region, and the (sub) tropical regions of the Americas	Chikungunya	Meningitis, encephalitis, meningoencephalitis, seizures, polyneuropathy and GBS
The Americas, Africa, the Middle East, Asia, and the Pacific Islands	Dengue Fever	Encephalitis, meningitis, myositis, ADEM, optic neuritis, myelitis, and GBS
Africa and South America	Zika	GBS, transverse myelitis, meningoencephalitis, ophthalmological manifestations, and other neurological complications

*These are exposure scenarios from developing countries or geographical locations where MS is less prevalent and where many people from a minority ethnic or racial background in North America, Northern Europe, and Australasia originate from.
HTLV-1: human T-cell lymphotropic virus type 1, ADEM: Acute Disseminated Encephalomyelitis, GBS: Guillain-Barré syndrome

Figure 1: Prevalence of Multiple Sclerosis in People from a Minority Ethnic or Racial Background Compared to White European or North American White populations in Selected Countries

The figures represent prevalence rates of MS per 100,000 reported in people from a minority ethnic or racial background relative to the prevalence of MS in the White population of selected countries based on available evidence. In some countries, MS in people from a minority ethnic or racial background has surpassed the recommended referenced scale for global MS high prevalence (between 101 to >200 per 100,000 people).(3)

Figure 1A: Prevalence of MS in White, Black, Hispanic, and other non-Hispanic people defined as Asian, Native American, Alaska natives and multi-race people living in the continental USA using an algorithm based on geography and name (6) and self-identified Hispanic people in Puerto Rico (7).
Figure 1B: Prevalence of MS in First Nations(18), Iranian people of Canada (15) and Iranian people in Iran (16) and White People in Canada.
Figure 1C: Prevalence of MS in Māori people and White people in New Zealand (19)
Figure 1D: Prevalence of MS in Black, South Asian and White people in the United Kingdom (4)

Figure 2: Social Determinants of Health and the Diagnostic Process in Multiple Sclerosis
When seeking a diagnosis of MS social determinants of health (SDOH) can affect the diagnostic process resulting in diagnostic errors. The circle framework encompasses the relative SDOH (the result of harmful societal forces like structural racism) structured around five common domains: healthcare care access and quality, neighborhood and built environment, community, education, and economic stability. The close arrows signify known factors that can lead to poor outcomes in the diagnostic process. The open arrows represent potential factors that can confound the diagnostic process. People of minority ethnic or racial have access to care barriers (10, 86, 87), disparities in the neighborhood and built environment (such as geographic regions that have a scarcity of neurologists) (42), poor lived experiences (such as experiencing more severe symptoms at diagnosis) and poor perceptions of the disease (such as limited familiarity with MS and its etiology) (10, 86-89, 95), less education (10) and less economic stability (10, 42). To decrease the potential for diagnostic errors, the healthcare provider needs to consider the SDOH and integrate existing comorbidities (71-76), immigrant and travel exposures (15, 45, 46, 48, 76, 77, 94) to prevent diagnostic errors. Diagnostic errors can be defined as delayed (where a diagnosis should have been made earlier) (31, 88-90), wrong (the original diagnosis is found to be incorrect) or misdiagnosis (where the diagnosis is not made)(83, 84). System and physician-based factors will also need to be considered which include health system vulnerabilities, lack of cultural competence and humility, and explicit and implicit biases.

Search Strategy and Selection Criteria

We searched PubMed, and MEDLINE for publications in English from January 1, 2008, and April 1, 2024. Keywords used in addition to “diagnosis”: “multiple sclerosis” AND “race and ethnicity”; “Black/African/African American”, OR “Hispanic/Latino/Latina/Latinx” OR “Middle Eastern/MENA” OR “Asian” and countries within this category (example: Iran, Pakistan, etc.) OR “Native American/indigenous” and populations within (example: First Nations, Midori, etc.). Separately, “migrant/immigrant,” was also queried in the countries of relevance to the study. Inclusion criteria: diagnosis of MS and people of ethnic and racial background in predesignated countries. Case series or abstracts were excluded. Papers pertinent to approaches to the differential diagnosis of MS specifically in minority racial and ethnic people in the United States, Canada, Northern Europe, and Australasia were identified and reviewed and important contemporary data were highlighted as references throughout the manuscript. Additional references were gathered from retrieved publications. Original research articles and, when appropriate, high-impact reviews were included. The final reference list was generated based on relevance and originality.

Appendix 1:

The “MS Differential Diagnosis Consortium” was conceived by the Americas Committee for Treatment and Research in Multiple Sclerosis (ACTRIMS). ACTRIMS recruited AJS as Chair with JAC as ACTRIMS representative and invited the International Advisory Committee on Clinical Trials in MS, European Committee for Treatment and Research in Multiple Sclerosis, Consortium of Multiple Sclerosis Centers, and Multiple Sclerosis International Federation to propose representatives to serve on a Steering Committee. This committee, comprised of AJS, JAC, BLB, SDN, BH, and RAM, identified priorities for updating recommendations to approaches to MS differential diagnosis to be addressed by four working groups. These working groups were focused on a comprehensive update to approaches to MS differential diagnosis and expanded considerations for MS differential diagnosis based on minority ethnic people (MEP) in geographic areas where White non-Hispanic people are the dominant population diagnosed with MS, based on the reported health disparities experienced by these populations in these areas (North America, Australasia, and Northern Europe). The Steering Committee invited two co-chairs to lead these working groups (LA and WR,III for the present manuscript). International experts in the diagnosis of MS comprising diverse representation of sex, academic rank, geographic region of practice, and clinical focus were identified for each working group by the Steering Committee and working group co-chairs. For the present manuscript, priority was given to experts in MS and minority ethnic people. Authors that self-identify with culturally and linguistically diverse communities in their respective countries (United States, Canada, Northern Europe, and Australia) represent 38.8% (n=7). The task force acknowledged that race and ethnicity is a complex multidimensional social construct that is dynamic, and shaped by geographic, cultural, and sociopolitical forces. LA facilitated electronic meetings and communication to iteratively create and revise drafts of each manuscript section, table, and figure based on published evidence and expert opinion. Consensus within the subgroup and by the Steering Committee as a whole was reached and recommendations developed through a series of conference calls and subgroup meetings.