

Differential diagnosis of multiple sclerosis in Latin America

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Abstract

Improvement of multiple sclerosis (MS) diagnoses leads to earlier and correct disease management. The differential diagnostic workup for MS comprises a large variety of medical conditions. There are general guidelines and criteria for diagnosing MS worldwide, but awareness of regional differences needs to be kept in mind. Latin American patients who are screened for MS diagnoses may require an approach that is not exactly the same as that used for patients in North America, western Europe or Asia. In the present review, the conditions that are important for the differential diagnoses of MS in Latin America are reviewed. They include infections, metabolic diseases, nutritional deficits and other autoimmune conditions that physicians in charge of these patients need to be familiar with.

Keywords: Multiple sclerosis, Latin America, central nervous system, epidemiology, diagnoses

Date received: 13 April 2017; revised: 6 May 2017; accepted: 15 May 2017

Introduction

Correctly diagnosing multiple sclerosis (MS) is achieved through clinical observation, knowledge, correct interpretation of findings from history, examination, imaging and other examinations. Misdiagnosis of MS comes with a burden of psychosocial, economic, personal and professional losses to patients and should be avoided at all costs.¹ For diagnosing of MS to be improved, it is important to consider the conditions that are particular to the region of the world where the patient was born and/or lives. While general overall criteria must be used for diagnosing MS everywhere, awareness of regional differences needs to be kept in mind. Therefore, Latin American patients who are screened for MS may require an approach that differs from what is used in North America, western Europe or Asia.

The cornerstone of MS diagnoses continues to be the dissemination of lesions in the central nervous system over time and space.² However, MS is not the only condition that presents this type of dissemination, and exclusion of other conditions with similar clinical characteristics is paramount. Infectious, degenerative, metabolic, nutritional, autoimmune and neoplastic diseases may mimic MS and wrong diagnoses (and treatment) may prove harmful to patients.³ Since MS has no biomarker, the clinical

workup must cover the potential differential diagnoses in a particular patient. The difficulties in diagnosing MS increase when clinically isolated syndromes and radiologically isolated syndromes are taken into consideration. Likewise, when MS onset occurs at the extremes of age, the numbers of possible differential diagnoses are vastly increased. Extensive recent reviews cover these topics.^{3–5} The “red flags” for diagnosing MS are generally the same everywhere in the world (extremes of age, atypical presentations and concomitant systemic disease). However, some regional aspects need to be considered. In the present review, we highlight conditions that are more prevalent in Latin America and which must always be taken into consideration when a patient born and/or raised on this continent has a suspected diagnosis of MS.

Infectious diseases

Although many infections affecting the CNS (central nervous system) may present signs and symptoms that mimic MS, the present review concentrates on those that are more prevalent in Latin America and must be investigated in the differential diagnostic workup. The list presented below is by no means complete.

Syphilis. The manifestations of *Treponema pallidum* infection of the CNS are not uniform, but follow a



typical pattern. Gait disorders, cognitive dysfunction, visual and auditory deficits, paresis and paresthesia are all symptoms that may confound the diagnoses of neurosyphilis and MS.^{6,7} Syphilis has been known as “the great imitator” and should not be ruled out from the differential diagnostic workup in neurological diseases. The prevalence of *Treponema pallidum* infection in the adult population in Latin America is high and all antenatal services regularly test women for syphilis, irrespective of whether they form part of the at-risk population.⁸ Magnetic resonance imaging (MRI) in neurosyphilis mostly shows a pattern of vasculitis and infarction, which helps in the differential diagnosis with MS.⁹ Due to the inexpensive and simple methods used in blood testing for syphilis, these can be regularly requested in the differential diagnosis workup for MS.

Human immunodeficiency virus (HIV). The neurological manifestations of HIV are not only due to viral infection but also reflect other infections of the CNS that were facilitated by immunodeficiency. A few decades ago, manifestations of HIV in the CNS were virtually impossible to differentiate from MS,¹⁰ but even with the advances in MRI techniques, some cases of confounded diagnoses between MS and HIV have been described.¹¹ With the further description of progressive multifocal leukoencephalopathy (PML) as a complication of HIV/AIDS as well as a complication of some treatments used for MS, understanding of this differential diagnosis has become paramount.¹² In addition, cryptococcal infection of the CNS may also be a complication of certain MS treatments or a concomitant infection found with HIV/AIDS.^{13,14} Most patients with signs and symptoms related to the CNS are investigated for HIV/AIDS at least with a blood test.

Borreliosis. True Lyme’s disease is rarely found in Latin America. It is caused by the spirochete *Borrelia burgdorferi*, which is transmitted by the tick *Ixodes ricinus*. While it is endemic in North America and Europe, only a few cases of Lyme borreliosis have been described in Latin America.¹⁵ However, there is another form of this tick-borne disease that can be found in Latin America: Baggio-Yoshinari syndrome, which is transmitted by *Amblyomma* and/or *Rhipicephalus* ticks.¹⁶ In this syndrome, there is no positive reaction for *Borrelia burgdorferi* in plasma, and microscopy on peripheral blood reveals a mixture of *Mycoplasma spp*, *Chlamydia spp* and spirochete-like microorganisms.^{16,17} Patients with Baggio-Yoshinari syndrome may present a variety of neurological signs and

symptoms mimicking MS, but these are usually accompanied by systemic manifestations that point away from MS. Blood tests for this condition are not easily available and must usually be obtained via universities or specialized institutions.

Neurotuberculosis. Pathological manifestations of *Mycobacterium tuberculosis* affecting the CNS are usually difficult to diagnose. Although the most common manifestation is tuberculous meningitis (no need for differential diagnosis with MS), other manifestations may be more complicated to diagnose.¹⁸ Tuberculomas, cerebral miliary tuberculosis, tuberculous encephalopathy, tuberculous abscess, tuberculous encephalitis and tuberculous arteritis may require extensive workup for diagnoses and may mimic MS at least at the onset of infection.¹⁹ Considering that tuberculosis is a prevalent condition in Latin America, chest radiographies and tuberculin skin tests are routine evaluations in most medical services.

Neurocysticercosis. Neurocysticercosis is the most common parasitic disease of the human CNS. It is a pleomorphic disease with a diverse array of clinical manifestations varying from asymptomatic cases to acute or chronic syndromes.²⁰ Although the main presentations of the disease are related to epilepsy and/or intracranial hypertension, the character of remission and exacerbation of symptoms may require differential diagnoses with MS.²¹ Infestations in the parenchymal CNS analyzed through MRI show different stages: a vesicular cystic stage that can present T2 hyperintense scolex without enhancement; a colloidal stage in which the hyperintense cyst is surrounded by edema and cyst wall enhancement; or a nodular/granular stage in which the cyst retracts and may present ring enhancement. These can mimic MS lesions and, particularly in areas of low endemic infestation, where physicians are not used to seeing these patients, neurocysticercosis may be a confounding factor for MS diagnoses.²² Calcified lesions in imaging examinations can aid in the differential diagnosis of MS and other neurological diseases, especially when these are spread through the parenchyma.²³ Spinal fluid findings may not help, due to the presence of a high IgG index and oligoclonal bands in some cases.^{22,24} In addition, the cost of highly sensitive and specific immunologic tests for neurocysticercosis limits its overall use.²⁵

Human T-cell lymphotropic virus type 1 (HTLV1). Tropical spastic paraparesis, or HTLV1-associated myelopathy, is a condition that may

mimic primary progressive MS. HTLV1 can cross the blood-brain barrier and thus enter and infect the cells of the central nervous system. Activation of lymphocytes induces release of pro-inflammatory cytokines, further disrupting the integrity of the blood-brain barrier.²⁶ High prevalence of HTLV1 and HTLV2 is observed in Central and South America and the Caribbean, where clusters of infected people can be found.²⁷ HTLV is transmitted mainly through sexual contact and blood, and from mother to child via breastfeeding. HTLV1 is associated with other conditions in addition to myelopathy: T-cell leukemia/lymphoma and HTLV-associated uveitis and dermatitis.²⁷ It is possible that treatment with monoclonal antibodies exacerbates HTLV1 disease, which might pose a problem for a mistaken diagnosis of MS in a patient who is really suffering from HTLV1-associated conditions.²⁸ Patients with progressive and spastic paraparesis in Latin America are often investigated for the presence of HTLV1/2 antibodies in plasma and spinal fluid.

Arboviruses. Dengue, Chikungunya and Zika are diseases caused by arboviruses that are endemic to certain parts of Latin America. These conditions may have manifestations related to the central and peripheral nervous systems and have recently become important in the diagnostic workup for brain demyelination on this continent.^{29–31} It is important to keep in mind that travelers may also present neurological symptoms related to arbovirus infection while visiting endemic countries. Upon suspicion of these arboviruses, health authorities must be communicated and blood tests can be helpful in the identification of the disease.

Metabolic diseases

These are more prevalent in young patients but occasionally an adult patient diagnosed with MS may, in fact, present a misdiagnosed metabolic disease. The extensive list of leukodystrophies that may mimic MS³² does not differ in Latin America and, therefore, these inherited diseases will not be discussed here. However, it is important to highlight at least one differential diagnosis.

Hemophagocytic lymphohistiocytosis. This condition is considered to be a differential diagnosis in pediatric MS, but the systemic manifestations of the disease usually lead to the correct diagnosis.³³ The condition is characterized by a severe inflammatory reaction that occurs due to defective transportation, processing and functioning of cytotoxic granules in natural killer cells and cytotoxic T lymphocytes (hereditary forms), and also due to

infections, autoimmune diseases, malignancies and acquired immune deficiency.³⁴ Dengue fever, an endemic condition in many areas of Latin America, has been described as the trigger to hemophagocytic syndrome³⁵ and a cause of demyelinating lesions in the CNS.³⁶ Therefore, although exceptionally rare, this combination of dengue fever and hemophagocytic syndrome might evolve with demyelinating lesions in the CNS and mimic MS.

Nutritional deficits

Deficiencies of some nutrients in the poorest areas of Latin America may lead to diseases that affect the CNS and can mimic MS. Some of these conditions are detailed below.

Vitamin B12. High rates of low or marginal vitamin B12 status are systematically found in many locations in Latin America and the Caribbean.³⁷ While folic acid supplementation seems to have been effective over the last decade, vitamin B12 deficiency still remains a public health issue in some areas.³⁸ The neurological manifestations of vitamin B12 deficiency include cognitive impairment, dementia, depression, peripheral neuropathy and subacute combined degeneration of the spinal cord.³⁹ These may manifest as associations of gait, mood and cognitive disorders that could mimic MS, particularly in the primary progressive form. In addition, vitamin B12 deficiency may evolve with inflammation and neurodegeneration, thus altering brain and spinal cord MRI findings.⁴⁰ Therefore, the differential diagnostic workup for MS in Latin America includes investigation of serum levels of vitamin B12.

Copper deficit. Unrecognized copper deficiency in adults may manifest as a chronic and progressive myelopathy, with prominent gait difficulty due to sensory ataxia and lower limb spasticity.⁴¹ This may be confounded with primary progressive forms of MS, and MRI findings are not distinguishable from those associated with vitamin B12 deficiency.⁴² Although rarely mentioned in the literature, excessive zinc consumption via seafood can induce copper deficiency and myelopathy.⁴³ Thus, the differential diagnostic workup in neurological diseases can be particularly challenging among Latin American patients who have inadequate dietary habits. To help in the identification of copper deficiency, it is important to remember that this condition is often associated to hematological pathology (anemia, neutropenia and thrombocytopenia). Furthermore, patients can present peripheral neuropathy and, more rarely, optic neuropathy in cases of copper deficiency.

Other vitamins and nutrients. Although nutritional conditions in Latin America and the Caribbean have improved, some deficiencies are still observed.⁴⁴ The signs and symptoms relating to malnutrition are mostly anemia and malformations, which do not pose differential diagnoses with MS.⁴⁵ In specific situations like the epidemic of optic and peripheral neuropathy in Cuba in the early 90s, there may be a link between nutrition deficiencies and differential diagnoses for demyelinating diseases.^{46,47}

Alcohol and illicit drugs. These are conditions that often accompany malnutrition and infections (HIV, HTLV, syphilis and tuberculosis) and which have been discussed as potential confounders in MS diagnoses. Considering the MRI findings in the CNS of individuals with addictions of this nature,^{48,49} a careful medical history obtained from the patient and the family is important, to rule out alcohol and illicit drug abuse as potential causes of neurological signs and symptoms.

Neoplastic diseases

These are not particularly different in Latin America, compared with the rest of the world. Lymphomas of the CNS are important conditions for differential diagnoses with tumefactive MS lesions in the brain^{50,51} and with brain abscesses.⁵² Newer MRI techniques and more detailed examination of the images may help in the differential diagnoses.⁵³

Other autoimmune conditions

It is important to take into consideration the prevalence of other autoimmune diseases in Latin America. Therefore, the diagnostic workup for MS in patients from Latin American countries includes conditions that are not commonly found in other parts of the world.

Neuromyelitis optica (NMO). NMO-spectrum disorders (NMOSD) and MS are different diseases, with distinct etiopathogenic backgrounds, prognoses and therapeutic approaches. NMO and NMOSD account for 18.3% of all demyelinating syndromes diagnosed in specialized services in Latin America.⁵⁴ These conditions are more prevalent among African descendants and, according to the ethnic background of the region, can vary from 6.8% to 11.1% in Sao Paulo (predominantly white population) to 20.5% in Rio de Janeiro (predominantly Afro-descendant population).^{54,55} In comparison, the prevalence among European Caucasians is less than 2%.⁵⁶ The higher prevalence of NMO and NMOSD observed among individuals of both Asian and Latin American origins was reflected in the paper from the group revising the McDonald criteria for

diagnosing MS.² It has been suggested that, unless the neurological presentation of a Latin American patient could be considered to be the “typical Western-type MS”, it might be advisable to test for biomarkers for NMO/NMOSD. In addition, it is important to remember that NMO can be confounded with MS because of the imperfect sensitivity of anti-aquaporin-4 autoantibody assays and the presence of brain lesions in NMO.² Patients with NMO or NMOSD presenting anti-myelin oligodendrocyte glycoprotein (anti-MOG) pose further challenges to the differential diagnoses with MS, since they may have milder disease.⁵⁷ Furthermore, myelopathies and ophthalmological diseases relating to nutritional deficits may impose extra difficulties in the differential diagnosis of NMO/NMOSD in Latin American populations.⁵⁸

Acute disseminated encephalomyelitis (ADEM). ADEM is an immune-mediated, inflammatory demyelinating syndrome that predominantly affects the white matter of the central nervous system of children.⁵⁹ When patients are promptly diagnosed with ADEM and treated, they tend to have a favorable outcome with full recovery. Suspicion of ADEM arises on a clinical basis from evidence of acute polyfocal and monophasic neurological deficits, including encephalopathy, often following infection or vaccination of the patient. MRI typically demonstrates white matter lesions of the brain and spinal cord, and frequent involvement of thalami and basal ganglia.⁶⁰ With this complete and classical presentation, ADEM should not be difficult to differentiate from NMOSD and MS at specialized centers. However, children with polyphasic presentations of ADEM, spinal cord lesions extending for more than three continuous vertebral segments and large cerebral lesions may be misdiagnosed.^{61–63}

The calendar of vaccinations in Latin America,^{64,65} the parents' attitudes towards vaccination of their children,^{66,67} and infection profiles among children in Latin American countries^{68,69} may influence the prevalence and bouts of ADEM in the region.

Conclusion

In conclusion, the present review has highlighted important aspects of the differential diagnosis of MS in Latin America. Although comprehensive, it is by no means complete, and this subject requires continuous updates, studies and research. It is paramount to keep in mind that Latin America is a large part of the Americas and epidemiological data presented here are not the same in all countries and regions.

Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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