Differential diagnosis of suspected multiple sclerosis: global health considerations

Jorge Correale, Andrew J Solomon, Jeffrey A Cohen, Brenda L Banwell, Fernando Gracia, Tirisham V Gyang, Fernando Hamuy Diaz de Bedoya, Mary P Harnegie, Bernhard Hemmer, Anu Jacob, Ho Jin Kim, Ruth Ann Marrie, Farrah J Mateen, Scott D Newsome, Lekha Pandit, Naraporn Prayoonwiwat, Mohammad A Sahraian, Douglas K Sato, Deanna Saylor, Fu-Dong Shi, Aksel Siva, Kevin Tan, Shanthi Viswanathan, Mike P Wattjes, Brian Weinshenker, Bassem Yamout, Kazuo Fujihara

The differential diagnosis of multiple sclerosis can present specific challenges in patients from Latin America, Africa, the Middle East, eastern Europe, southeast Asia, and the Western Pacific. In these areas, environmental factors, genetic background, and access to medical care can differ substantially from those in North America and western Europe, where multiple sclerosis is most common. Furthermore, multiple sclerosis diagnostic criteria have been developed primarily using data from North America and western Europe. Although some diagnoses mistaken for multiple sclerosis are common regardless of location, a comprehensive approach to the differential diagnosis of multiple sclerosis in Latin America, Africa, the Middle East, eastern Europe, southeast Asia, and the Western Pacific regions requires special consideration of diseases that are prevalent in those locations. A collaborative effort has therefore assessed global differences in multiple sclerosis differential diagnoses and proposed recommendations for evaluating patients with suspected multiple sclerosis in regions beyond North America and western Europe.

Lancet Neurol 2024; 23: 1035–49

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Department of Neurology, Fleni, Buenos Aires, Argentina (Prof J Correale MD); **Institute of Biological Chemistry and Biophysics, CONICET/University of Buenos Aires, Buenos Aires, Argentina** (Prof J Correale); **Department of Neurological Sciences, Larner College of Medicine at the University of Vermont, Burlington, VT, USA** (Prof A J Solomon MD); **Department of Neurology, Mellen Center for Multiple Sclerosis Treatment and Research, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA** (Prof J A Cohen MD); **Division of Child Neurology, Department of Pediatrics, The Children's Hospital of Philadelphia, Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA** (Prof B L Banwell MD); **Hospital Santo Tomás, Panama City, Panama; Universidad Interamericana de Panamá, School of Medicine, Panama City, Panama** (F Gracia MD); **Department of Neurology, The Ohio State University, Columbus, Ohio, USA** (T V Gyang MD); **Universidad Nacional de Asunción, Centro Nacional de MS -Ministerio de Salud-Hospital IMT, Paraguay** (Prof F H D de Bedoya MD); **Cleveland Clinic Libraries, Cleveland Clinic, Cleveland, Ohio, USA** (M P Harnegie MLS); **Department of Neurology, Klinikum Rechts der Isar, School of Medicine and Health, Technical University of Munich, Munich Cluster for Systems Neurology, Munich, Germany** (Prof B Hemmer MD); **Cleveland Clinic, Abu Dhabi, United Arab Emirates** (Prof A Jacob MD); **Department of Neurology, National Cancer Center, Goyang, South Korea** (Prof H J Kim MD); **Departments of Internal Medicine and**

Introduction

Successive revisions to multiple sclerosis diagnostic criteria have facilitated earlier diagnosis, yet these criteria were developed predominantly on the basis of data from White populations from western Europe and North America.[1] In Latin America and South Korea, the 2017 revision of the McDonald criteria for multiple sclerosis improved sensitivity and shortened the time to diagnosis.[2,3] However, the specificity of the new criteria was lower than that of the older criteria and led to lower rates of timely multiple sclerosis diagnosis in other cohorts, including patients in Argentina, Croatia, Italy, South Korea, and The Netherlands.[3] Latin America, Asia, and Africa have historically been considered to have low or medium multiple sclerosis prevalence (3–10 times lower than in the USA, Canada, western Europe, and Australia).[4] However, because of the large populations of Latin America, Africa, and Asia, the number of individuals with multiple sclerosis in these regions is substantial.[5,6] Further research is needed to evaluate the performance of the 2017 McDonald criteria in groups with different genetic characteristics or exposure to distinct environmental factors in diverse regions.[7]

Similar to the McDonald criteria, recommendations concerning approaches to differential diagnosis of multiple sclerosis have focused on North America and western Europe, where the condition is most prevalent.[8] Although the disorders most frequently mistaken for multiple sclerosis are the same worldwide,[9,10] some disorders that mimic multiple sclerosis but are uncommon in North America and western Europe are more prevalent in Latin America, Africa, the Middle East, eastern Europe, southeast Asia, and the Western Pacific regions.[11,12] Knowledge of region-specific conditions that can mimic multiple sclerosis is essential for clinicians. Additional factors can complicate accurate diagnosis of multiple sclerosis, including low awareness of multiple sclerosis symptoms among the general public and health-care providers, and restricted access to experienced neurologists, specialised imaging, and laboratory testing. Moreover, prevalent infectious diseases and nutritional deficiencies can also mimic clinical and imaging features of multiple sclerosis. To address these barriers, locally tailored strategies need to align with the specific needs identified within each country.[13]

This Personal View was prepared by members of the Multiple Sclerosis Differential Diagnosis Consortium, which was initiated by the Americas Committee for Treatment and Research in Multiple Sclerosis. We propose recommendations for multiple sclerosis differential diagnosis across Latin America, Africa, eastern Europe, the Middle East, southeast Asia, and the Western Pacific. We consider key alternative diagnoses by type of presentation, potential genetic causes, challenges in low-income settings, and recommendations to promote best practices.

Worldwide differential diagnosis of multiple sclerosis

Among people with suspected multiple sclerosis who were referred to tertiary care centres, alternative diagnoses were identified in 16% of patients in Argentina[14] and in 26% of patients in Kuwait and Lebanon.[9] Similar studies in the USA, Spain, and Italy reported misdiagnosis rates of 7·1%–24·4%.[10,15–17] Diagnoses most frequently mistaken for multiple sclerosis were the same in all regions included in these studies (appendix pp 7–9), and included cerebrovascular disease, migraine, functional neurological disorders, spondylopathy, non-specific white matter lesions, neuromyelitis optica spectrum disorder (NMOSD), and peripheral neuropathy.

Community Health Sciences, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada (Prof R A Marrie MD); Department of Neurology, Massachusetts General Hospital, Harvard University, Boston, USA (F J Mateen MD); Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA (Prof S D Newsome DO); Center for Advanced Neurological Research, KS Hedge Medical Academy, Nitte University, Mangalore, India (Prof L Pandit MD PhD); Division of Neurology, Department of Medicine and Siriraj Neuroimmunology Center, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (Prof N Prayoonwiwat MD); MS Research Center, Neuroscience Institute, Teheran University of Medical Sciences, Iran (Prof M A Sahraian MD); Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, Brazil (Prof D K Sato MD); Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA (D Saylor MD); University Teaching Hospital, Lusaka, Zambia (D Saylor); Tianjin Medical University General Hospital, Tianjin, China (Prof F-D Shi MD); National Clinical Research Center for Neurological Disorders, Beijing Tiantan Hospital, Beijing, China (Prof F-D Shi); Istanbul University Cerrahpasa, School of Medicine, Department of Neurology, Clinical Neuroimmunology Unit and MS Clinic, Istanbul, Türkiye (Prof A Siva MD); Department of Neurology, National Neuroscience Institute, Singapore (Prof K Tan MD); Duke-NUS Medical School, Singapore (Prof K Tan); Department of Neurology, Kuala Lumpur Hospital, Kuala Lumpur, Malaysia (S Viswanathan MD); Department of Neuroradiology, Charité Berlin, Corporate Member of Freie Universität zu Berlin, Humboldt-Universität zu Berlin, Berlin, Germany (Prof M P Wattjes MD); Department of Neurology, University of Virginia,

Misinterpretation of radiological findings in the context of clinical syndromes that are atypical for multiple sclerosis frequently contributed to multiple sclerosis misdiagnoses.[14,15,18] Therefore, understanding of typical multiple sclerosis presentations[7] and adherence to consensus standardised image acquisition, interpretation, and reporting procedures, as recommended in the joint guidelines from the Magnetic Resonance Imaging in Multiple Sclerosis study group (MAGNIMS), the Consortium of Multiple Sclerosis Centers (CMSC), and the North American Imaging in Multiple Sclerosis Cooperative (NAIMS)[19] are crucial to avoid misdiagnosis.

A practical approach to the differential diagnosis of multiple sclerosis in any region also requires a thorough medical history and examination, to determine whether the clinical picture is consistent with multiple sclerosis, and vigilance for features suggesting an alternative diagnosis. Furthermore, the diagnostic process should involve conducting an appropriate diagnostic workup, guided by the clinical and epidemiological characteristics of each patient.[8]

Key alternative diagnoses prevalent outside of North America and western Europe

The differential diagnosis of multiple sclerosis in people currently or formerly living in Latin America, Africa, eastern Europe, the Middle East, southeast Asia, and the Western Pacific (figure 1) must include attention to CNS inflammatory diseases, infectious diseases, nutritional disorders, and genetic conditions that are prevalent in these regions but encountered less frequently in countries such as Japan, Australia, New Zealand, Canada, and the USA, or in western Europe.[11,12] Tables 1, 2, and the appendix (pp 7–16) summarise key clinical and MRI features of these alternate diagnoses when considering people with suspected relapsing remitting multiple sclerosis or primary progressive multiple sclerosis.

CNS inflammatory diseases

The prevalence of CNS inflammatory diseases that commonly mimic multiple sclerosis varies across different regions of the world. For instance, the prevalence of NMOSD is higher in east Asia (6·9 per 100 000 people), the Caribbean (27 per 100 000 people) and South America (17·9 per 100 000 people), and among Indigenous Australian and New Zealand populations (1·5 per 100 000 people)[20–22] compared with the USA, Canada, western Europe, and among White individuals in Australia (0·72–1 per 100 000 people).[21,23–24] Differences in prevalence across various regions might be influenced by racial and ethnic factors, which can also affect disease characteristics and outcomes. Although NMOSD occurs globally, neurological symptoms, and brain MRI signs indicative of NMOSD have been reported to be more frequent in people who identify as Asian, African American, or African European patients, compared with people from USA, Canada, and western Europe. Consequently, clinicians should pay heightened attention to differentiating NMOSD from multiple sclerosis in these patient populations (table 1, figure 2,

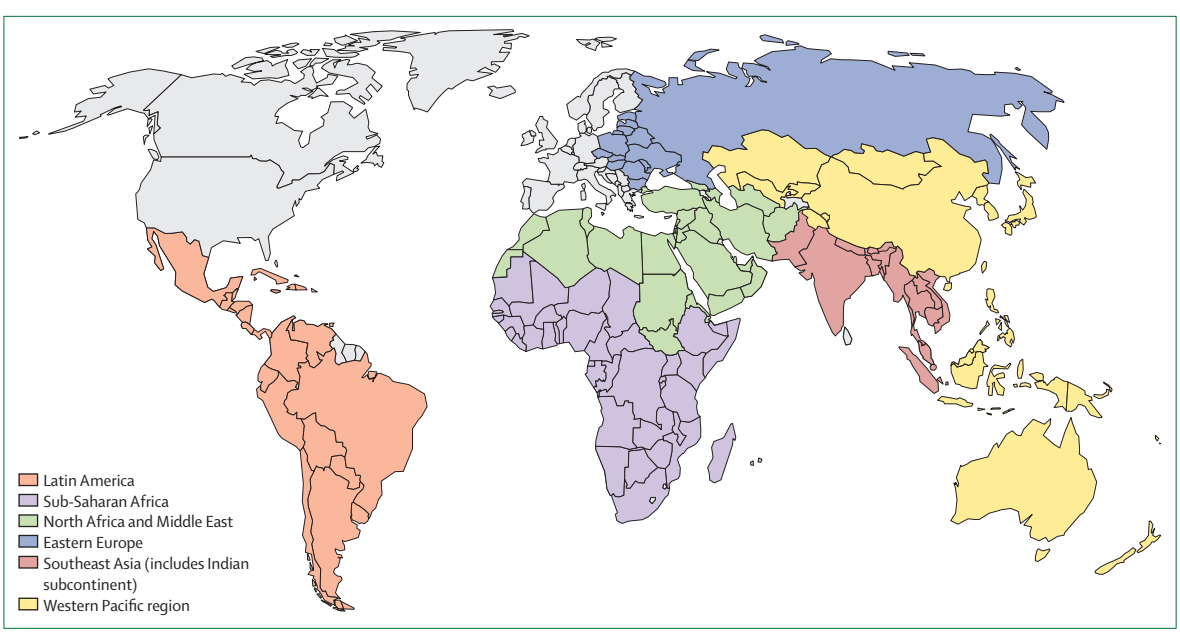

Figure 1: **Regions where potential differential diagnoses of multiple sclerosis have been considered in this Personal View**
Regions were classified based on the Global Burden of Diseases, Injuries, and Risk Factors study, with modifications. The term Latin America commonly refers to South America (excluding the Guianas, despite their location in north-central South America), Central America, Mexico, and the Caribbean islands. These countries show diverse social, cultural, and economic conditions, which are important factors to consider when discussing common health problems in these populations. Although Australia and New Zealand are geographically situated within the Western Pacific, overall their populations show closer alignment with those of the USA, Canada, and western Europe regarding the prevalence of multiple sclerosis and the differential diagnoses in the region.

appendix pp 10–14). The relative and absolute prevalence of NMOSD can vary depending on the population and geographical area under study. For example, in Olmsted County in the USA, the prevalence of NMOSD is as high as 3·9 per 100 000.[21] Therefore, when available, epidemiological data from the region where the person is being diagnosed should be considered.

Although how the prevalence of myelin oligodendrocyte glycoprotein antibody disease (MOGAD) varies around the world is uncertain,[25] the estimates of prevalence (1·26–3·42 per 100 000) and incidence (0·11–0·48 in 100 000 people per year) in Japan[26] are similar to the corresponding estimates in European countries.[27] By contrast, in adults presenting with isolated optic neuritis, a study found higher myelin oligodendrocyte glycoprotein IgG (MOG-IgG) seroprevalence in adults in people who self-identify as Asian, compared with people from the USA, Canada, and western Europe. However, seroprevalence did not differ with ethnic background in children with optic neuritis, or in patients with MOG-IgG-associated myelitis irrespective of age.[28] Because people can present with MOGAD at all ages,[25] clinicians should be cognisant of regional differences in disease expression (figure 2, appendix pp 7–14).

Infectious diseases

In Latin America, Africa, and southeast Asia, infectious diseases and nutritional deficits are common and often occur at the same time. Malnutrition impairs immune function, thereby increasing susceptibility to infections. Conversely, infectious diseases can compromise nutritional status. Systemic symptoms, such as fever, erythema of the face and neck, maculopapular rash, coryza, diarrhoea, vomiting, and persistent headache are red flags that should prompt evaluation for an infectious disease. Assessments to identify the specific infection include testing for infectious agent-specific antibodies in serum, CSF, and saliva; viral RNA detection by PCR assays in CSF; or viral and bacterial cultures. CNS manifestations of infectious diseases depend on the causative agent, route of infection, and individual factors, such as the immune status of the person affected. Specific infections that mimic multiple sclerosis are relatively uncommon in high-income countries (according to

Charlottesville, VA, USA (Prof B Weinshenker MD); **Neurology Institute, Harley Street Medical Center, Abu Dhabi, United Arab Emirates** (Prof B Yamout MD); **Department of Multiple Sclerosis Therapeutics, Fukushima Medical University School of Medicine and Multiple Sclerosis and Neuromyelitis Optica Center, Southern TOHOKU Research Institute for Neuroscience, Koriyama, Japan** (Prof K Fujihara MD)

Correspondence to:
Prof Jorge Correale, Fleni, Buenos Aires 1428, Argentina
jcorreale@fleni.org.ar

or

	Key findings	Regions with high disease prevalence
Acute optic neuritis		
NMOSD	Severe unilateral or bilateral visual loss, relapsing optic neuritis, lesions in the area postrema, diencephalic syndromes, and myelopathy might also develop. Coexistence of autoimmune diseases. About 80% of people with NMOSD are anti-AQP4 antibodies positive. Neutrophils are frequently present in CSF.	East Asia, Latin America, and the Caribbean*
Behçet's disease	Recurrent oral and genital aphthae ulcers and uveitis. Most common in the Middle East, Mediterranean, and Asian countries. Increased risk is associated with *HLA-B51* and *HLA-B27*.	Türkiye, Japan, China, and South Korea
Brucellosis	Optic neuropathy, meningoencephalitis, or spinal cord syndrome. Associated with agricultural or animal exposure, most commonly drinking contaminated cow, sheep, or goat milk. Diagnosis by specific antibodies (against *Brucella*) in serum and CSF.	Middle East, Mediterranean Europe, Africa, and South America
Toxocariasis	Unilateral optic neuropathy with retinal damage including retinal granuloma, epiretinal membrane, macular oedema, and retinal detachment. Often associated with a history of raw meat ingestion. Confirmation by *Toxocara* IgG antibodies using ELISA test.	Toxocariasis has been reported in many countries worldwide, with most cases occurring in Asia, India, and Africa
Myelitis or spinal cord syndrome		
NMOSD	Severe unilateral or bilateral visual loss, relapsing optic neuritis, area postrema syndrome, diencephalic syndromes, and myelopathy might also develop. Coexistence of autoimmune diseases. About 80% of people with NMOSD are anti-AQP4 antibodies positive. Neutrophils are frequently present in CSF.	East Asia, Latin America, and the Caribbean*
Brucellosis	Spinal cord syndrome associated with optic nerve involvement and meningoencephalitis. Associated with agricultural or animal exposure. Diagnosis confirmed by CSF culture to identify the bacteria, and specific antibodies in serum and CSF	Middle East, Mediterranean Europe, Africa, and South America
Picornavirus (enterovirus 71 and coxsackie virus A and B)	Acute flaccid myelitis. Outbreaks mostly affect children and young adults.	Asia-Pacific region, western Europe, North America, Australia
Flavivirus (dengue virus and less frequently West Nile virus)	Spastic myelitis. MRI shows diffuse signals of inflammation. Red flags: for a diagnosis of flavivirus rather than multiple sclerosis general symptoms include erythema, rash, coryza, diarrhoea, and fever. Diagnosis confirmed by specific viral antibodies in serum, CSF, or saliva, and PCR in CSF.	Dengue: east Asia, Latin America, Indian subcontinent, Africa; West Nile virus: South America, Indian subcontinent, Africa, and eastern Europe, with previous outbreaks in North America
Vitamin B12 deficiency or dysmetabolism	Progressive myelopathy with symptoms attributable to the posterior and lateral columns. Can be associated with neuropathy and megaloblastic anaemia. Diagnosis confirmed by serum concentrations of B12 and methylmalonic acid.	Indian subcontinent, Middle East, Africa, and regions of Latin American
Folic acid deficiency or dysmetabolism	Progressive myelopathy, diplopia, and incoordination. Diagnosis confirmed by serum concentrations of folic acid and methylmalonic acid, homocysteine, and assay for *MTHFR* gene mutations.	Africa, Indian subcontinent, some countries in South America
Brainstem		
Enterovirus	Brainstem encephalitis causing neurogenic pulmonary oedema. Presence of myoclonus and ataxia. Skin rash of hand, foot, and mouth disease is typical. Enterovirus 71 can be isolated from a stool, throat swab, or CSF.	Asia-Pacific region, western Europe, North America, and Australia
Behçet's disease	Acute or subacute brainstem syndrome, as well as cerebellar and motor symptoms.	Türkiye, Japan, China, and Korea

(Table 1 continues on next page)

	Key findings	Regions with high disease prevalence
(Continued from previous page)		
Multifocal CNS syndromes		
Balo concentric sclerosis	Atypical lesions defined radiologically or pathologically by alternating bands of demyelination and preserved white matter; reported as tumefactive demyelinating lesions or NMOSD.	East Asian, with the highest prevalence in China, Taiwan, and the Philippines
CADASIL	Microangiopathy commonly found in subcortical white matter that is associated with headache, stroke, and dementia. Familial basis diagnosed by mutation of *NOTCH3* gene.	East Asian populations with the highest prevalence in Japan, China, and South Korea
Vitamin E deficiency or dysmetabolism	Spinocerebellar degeneration syndrome, ophthalmoplegia, photoreceptor damage. Diagnosis confirmed by serum vitamin E concentrations and mutations of the *TTPA* gene.	Indian subcontinent, Middle East, Africa, and different regions of Latin American
Neuroborreliosis	First stage involves skin lesion (erythema migrans). Second stage involves neurological symptoms: lymphocytic meningitis, cranial neuropathies, and painful myeloradiculoneuritis. Diagnosis is confirmed by CSF ELISA or immunofluorescence assay, followed by a confirmatory western blot.	USA, Canada, western and eastern Europe, and China
Tuberculosis	Main clinical manifestations are meningitis, cerebrovascular complications, tuberculoma or tuberculous brain abscess, and cranial nerve palsies, particularly the sixth cranial nerve. Optic nerve involvement can be associated to optochiasmatic arachnoiditis. Diagnosis confirmed by detection of the mycobacterium bacilli in the CSF, by smear examination, bacterial culture, or PCR. Alternative CSF ADA measurements or T-cell-based interferon-γ release assays can serve as diagnosis tests.	Latin America and the Caribbean, Africa, eastern Europe, Indian subcontinent, and Asia
Neurocysticercosis	Main presentations are related to epilepsy and intracranial hypertension. Diagnosis confirmed by serological test to detect antibodies to *Taenia solium* in serum EITB assay.	Sub-Saharan Africa, Indian subcontinent, southeast Asia, Mexico, and South America
CMV	The most common manifestation of neurological CMV disease is retinitis followed by encephalitis, polyradiculopathy, and multifocal neuropathy. CMV polyradiculopathy presents as an ascending subacute leg weakness, paraesthesia, and urinary retention, simulating spinal cord syndrome. Confusion, cranial nerve palsies, and hyperreflexia are signs of ventriculoencephalitis. Diagnosis confirmed by detection of CMV DNA in the CSF.	USA, Canada, Europe, some countries in South America, Indian subcontinent, Middle East, Asia, and Africa
Arbovirus (chikungunya and zika)	Acute arboviral infections are most frequently asymptomatic or trigger flu-like symptoms. Ocular complications are often associated with long-term impairment. Other neurological impairments that can be directly triggered by arboviruses include encephalitis, meningitis, myeloneuropathy, and acute and long-term cognitive impairments.	Indian subcontinent, sub-Sahara Africa, Latin America, and east Asia

A fully referenced version of the table is provided in the appendix, pp 17–23. The disorders are presented acording to more frequent topographic location. ADA=adenosine deaminase. AQP4=aquaporin 4. CADASIL=cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy. CMV=cytomegalovirus. EITB=enzyme-linked immunoelectrotransfer blot. HLA=human leukocyte antigen. *MTHFR*=methylenetetrahydrofolate reductase. NMOSD=neuromyelitis optica spectrum disorders. *TTPA*=alpha-tocopherol transfer protein. *Despite NMOSD being less common than multiple sclerosis in North America, with a lower NMOSD to multiple sclerosis ratio (compared with Asia, Latin America, and the Caribbean), the absolute prevalence of NMOSD is not different to that in some areas of the USA.

Table 1: **Differential diagnoses of relapsing remitting multiple sclerosis in regions beyond North America and western Europe**

Prof Kazuo Fujihara, Department of Multiple Sclerosis Therapeutics, Fukushima Medical University School of Medicine and Multiple Sclerosis and Neuromyelitis Optica Center, Southern TOHOKU Research Institute for Neuroscience, Koriyama, Japan
fujikazu@med.tohoku.ac.jp

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See **Online** for appendix

the World Bank classification, this includes Canada, the USA, western Europe, Australia, New Zealand, and Japan) but are more prevalent in lower-middle-income countries. Nevertheless, these infections can occur in North America and western Europe owing to travel, immigration, and the changing geographical distribution of disease vectors. Thus, infections introduced into a new region can produce local epidemics or eventually become endemic (eg, zika and chikungunya viruses).[29] Tables 1 and 2 summarise the primary findings on ocualr compromise, encephalitis, meningitis, and myeloneuropathies, and identify the geographical regions with the highest incidence of infectious diseases that mimic relapsing remitting multiple sclerosis and primary progressive multiple sclerosis.

Infectious optic neuritis or optic neuropathy

Some infectious diseases that are highly prevalent in Africa, Asia, and Latin America can present with symptoms resembling optic neuritis. Infections can affect the optic nerve directly or indirectly by triggering inflammatory, degenerative, or vascular processes. Infectious optic neuropathies might be associated with other ocular symptoms, including anterior uveitis, retinitis, chorioretinitis, and retinal vasculitis.[30] The true incidence of ocular involvement in infectious optic neuropathies is difficult to estimate because no rigorous epidemiological data are available.[31]

Optic neuropathy caused by *Treponema pallidum* occurs as a late manifestation in approximately 5·1% of people who have syphilis with the proportion varying from 2% in 2016 to 6·5%, in 2021, in a study done in China. In South Korea the proportion of people who have syphilis in 2021, was 11·1%. (figure 3).[33,34] The US Centers for Disease Control and Prevention reports that the proportion of people with syphilis who have optic neuropathy is 0·17–3·9%;[35] these figures align with data from a study in England, estimating that optic neuropathy affects approximately 0·6% of people with syphilis.[36] Concurrent involvement of other cranial nerves is an important clue to a syphilitic cause of optic neuritis. Toxocariasis can lead to chronic granulomatous endophthalmitis, identified as a central vitreous mass, and to optochiasmatic arachnoiditis that can resemble multiple sclerosis-related optic neuritis clinically.[37] By contrast, cranial nerve palsy is observed in 20–52% of patients with tuberculous meningitis. This finding can be valuable in the diagnosis of tuberculosis with ophtalmic manifestations.[38]

	Key clinical findings	Screening	Regions with high prevalence
Metabolic			
Vitamins B12 and folic acid deficiency or dysmetabolism	Progressive, symmetrical myelopathy involving the dorsal columns, spinocerebellar tracts, and lateral corticospinal tracts	Clinical history of nutritional deficits, gastrointestinal resection, or personal or family history of megaloblastic anaemia. T2 hyperintensities are seen as an inverted V in the dorsal and lateral columns of the cervical spinal cord. Contrast enhancement is uncommon and when present it is mild. Diagnosis confirmed byserum concentrations of vitamin B12, folic acid, methylmalonic acid, homocysteine, and enzyme assay for MTHFR	Indian subcontinent, Middle East, Africa, and some regions of Latin American
Vitamin E deficiency or dysmetabolism	Limb and truncal ataxia with hyporeflexia, loss of or decreased vibratory sense, decreased night vision, and restricted upward gaze	Clinical history of nutritional deficits, gastrointestinal resection, fat malabsorption, or Crohn's disease. T2-hyperintensities periventricular and deep white matter. Diagnosis confirmed by serum vitamin E concentration, mutations of the *TTPA* gene	Indian subcontinent, Middle East, Africa, and some regions of Latin American
Toxic			
Lathyrism	Weakness, fatigue, spastic paraparesis, atrophy of leg muscles, and skeletal deformities particularly at the knees and feet	History of consumption of grass peas. Signs of upper motor neuron damage, associated with vascular damage, such as dissecting aneurysm, and damage to the bone growth, such as bowing of legs, kyphoscoliosis, or failure of fusion of the vertebral and iliac epiphyses	India, Pakistan, Bangladesh, and Ethiopia
Hereditary			
Hereditary spastic paraparesis	Predominant pyramidal signs in the lower limbs, sometimes with involvement of the lower motor neurons and optic atrophy	Family history and consanguinity are associated with the autosomal recessive forms. Diagnosis confirmed by relevant genetic tests, most commonly mutation linked to *SPG4* locus in the spastin-encoding gene	Autosomal dominant forms (*SPG4, 3A, 31,* and *10*) in North America and northern Europe. Autosomal recessive (*SPG11, 15, 35, 45,* and *5A*) in North America (Amish communities), and the Middle East
Infections			
Brucellosis	Progressive spinal cord syndrome	History of agricultural or animal exposure. On MRI, nerve root involvement, spondylitis, and intramedullary or paravertebral abscesses. Diagnosis confirmed by serology by specific antibodies in serum and CSF	Middle East, Mediterranean Europe, Africa, and South America
HTLV-1	Subacute or chronic spinal syndrome	Short or extensive T2-hyperintense lesions at both cervical and thoracic levels might be seen, with spinal cord atrophy at a later stage. Diagnosis confirmed by demonstration of anti-HTLV-1 antibodies or HTLV-1 genomes in blood and CSF	Japan, Africa, Caribbean islands and east coast of South America, and Brazil

A fully referenced version of the table is provided in the appendix, pp 17–23. HTLV-1=human T-lymphotropic virus type I. T2=type 2. MTHFR=methylenetetrahydrofolate reductase. SPG4=spastic paraplegia type 4. TTPA=alpha-tocopherol transfer protein.

Table 2: **Differential diagnoses of primary progressive multiple sclerosis beyond North America and western Europe**

Infections with brainstem or cerebellar involvement

Enterovirus 71 is the most frequent infectious cause of posterior brainstem syndromes (sometimes with spinal cord manifestations) that mimic multiple sclerosis, and are the highly prevalent in the Asian and Western Pacific region.[39] West Nile virus can also affect the brainstem plus the spinal cord, cerebral cortex, basal ganglia, and thalamus. Although initially recognised in Africa, the virus was subsequently identified as endemic in eastern Europe, the Middle East, and Asia.[40] Human T-lymphotropic virus type I (HTLV-1) infection, which is endemic in southwestern Japan, the Caribbean, South America, and west Africa,[41] can cause lesions in the intracranial corticospinal tract, medial lemniscus, and middle cerebellar peduncle.[42]

Infectious myelitis

Infectious myelitis can have clinical and radiological characteristics similar to those of multiple sclerosis-related myelitis, but more commonly presents with longitudinally extensive lesions atypical of multiple sclerosis. The prevalence of causative agents varies geographically, and the highest frequency of infectious myelitis occurs in Latin America, southeast Asia, and Africa. Myelitis caused by infection with viruses of the human herpes family, most commonly types 1, 2, 6, and 7, is associated with longitudinally extensive MRI T2 lesions with variable contrast enhancement and haemorrhage.[43] Similarly, longitudinally extensive myelitis due to cytomegalovirus has been documented in both immunocompetent and

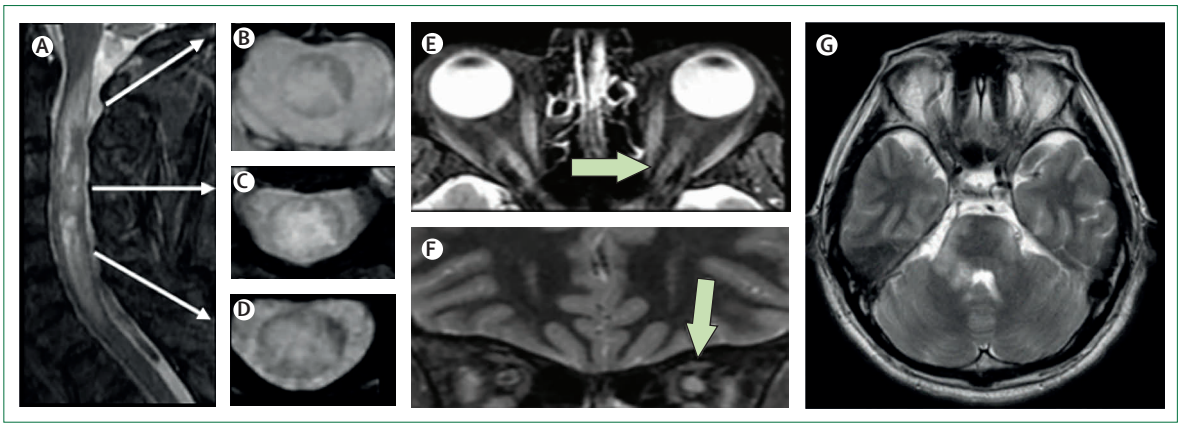

Figure 2: **MRI scans of demyelinating diseases that mimic multiple sclerosis**
(A–D) Sagittal and axial T2-weighted images of extensive myelitis in the spinal cord of a patient with aquaporin 4-IgG-positive neuromyelitis optica spectrum disorder. Arrows indicate the spinal cord levels from which the axial images were taken. (E, F) Axial and coronal T2-weighted images of the optic nerve in a patient with AQP4-IgG-positive neuromyelitis optica spectrum disorder. (G) Axial T2-weighted image of brainstem lesions in a patient with myelin oligodendrocyte glycoprotein antibody-associated disease.

immunosuppressed individuals.[43] Myelitis is a rare manifestation of varicella zoster virus infection occurring during viral reactivation, and can closely simulate longitudinally extensive inflammatory myelitis suggestive of NMOSD (figure 3). Picornaviruses (poliovirus, enterovirus 68, enterovirus 71, coxsackie virus A and B) and flaviviruses (West Nile and dengue viruses) can also present with myelitis. In endemic areas, including eastern and southern Asia, South America, Middle East, and Africa, acute myelitis can occur during outbreaks of enterovirus 68 and enterovirus 71 infections. However, strains of picornavirus have also been identified in patients with acute flaccid paralysis in the USA, Canada, and Europe.[44] Clinically, patients present with fever and myalgias, followed by acute onset of asymmetric flaccid weakness, similar to poliomyelitis, with upper limbs often more affected than lower limbs. In some cases, brainstem motor nuclei are affected, causing facial and bulbar weakness.[42] Although uncommon, spinal cord grey matter involvement with MRI T2 hyperintensity of the anterior horns should prompt consideration of picornavirus infections.[45]

Chronic progressive spastic paraparesis caused by HTLV-1 can be mistaken for primary progressive multiple sclerosis. Spinal cord atrophy is the most frequent finding, but MRI can show longitudinally extensive T2 hyperintensity in the lateral columns extending to the dorsal columns, with contrast enhancement (figure 3)[43,46] that can help to differentiate HTLV-1 from multiple sclerosis. Eosinophils in the CSF are often associated with myelopathies caused by parasitic infections. In the Middle East, *Toxocara canis*, which is diagnosed by blood and CSF antibodies, is a relatively common infectious cause of myelopathy.[47]

Infections with supratentorial involvement

Infections that can manifest as supratentorial MRI lesions resembling multiple sclerosis are prevalent In Latin America, Africa, the Middle East, and southeast Asia. Prevalence of cytomegalovirus is highest in Asia, Africa, and the Middle East.[48] CNS infections rarely involve the corpus callosum or periventricular areas, but because cytomegalovirus exhibits neurotropism for ependymal and capillary endothelium, periventricular lesions can mimic lesions caused by multiple sclerosis. Gadolinium enhancement of the ependymal surface, often seen in immunocompromised patients, suggests ventriculo-encephalitis.[49] The presence of concurrent retinitis points to a viral cause. Other infections, including toxocariasis, tuberculosis, cysticercosis, arbovirus (eg, chikungunya, dengue, zika), HIV, neuroborreliosis, and hepatitis C, can also produce supratentorial white matter brain lesions resembling those seen in multiple sclerosis (figure 3).[50–53]

HIV infection is also important to consider in the differential diagnosis of multiple sclerosis, especially in patients with MRI white-matter lesions and a relapsing clinical course. The presence of severe immunosuppression, coupled with risk factors for HIV infection, should prompt consideration of HIV diagnosis.[54]

Although the epidemiology of human toxocariasis remains incompletely characterised, seroprevalence is 4–12 times higher in Latin America, Africa, southeast Asian, and Middle East than in North America and western Europe.[55] MRI findings in patients with toxocariasis can resemble those of early multiple sclerosis and include hyperintensities on T2-weighted images with T1 post-contrast ring enhancement. Eosinophilia in blood or CSF can aid diagnosis.[56]

The prevalence of neuro cysticercosis is highest in the Indian subcontinent, southeast Asia, sub-Saharan Africa, Mexico, and South America (figure 3).[57] In these regions, CT scans reveal brain calcifications, probably reflecting resolved cysts, in 10–20% of people with

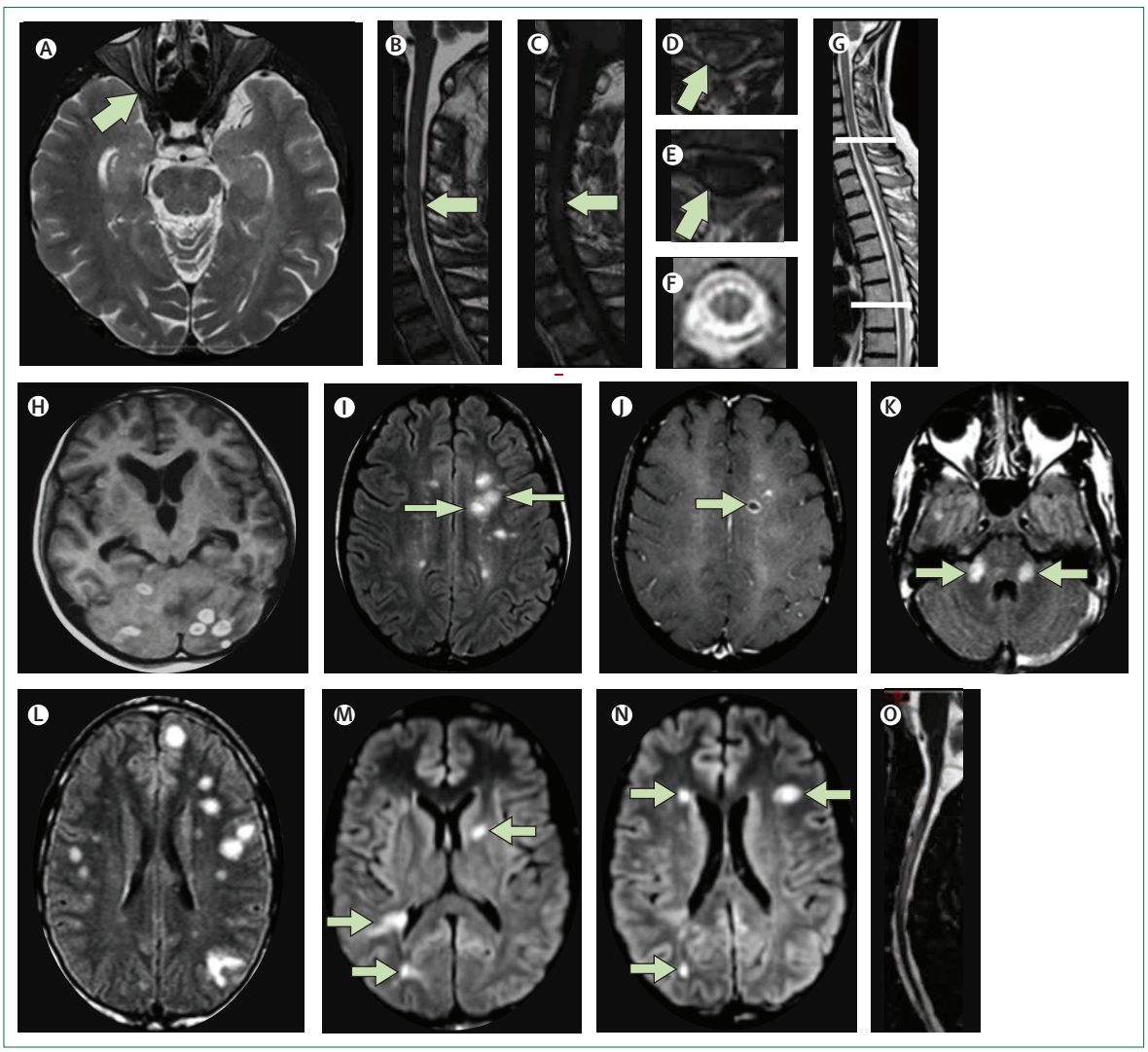

Figure 3: **MRI scans of infectious diseases that mimic multiple sclerosis**
(A) Axial T2-weighted image of syphilitic right optic neuritis. (B) T1-weighted sagittal image with gadolinium, (C) T2-weighted sagittal, and (D-E) axial T2-weighted images of varicella zoster virus-associated cervical myelitis at different levels (white arrows). (F-G) sagittal and axial T2 images of thoracic spinal cord atrophy (F) with hyperintensities in bilateral anterior horns, and (G) atrophy evident between upper and lower lines in human T-lymphotropic virus type I associated myelopathy. (H) Contrast-enhanced multiple tuberculomas in bilateral posterior lobes. (I, J) Axial contrast-enhanced T1-weighted images showing supratentorial lesions resulting from neurocysticercosis infection; the lesions are hyperintense in FLAIR imaging, mimicking open-ring enhancement observed on T1-weighted image post-gadolinium administration in people with multiple sclerosis (K, L) Axial FLAIR images of a patient presenting with neuroborreliosis manifesting with disseminated white matter lesions in the brain. (M, N) Axial FLAIR images showing white matter lesions produced by hepatitis C infection. (O) Sagittal T2-weighted image of the cervical and upper thoracic spinal cord of a patient with brucellosis presenting with longitudinally extensive transverse myelitis. Panel (H) reproduced with permission of the publisher from Ceylan and Gencer.[32] Figures (I–N) reproduced, with permission, from Rocha AF et al.

cysticercosis who do not have seizures or headaches the most common symptoms of neurocysticercosis.[58] The typical presentation of this disease includes seizures and intraparenchymal brain cysts that can imitate tumefactive demyelinating lesions.[59] In people with lesions outside the parenchyma, cysticercosis is associated with parasitic larvae in the subarachnoid space or the basal cisterns, resulting in obstructive hydrocephalus and intracranial hypertension.[60]

Prevalence of tuberculosis is highest in southern Asia, Africa, and some South American countries. The incidence of tuberculosis is decreasing worldwide except in eastern Europe, where it is stable, and Africa, where it is increasing and linked to high rates of HIV co-infection.[61] Meningitis is the most frequent CNS presentation. White matter can also be affected, with MRI showing microvascular necrosis with perivascular macrophage reaction, demyelination, and focal glial nodules (figure 3). Furthermore, large demyelinating MRI lesions with open-ring contrast enhancement can be present in people who have tuberculosis and neurocysticercosis.[62]

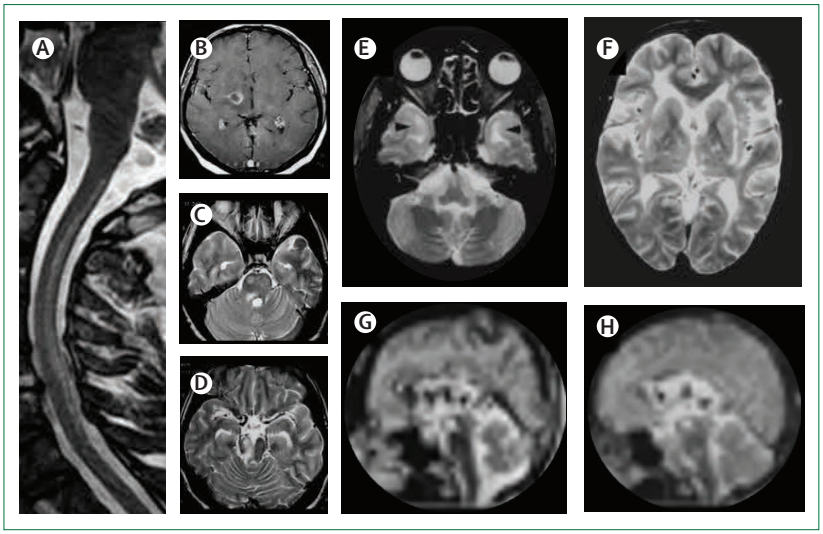

Figure 4: **MRI scans of patients with nutritional deficits or diseases with genetic backgrounds that mimic multiple sclerosis**
(A) Sagittal T2-weighted image showing myelopathy associated with vitamin B12 deficiency. (B) Axial contrast-enhanced T1-weighted image and (C, D) axial T2-weighted images showing lesions of Behçet's syndrome. Axial (E, F) and sagittal (G, H) T2-weighted images of bilateral, multiple hyperintense lesions in cerebral subcortical white matter, basal ganglia, corpus callosum,, and brainstem in a patient with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. Panels (B–D) were provided by Aksel Siva. Figures (E–H) are reproduced from Iwatsuki and colleagues, with permission from Tohoku University Medical Press.

Borrelia infection is endemic in areas of the USA, central and northern Europe, and northern China.[63] Although neuroborreliosis usually causes radiculitis and cranial neuritis, it can also rarely lead to multifocal neurological symptoms and MRI findings resembling multiple sclerosis (figure 3).[64] MRI findings in neuroborrelioses usually do not meet criteria for multiple sclerosis but rather show contrast enhancement of the meninges, cranial nerves, and nerve roots that is atypical for multiple sclerosis. The involvement of other tissues (eg, skin, joints, or heart) would also suggest that the patient does not have multiple sclerosis. Furthermore, exposure history in endemic areas, marked CSF pleocytosis, high CSF protein concentrations of more than 100 mg/dL, which can vary according to the clinical presentation, and elevated antibody synthesis against the bacteria further aid in distinguishing neuroborreliosis from multiple sclerosis.

Although hepatitis C is a global health problem, 90% of chronically infected patients live in central and east Asia, north Africa, and the Middle East.[65] Hepatitis C-associated cryoglobulinemia can present as small cerebral vessel vasculitis resembling demyelinating lesions (figure 3).

Brucellosis is common in the Arabian Peninsula, South America, and Mediterranean countries; patients can present with cranial and peripheral neuropathy, myelitis (figure 3), seizures, and lymphocytic meningitis. MRI can show granulomatous lesions, meningeal enhancement, lacunar infarcts, or venous sinus thrombosis.[66] The presence of specific intrathecal antibodies against *Brucella abortus* and *Brucella melitensis*, lymphocytosis, elevated protein concentrations, decreased glucose concentrations, and clinical remission after antibiotic treatment support the diagnosis of brucellosis.[66]

Nutritional deficiencies

In low-income and lower-middle-income countries, there is an increased risk of nutritional deficiency, which can result in CNS diseasesthat can present with symptoms similar to multiple sclerosis (table 2, appendix pp 10–16). Vitamin B12 deficiency has most frequently been observed in the Indian subcontinent, the Middle East, Africa, and various regions of Latin America. In these areas, vitamin B12 intake is roughly 60% below the US Recommended Dietary Allowance for adults (2·4 µg/day), although intake differs between studies, possibly owing to assay variations. In low-income countries, 5–49% of the population have vitamin B12 deficiency (concentration<148 pmol/L in blood), with marginal deficiencies (148–221 pmol/L) in 13–23% of the population.[67,68] By contrast, in high-income countries, values are 256–300 pmol/L. Vitamin B12 malabsorption due to conditions including tropical sprue or parasitic infections can contribute to deficiency, particularly in southern India, the Philippines, and the Caribbean.[67]

Vitamin B12 deficiency can lead to progressive spinal cord degeneration, optic neuropathy, cognitive dysfunction, and sensory deficits, which can mimic progressive multiple sclerosis. Vitamin B12 deficiency typically causes longitudinal and symmetrical MRI T2 hyperintensity in the posterior and lateral columns of the cervical and thoracic spinal cord (figure 4).[70] Vitamin B12 deficiency can also be associated with macrocytic anaemia and peripheral neuropathy, although their presence does not always co-occur with myelitis or optic neuropathy.[71] Elevated blood concentrations of methylmalonic acid and total homocysteine are sensitive indicators of vitamin B12 deficiency and are associated with such neurological presentations.[72]

Although less common than vitamin B12 deficiency, vitamin E deficiency causes sensory symptoms, ataxia, limitation of upward gaze, visual field constriction, and cognitive deficits resembling those experienced by people with multiple sclerosis.[73] Vitamin E deficiency (blood concentration of <12 µmol/L) is prevalent in Asia (25–55% of the population), Africa (12–61% of the population), Central and South America (20% of the population), and the Middle East (0·7–17% of the population). People in these regions, particularly children and elderly, might face an elevated risk of deficiency due to poor nutrition and a high prevalence of oxidative stressors, such as endemic infections (eg, malaria).[74] The reported differences in prevalence across regions reflect variation in defns of normal range, study design, and target populations. Peripheral neuropathy, anaemia, and acanthocytosis are important rewarning signs that can help differentiate vitamin E deficiency from multiple sclerosis.[73–75]

Therefore, in low-income countries in particular, nutritional deficiencies should be considered in the differential diagnosis of multiple sclerosis. Systemic symptoms, MRI warning signals, such as symmetric longitudinal lesions, the absence of CSF-restricted oligoclonal bands, and the evaluation of specific nutrients or their metabolites can assist in diagnosis. The Cuban outbreak of optic neuropathy and dorsolateral myelopathy in the 1990s, caused by a dietary deficiency of B vitamins and sulphur-containing amino acids, underscores the importance of assessing nutrients as potential causes of neurological deficits.[75]

Effects of genetic background

Genetic background variations contribute to the different distributions of diseases that can mimic multiple sclerosis.

Behçet's disease

Behçet's disease is a systemic vasculitis that is most prevalent in men younger than 25 years. This condition frequently presents with an acute or subacute brainstem syndrome and relapsing remitting course. Countries with high prevalence include Türkiye, Japan, China, and South Korea, where Behçet's disease incidence is reported to be 20–200 times higher than in northern and central Europe and the USA.[76–77] The geographical distribution of *HLA-B51* closely aligns with Behçet's disease prevalence.[76] In Germany, migration studies showed a 20-times higher prevalence of Behçet's disease among individuals of foreign origin, with 92% of the patients being of Turkish descent. However, the prevalence of Behçet's syndrome in patients of Turkish origin living in Germany was substantially lower than reported in Türkiye, suggesting as-yet unidentified environmental factors that also play a role.[79]

Despite clinical similarities with multiple sclerosis, supratentorial white matter lesions on MRI are uncommon in neuro Behçet's disease and, when present, are more likely to be subcortical than periventricular (table 1, appendix pp 10–14). By contrast, brainstem lesions atypical for multiple sclerosis are the most common MRI finding and can aid diagnosis. Lesions in Behçet's disease are large, diffuse, and extend towards the diencephalic, thalamic, and basal ganglia regions (figure 4).[80] These MRI differences are not always discriminative. Non-neurological manifestations of Behçet's disease anterior or posterior uveitis, recurrent genital and oral ulcerations, and skin manifestations such as erythema nodosum or a hypersensitivity reaction (pathergy test) can aid diagnosis.[76]

CADASIL leukoencephalopathy and CARASIL

CADASIL is the most prevalent heritable cause of stroke and vascular dementia in adults. In Japan, China, and South Korea, the causative *NOTCH3* mutations are found in 3·5–6·5% of people who have small vessel occlusion stroke, compared with 0·5% of patients in North America and western Europe.[81,82] Some clinical features resemble those of multiple sclerosis, including recurrent neurological deficits, gait impairment, urinary incontinence, and pseudobulbar affect (table 1).[82] Although brain MRI T2 hyperintensities can resemble those of multiple sclerosis, lesions in the external capsule and anterior temporal poles, lacunar infarcts, brainstem involvement in regions supplied only by perforating arteries, and microbleeds suggest a diagnosis of CADASIL (figure 4, appendix pp 10–14).[83] Diagnosis of CADASIL involves *NOTCH3* gene sequencing or a skin biopsy showing granular osmophilic depositions.

CARASIL is caused by mutations in the *HTRA1* gene and primarily affects people of Japanese or Chinese descent. About half of the affected individuals are born to consanguineous parents and present onset of neurological deficits in early adulthood, with symptoms sometimes resembling those of multiple sclerosis.[84] Clinical indicators of CARASIL include migraine with aura, mood changes, alopecia in adolescent men, and early-onset pyramidal and extra-pyramidal symptoms with white matter lesions. MRI typically reveals multiple lacunar infarctions. Genetic testing for *HTRA1* gene mutations confirms CARASIL diagnosis.[84]

Moyamoya disease

Moyamoya disease is characterised by occlusion or stenosis of the intracranial internal carotid artery and fluctuating neurological symptoms. The disease is strongly associated with *RNF213* mutations and is more prevalent in east Asia than in the USA and western Europe. Brain MRI shows T2 lesions in the cerebral deep or superficial grey matter and can show ischaemic features, such as diffusion restriction. Factors distinguishing moyamoya disease from multiple sclerosis include internal carotid artery stenosis, abnormal vascular networks, and a history of haemorrhagic events.[85]

Oligoclonal band prevalence

The presence or absence of CSF oligoclonal bands often informs diagnosis of multiple sclerosis but genetic background can affect their prevalence. In Brazil, China, Japan, India, Lebanon, and Malaysia oligoclonal band positivity rates among people suspected of having multiple sclerosis range from 30% to 60%,[86–91] compared with 90–95% in North America and western Europe.[92] Differences in genetic susceptibility, mainly related to HLA class II loci, have been implicated.[93] However, in some studies, the apparent low prevalence of CSF oligoclonal bands might be due to misdiagnosis of multiple sclerosis. After excluding other CNS inflammatory demyelinating disorders, the prevalence of oligoclonal bands reported in South Korean people with multiple sclerosis (88·6%) was similar to that reported in North America and western Europe.[94]

Panel: **Main barriers to early diagnosis of multiple sclerosis in Latin America, Africa, the Middle East, eastern Europe, southeast Asia, and the Western Pacific regions and recommendations to promote best practices**

Early diagnosis of multiple sclerosis and subsequent start of treatment can reduce future patient disability and decrease health-care costs. However, diagnostic delays persist due to several obstacles. The characteristics of these barriers vary worldwide, being more severe in resource-limited regions, due to shortages of health-care professionals, neuroimaging facilities, and laboratory supplies to implement recommendations around diagnosis. However, some of the obstacles are also present in high-income countries. The most substantial obstacles and our recommendations to promote best practices are:

Low awareness of multiple sclerosis symptoms among the public

- Educational efforts, such as engaging mass media, advocacy services, and patients' associations might improve recognition of early symptoms among the general public

Low awareness of multiple sclerosis symptoms among health-care professionals

- Accessible education and online training programmes might provide cost-effective opportunities to improve awareness of multiple sclerosis symptoms among health-care providers, improving early diagnosis. In regions with few neurologists, these programmes should also be aimed at non-neurologist physicians who might be the patients' first contact (eg, ophthalmologists), and should encourage referral to a neurologist, where possible.
- Disease registries can provide health-care professionals with information about local specific diseases that can mimic multiple sclerosis

Shortage of health-care professionals who have sufficient training to diagnose multiple sclerosis

- Telemedicine can provide accessible and cost-effective education and training for health-care professionals in low-income and middle-income regions. Neuroradiologists, neurologists, and multiple sclerosis neurologists should receive training from experienced physicians through telemedicine
- Promoting the use of contemporary diagnostic criteria among local neurologists through training programmes and developing national diagnosis guidelines or standards for multiple sclerosis care should facilitate early diagnosis. Following the Magnetic Resonance Imaging in Multiple Sclerosis study group, Consortium of Multiple Sclerosis Centers, and North American Imaging in Multiple Sclerosis Cooperative recommendations, diagnosis should include the standardisation of the initial brain and spinal cord MRI protocol, ensuring uniform image acquisition methods, and considering the definition of various types of lesions. Use of gadolinium-based contrast agents can contribute to showing dissemination in time on the baseline MRI scan and facilitate the differential diagnosis based on the enhancement pattern
- Efforts should be made to retain well trained neurologists and reduce emigration for economic reasons

Scarcity of diagnostic equipment in low-income and middle-income regions

- Improving the availability and accessibility of MRI scanners and laboratory equipment in low-income countries is likely to be complex and challenging, even though they are cost-effective, requiring initiatives that take into account the needs of individual countries
- Efforts to establish a reference laboratory in each country and develop laboratory tests utilising dried blood spots for the detection of pertinent antibodies, antigens, or nucleic acids might prove valuable
- Integrating diagnoses between points of care and reference laboratories, along with swifter transmission of results from reference laboratories to points of care, would facilitate diagnosis. Portable low-field MRI scanners sensitive to multiple sclerosis lesions could reduce costs and travel-associated barriers

Differential diagnosis of multiple sclerosis in low-income and middle-income regions

Clinicians working in Latin America, southeast Asia, and Africa have financial constraints that can impede use of contemporary multiple sclerosis diagnostic criteria. A multipartite approach to improve regional access to resources is likely to be complex and challenging (panel),[95] requiring country-specific interventions adapted to the sociopolitical context. Data from 107 countries (representing 82% of the world's population) indicated that the most significant barriers to implementing the 2017 McDonald criteria were low awareness of multiple sclerosis symptoms, both in the general public and among health-care professionals. Additionally, 47 (44%) of 107 countries had few neurologists with experience in the diagnosis and treatment of multiple sclerosis.[4] Many regions, especially sub-Saharan Africa and southeast Asia, still had very few multiple sclerosis specialists. In addition, MRI an important aid to accurate multiple sclerosis diagnosis was not available in 36 (34%) of 107 of the countries, particularly in low-income settings, due to cost.[13] For instance, fewer than 100 MRI units in the west African region serve a population of nearly 400 million inhabitants.[96] When available, MRI might be of suboptimal quality. Furthermore, the absence of standardised MRI acquisition and reporting protocols, and the absence of neuroradiologists with expertise in multiple sclerosis and other demyelinating diseases are additional barriers to accurate diagnosis. Recently published

recommendations from MAGNIMS-CMSC-NAIMS might aid in addressing these issues, even in countries with scarce resources.[18] These recommendations outline simplified and shortened MRI protocols for diagnosis and monitoring purposes, making them easier to use and reducing inconsistencies in quality and inter-centre variability.[19]

In many low-income countries, access to useful tests for multiple sclerosis differential diagnosis, including AQP4-IgG, MOG-IgG by cell-based assays, and viral tests, is low.[13] Barriers also exist to optimal oligoclonal band testing, in which isoelectric focusing on agarose gel is followed by immunoblotting or immunofixation for IgG, and kappa free light index quantification. In some countries in Latin America and sub-Saharan Africa, these methods are not available; methods that are used, such as agarose gel electrophoresis, isoelectric focusing on a polyacrylamide gel, and silver staining, have lower sensitivity and have low specificity for IgG.[97] In addition, many centres need to send samples to reference laboratories, possibly compromising specimen integrity. Kappa free light chain index values, which can be determined more easily than oligoclonal bands at a lower cost, and might be a reasonable alternative.[98]

The absence or inaccessibility of transportation, residence in rural areas, and the distance to health-care facilities are additional barriers to obtaining diagnosis and treatment. Although these travel difficulties are more common in low-income and middle-income countries, they are also present in higher-income countries.

Numerous populations worldwide are underrepresented in multiple sclerosis research and guideline development, owing to economic constraints. In low-income countries, the shortage of neurologists with subspecialty expertise in multiple sclerosis, combined with the scarcity of neuroimaging facilities or laboratory tests to exclude other diseases, contributes substantially to the misunderstanding or incorrect application of core elements of the McDonald 2017 criteria, leading to inaccurate diagnoses.[4,13] The issues of errors in the assessment for MS-typical syndromes, MRI fulfillment of dissemination in space criteria, and the clinical determination of fulfillment of dissemination in time criteria also apply to high-income and middle-income countries in which patients must pay for their own clinical and paraclinical investigations.

Conclusions and future directions

Because multiple sclerosis susceptibility and clinical course are influenced by genetic variations,[99] environmental factors,[100] ethnicity,[101] and access to health care,[102] it is crucial to account for geographical and socioeconomic factors during differential diagnosis. Socioeconomic factors including income, education, housing, and race, can all affect multiple sclerosis diagnosis. Lower socioeconomic status is linked to diminished access to health-care systems, leading to challenges in obtaining accurate diagnosis. The prevalence of some specific disorders that can mimic multiple sclerosis in Latin America, Africa, the Middle East, eastern Europe, southeast Asia, and the Western Pacific differs from those in the USA, Canada, Australia, and western Europe. Although some contemporary cohorts of individuals misdiagnosed with multiple sclerosis from the Middle East and Latin America[11,14] had conditions and potential causes of misdiagnosis that were similar to those reported in North America and western Europe,[12,15–17] few data are available on the misdiagnosis of multiple sclerosis in low-income regions, such as sub-Saharan Africa and southeast Asia. Collaborative epidemiological studies from these regions are needed to provide a comprehensive understanding of differential diagnosis. To facilitate accurate multiple sclerosis diagnoses and reduce misdiagnosis, we must establish educational and training programmes. Expansive training programmes are essential to recognise local red flags for alternative diagnoses and understand contemporary causes of misdiagnosis. Although addressing social determinants of health is outside the role of neurologists, it is increasingly evident that overlooking geographical context can affect multiple sclerosis diagnosis and management.

Search strategy and selection criteria

Our Steering Committee (AJS, JAC, BLB, SDN, BH, and RAM) outlined key priorities for updating recommendations for the differential diagnosis of multiple sclerosis in regions outside North America and western Europe. A research librarian (MPH) completed a literature search in Ovid Medline from Jan 1, 2008, to Dec 31, 2022, using the keywords "multiple sclerosis", "diagnostic error", "missed diagnosis", "misdiagnosis", "diagnostic accuracy", and "differential diagnosis", combining "multiple sclerosis" with any of the other keywords, yielding 1430 unique citations. Covidence systematic review management software (Veritas Health Innovation, Melbourne, Australia) was used to review each abstract tailored to the focus of our Personal View. 476 papers were retained from this review, individually reviewed by AJS, and made available to all authors during manuscript development. When possible, non-English language abstracts and manuscripts were translated to English by Google Translate. Additional relevant literature, published between Jan 1, 2008, and April 1, 2024, was also identified from the authors' files Ovid Medline during manuscript development, or using the keywords "Latin America", "The Caribbean", "Asia", "Africa", "Middle East", "Western Pacific", "low-income countries", "healthcare disparities", "healthcare access", "ethnicity", "race", in combination with "multiple sclerosis", "misdiagnosis", or "diagnostic error".

Contributors
JG, ASS, JAC, and KF conceptualised this Personal View and developed the methods including the literature search, and contributed to writing

of the original draft, review, and editing of the manuscript. BLB, FG, TVG, FH, BH, AJ, HJK, RAM, FM, SDN, LP, MAS, DKS, DS, F-DS, AS, KT, SV, MW, and BY conceptualised this Personal View, developed the methods including the literature search, and contributed to review and editing of the manuscript. MPH did a literature search.

Declaration of interests

JC declares receiving grants or research contracts from Biogen and Merck; personal compensation for consulting from Merck; payment or honoraria for lectures from Biogen, Merck, Bristol Myers Squibb, Novartis, and Roche; and support for attending meetings and travel from Merck. JC is a deputy chair International Medical and Scientific Board of Multiple sclerosis International Federation (MSIF), unpaid; and has received equipment, materials, drugs, medical writing, gifts, or other services from Novartis (Investigator initiated award). AJS declares receiving grant funding from National Institute of Neurological Disorders and Stroke, National Institutes of Health and Bristol Myers Squibb (investigator initiated award); has done contracted research with Sanofi, Biogen, Novartis, Actelion, and Genentech; has received personal compensation for consulting from Emmanuel Merck, Darmstadt, Serono and Octave Bioscience; has received payments or honoraria for lectures from Emmanuel Merck, Darmstadt, Serono; has received expert testimony from The Jacob D Fuchsberg Law Firm and Koskoff Koskoff & Bieder; is a participant on a Data Safety Monitoring Board for the Patient Centered Research Institute, and Yale University; declares participation on an advisory board for Genentech, Biogen, Alexion, Celgene, Greenwich Biosciences, TG Therapeutics, and Horizon Therapeutics; and is a content Chair for the American Academy of Neurology (AAN) Institute Multiple Sclerosis Quality Measure Development Work Group and Section Editor for *Multiple Sclerosis and Related Disorders*. JAC declares personal compensation for consulting from Astoria, Bristol-Myers Squibb, Convelo, EMD Serono, FiND Therapeutics, INMune, and Sandoz; and serving as an editor of *Multiple Sclerosis Journal*. BLB is funded by the National Multiple Sclerosis Society, and National Institute of Health; is a consultant for Roche, and Sanofi; and is a Board Director AAN (unpaid). TG has served as a consultant and received compensation from Genentech, Horizon, Sanofi, Alexion, and Greenwich Biosciences. BH declares grants from the European Union, Bundesministerium für Bildung und Forschung, and Deutsche Forschungsgemeinschaft; received personal compensation for consulting from Sandoz, Novartis, and GLG consulting; holds patents for antibodies against KIR4·1 in a subpopulation of patients with multiple sclerosis (2012) and genetic determinants of neutralising antibodies to interferon (filed 2010); and participated in a Data Safety and Monitoring Board for Novartis, Allergy Care DSMB, TG Therapeutics, and Polpharma, and Advisory Board for Novartis. HJK declares a research grant from the National Research Foundation of Korea and research support from Aprilbio, UCB, and Eisai; has received consultancy fees from Altos Biologics, AstraZeneca, Biogen, Daewoong, Kaigene, Kolon Life Science, MDimune, Merck Serono, and Roche; declares honoraria for lectures from Alexion, Eisai, GCPharma, Handok, Mitsubishi Tanabe Pharma, and Sanofi Genzyme; has received personal compensation for participation on a Data Safety Monitoring Board from Sanofi-Genzyme; has received compensation as Co-editor for the *Multiple Sclerosis Journal* and Associate Editor for the *Journal of Clinical Neurology*; and is a Vice President of Pan-Asian Committee on Treatment and Research in Multiple Sclerosis (unpaid). RAM declares grants or contracts from Biogen, Idec, and Roche. FM has received research funding to her institution from Sumaira Foundation, Genentech, Biogen, Horizon Therapeutics, US National Histitute Institute of Health, US Department of State, Foundation Pierre Fabre, and Novartis; has received consulting fees from Alexion, EMD Serono, Genentech, TG Therapeutics, and Horizon Therapeutics; and declares shares of the startup company Brain Capture (not related to the content of this manuscript). SDN declares grants or contracts (paid directly to institution) from Biogen, Roche, Genentech, National MS Society, Department of Defense, and Patient Centered Outcomes Research Institute; has received personal compensation for consulting from Biogen, Roche, Genentech, Bristol Myers Squibb, EMD Serono, Greenwich Biosciences, Novartis, Horizon Therapeutics, and TG Therapeutics; and is a study lead principal investigator for a Roche clinical trial programme. MAS declares personal honoraria for lectures from Roche, Biogen, Cinnagen, NanoAlvand, Merck, Novartis, and Abidi. DKS declares grants or research contracts from CNPq / Brazil 425331/2016–4 and 308636/2019–8, and Brazilian National Council for Scientific and Technological Development; has received investigator initiated awards from TEVA, Merck, and Biogen; has received personal compensation for consulting from Roche, and Alexion; declares personal honoraria for lectures from Roche, Alexion, Horizon, Merck, Americas Health Foundation; and is a member of International Society of Neuroimmunology, International Advisory Board (unpaid), and Academia Brasileira de Neurologia, Educational Committee (unpaid). DS declares a pilot research grant from the National MS Society paid to the Institution; declares receipt of personal honoraria for lecturing from Roche Pharmaceuticals; declares travel support from Roche Pharmaceutical; and is a Committee member and chair of Multiple Sclerosis International Federation (unpaid). AS has received grants or contracts from the Turkish MS Society, Istanbul University-Cerrahpasa Research Support Funds, and The Scientific and Technological Research Council of Türkiye Health Sciences Research Grants; has received consulting fees from Roche, Merck-Serono, Biogen Idec/Gen Pharma of Turkey , Sanofi-Genzyme, Novartis, and Alexion; has received honoraria for lectures from Sanofi-Genzyme, Novartis, TEVA, and Roche; and has received support for attending meetings from Sanofi-Genzyme, Roche, Merck-Serono, and Alexion. KT declares personal consulting fees from Merck and Eisai; declares payment for lectures from Merck, Eisai, Roche, and Terumo Blood and Cell Technology; and is a member of the Organizing Committee Pan-Asian Committee for Treatment and Research in Multiple Sclerosis (unpaid). MW has received publication royalties from Springer and Elsevier; has received consultancy honoraria from Icometrix, Imcyse, Novartis, Sanofi, Merck, and Biologix; declares personal compensation for lectures or presentations from Alexion, Bayer Healthcare, Biogen, Biologix, Bristol Myers Squibb, Celgene, Genilac, Imcyse, Icometrix, Merck-Serono, Novartis, Roche, and Sanofi-Genzyme; and declares support for attending meetings from Merck-Serono. BGW declares royalties from RSR, Hospices Civils de Lyon, MVZ Labor PD Dr Volkmann und Kollegen GbR , and Oxford University; declares personal consulting fees from Roche, Horizon Therapeutics, Cambridge Pharmaceuticals, and Mitsubishi Tanabe; has received payments for lecture presentations from Roche and Horizon; has a patent planned for NMO-IgG for diagnosis of neuromyelitis optica; and declares participation on a Data Safety Monitoring Board and Advisory borads for Alexion MedImmune/VielaBio/Horizon, and UCB Biosciences. KF declares grants from Ministry of Education, Culture, Sports, Science and Technology of Japan and Ministry of Health, Welfare and Labor of Japan; has received personal compensation for consulting from Merck Biopharma, Japan Tobacco, and Abbvie; has received payment or honoraria forlectures and presentations from Biogen, Eisai, Mitsubishi Tanabe, Novartis, Chugai/Roche, Alexion, VielaBio/Horizon Therapeutics, Teijin, Asahi Kasei Medical, Merck, and Takeda; declares participation in an Advisory Board for Biogen, Mitsubishi Tanabe, Novartis, Chugai/Roche, Alexion, VielaBio/Horizon Therapeutics, and UCB; serves as President of the Pan-Asian Committee for Treatment and Research in Multiple Sclerosis (unpaid), President of the Japanese Society of Neuroimmunology (unpaid), is a Board Member of the Japan Multiple Sclerosis Society (unpaid), is a board member of theEuropean Charcot Foundation (unpaid), and is a Member of the International Medical and Scientific Board, MSIF (unpaid). All other authors declared no competing interest.

Acknowledgments

The Americas Committee on Treatment and Research in Multiple Sclerosis provided administrative and financial support for the Multiple Sclerosis Differential Diagnosis Consortium. The sponsor was not involved in the design, collection, analysis, or interpretation of data included in the publication, in the writing of the manuscript, or in the decision to submit for publication. We thank Mariano Marrodan and Hiroshi Kuroda for providing MRI images of some diseases that mimic multiple sclerosis.

Editorial note: The Lancet Group takes a neutral position with respect to territorial claims in published maps and institutional affiliations.

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