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Review

Application of the McDonald criteria in Latin America

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Abstract

The diagnosis of multiple sclerosis (MS) is based on neurological symptoms and signs, alongside evidence of dissemination of central nervous system (CNS) lesions in space and time. In the absence of a sensitive and specific diagnostic test, diagnostic criteria are needed for diagnosing MS. The caveat to the application of the McDonald criteria is that alternative diagnoses must be excluded. The prevalence, clinical phenotype and the differential diagnosis of MS may have variations in different populations, especially in Latin America (LATAM). Considering that MS diagnostic criteria were developed with data gathered largely from adult Caucasian European and North American populations, their applicability and accuracy in ethnical/genetic diverse populations may be affected. There are scarce data in our region about the reliability of MS criteria.

***Keywords*:** Diagnostic criteria, LATAM, multiple sclerosis

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Introduction

Since Charcot's description of multiple sclerosis (MS) in the 19th century, there has been an increasingly important need to accurately diagnose MS with minimal diagnostic variability and error.

Considering that no single clinical feature or diagnostic test is enough for the diagnosis of MS, diagnostic criteria have been developed based on the demonstration of lesions disseminated in space (DIS) and time (DIT), and after exclusion of alternative causes.

In response to the need for simpler and earlier diagnosis, these criteria have been modified in recent years, and with the advance of magnetic resonance imaging (MRI), radiological evidence is now used to meet DIS and DIT with increasing sensitivity. The 2001 McDonald diagnostic criteria allowed the application of MRI evidence for DIS and DIT for MS diagnosis in patients who had experienced a clinically isolated syndrome (CIS).[1]

In 2010, the International Panel on Diagnosis of MS reviewed the McDonald criteria and proposed a new algorithm for MS diagnosis, including input from the European Magnetic Imaging in MS (MAGNIMS) research group, and providing more sensitive criteria for DIS and DIT.[2]

Using them, a diagnosis of MS can be made in up to one-third of patients with a typical CIS on the basis of a single enhanced MRI scan.

Although the McDonald criteria are widely used throughout the world, they were developed with data gathered largely from adult Caucasian European and North American populations with a high incidence of MS, and their applicability for other populations has been questioned (paediatric cases, Asian and Latin Americans).

Despite this concern, studies investigating the McDonald criteria behaviour in cohorts with CIS in Asian countries (central Russia, Taiwan, Korea) have reported similarly good performance.[3–5]

Latin American (LATAM) countries are characterised by geographic, racial/genetic and sociocultural particularities, lower prevalence rates of MS, higher prevalence of infectious diseases, limited access to MRI in some locations and many other

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factors that could limit the widespread use of the criteria.

MS in LATAM

Geographically, LATAM extends over a vast area of the Americas (approximately 21,069,500 km^2) that stretches from the northern border of Mexico (latitude 32 degrees North) to the southern tip of South America (latitude 56 degrees South), including the Caribbean. It is estimated that about 580 million people live in this region.[6]

The inhabitants of LATAM are from a variety of ancestries, ethnic groups and races, therefore, it can be considered as one of the most diverse regions in the world. The original background of the region was composed of Native Americans; Europeans, mostly Spanish and Portuguese but also other nationalities; and Africans, who were initially brought to the region as slaves and came from different areas of that continent. As a consequence of centuries of intermixing, the population is heterogeneous and genetically complex.

MS for a long time was considered a rare neurological disease in areas such as the American Tropics and the southern latitudes of the Americas; however, in the recent years, there has been an increase in the frequency of cases diagnosed in LATAM. This phenomenon is probably due to multiple factors: a faster and easier diagnosis obtained through the advent of MRI, an increasing number of neurologists, an improved access to healthcare and probably a true increase in incidence.[7]

When interpreting the latitudinal prevalence in LATAM, it should be considered that the Argentinean population is predominantly Caucasian, whereas in Colombia and Ecuador it is predominantly mestizo (intermixing between Europeans and Native Americans); and this may explain the higher risk of MS in the southern part of the continent compared to the central region.

Epidemiological studies in different Chilean regions (latitude 56 degrees South to 17 degrees South) and the Argentinean Patagonia (latitude 55 degrees South to 36 degrees South) showed no gradient differences, suggesting that other human factors such as genetic and ethnicity could play important roles in determining the geographical distribution of MS regardless of the impact of latitude.[8]

There is strong evidence that in LATAM the frequency of MS is lower than in Europe and North America, but in terms of disease progression data are scarce.

In 2015, Rojas et al.[9] compared MS course between LATAM and other regions of the world (North America, Europe and Australia) using the Multiple Sclerosis Severity Score (MSSS) scale and data from the MSBase Registry.

A total of 9610 patients from Europe (6290, 65.6%), North America (1609, 16.7%), Australia (1119, 11.6%) and LATAM (592, 6.1%) were included. No differences were found in the MSSS among hemispheres ($p = 0.68$), regions ($p = 0.76$) or countries ($p = 0.50$) when data were adjusted in a multivariate model by MS disease course, latitude, age and specific treatment for MS.

Studies carried out in non-white populations have suggested a more rapid clinical progression and disability in individuals of African descent.[10]

In a Brazilian cohort of 150 relapsing–remitting MS (RRMS) patients followed for more than 10 years, Ferreira Vasconcelos et al.[11] showed that African-descent patients reached the progressive phase of the disease faster than those of non-African descent (11.0 versus 15.0 years, $p = 0.006$).

Some genetic studies have suggested that in patients of African descent susceptibility genes for MS may be located in chromosomal regions of white origin, whereas the genes that confer greater severity to the disease or produce optic-spinal symptoms may be located within chromosomal regions of African origin.[12]

McDonald criteria and their applicability in LATAM

In the absence of a sensitive and specific diagnostic test, reliable criteria are needed for diagnosing MS. These criteria have been constantly revised and updated to improve diagnostic accuracy, physician communication and clinical trial design. Considering they were validated in Caucasian populations, there is some uncertainty about their applicability across LATAM countries and confirmatory studies should be studied.

Only two studies from two LATAM countries, Brazil and Argentina, addressed the reliability of MS diagnostic criteria.

Ferreira Vasconcelos et al.[13] reported in 2008 the applicability of three sets of diagnostic criteria

established to define primary progressive MS (PPMS) (Thompson[14], McDonald 2001[1] and McDonald 2005[15]), in a cohort of 52 native Brazilian patients, 33% of whom were non-Caucasian, and African background was identified for up of three generations, followed-up from 1995 to 2006 (Table 1).

Thompson's criteria required at least one year of symptoms and positive cerebrospinal fluid (CSF) oligoclonal bands (OBs) with, in addition, at least nine T2-weighted white-matter lesions on MRI of the brain in a distribution typical for demyelination *or* four to eight brain lesions with at least one spinal cord lesion. Visual evoked potentials were of limited use for those patients who had equivocal imaging. The McDonald's 2001 criteria introduced the concept of using MRI as evidence of DIT (using MRI or continued progression of disability for one year) and DIS (using MRI or abnormal visual evoked potential). In both cases, clinical progression for one year and positive OBs were considered essential for diagnosing PPMS. Finally, the 2005 revision simplified the previous criteria and the requirement of an abnormal CSF was eliminated.

These various sets of criteria established to define PPMS were proposed for a European Caucasian population, and their applicability and accuracy in patients of different ethnicities were not addressed.

Table 1. Demographic characteristics of included patients.

Variable	$n = 52$
Female (*n*)	30
Male (*n*)	22
Caucasian (*n*)	35
Non-Caucasian (*n*)	17
Mean duration of disease (years)	10.5
Mean age at onset (years)	37

The rate of agreement among the three criteria in the Brazilian cohort of PPMS patients was calculated using Kappa statistics, and a p value <0.05 was considered statistically significant (Table 2).

The reasonably high rate (72%) of patients fulfilling all three sets of criteria showed that they had a good reproducibility and reliability and they could be applied in the Brazilian population whose genetic, racial and environmental characteristics are quite different from those of Caucasian populations from Western Europe.

Although MRI has become the most important tool in MS diagnosis, the majority of PPMS patients present with progressive myelopathy, spinal cord lesions may not be visualised and brain MRI may be normal. Within this context, CSF analysis is an extremely important diagnostic biomarker, especially in LATAM considering that regional inflammatory (neuromyelitis optica spectrum disorders), infectious (brucellosis, cysticercosis, tuberculosis, human T-cell lymphotropic virus type-1) and nutritional (vitamin B12 deficiency) diseases that are specific and frequently seen in the region must be excluded.

Carrá et al.[16] in a recent paper that presented the outcomes of a survey carried out among LATAM neurologists, pointed out the relevance of analysing CSF to detect OBs through the isoelectric focusing (IF) technique. In LATAM there are only a few centres duly validated to perform IF determinations, an important issue to face in the future.

The second paper dealing with the applicability of diagnostic criteria came from Argentina.

From January 2005 to June 2010, Patrucco et al.[17] followed a cohort of 101 consecutive patients with CIS at the MS Centre of the Italian Hospital of Buenos Aires, Argentina, in order to assess the accuracy of the new MRI criteria for DIS and DIT,

Table 2. Agreement Kappa index between the three set of criteria applied in the Brazilian cohort of patients with primary progressive multiple sclerosis.

Criteria	Kappa index for agreement	95% confidence interval	p
Thompson and McDonald 2001	0.78	0.52–1.0	**0.001**
Thompson and McDonald 2005	0.52	0.28–0.76	**<0.001**
McDonald 2001 and McDonald 2005	0.27	0.01–0.53	0.042
Thompson, McDonald 2001 and McDonald 2005	0.54	0.39–0.70	**<0.001**

based on a single MRI scan, used in the 2010 McDonald criteria to predict conversion to clinically definite MS (CDMS) (Table 3).

Demographic and ethnic characteristics were registered for each patient included. Ethnicity was analysed by direct genealogical interview and also by surnames as a paternally inherited social marker of ancestry.[18] Based on these data, the following ethnic groups were analysed: *European* (individuals of European descent); *mestizos* (intermixing between European and Native Americans); *zambos* (intermixing between Native Americans and African descendants) and *Native Americans* (unmixed Native American ancestry).[19]

Thirty-three per cent (33) of patients were European descendants, 53% (54) mestizos, 12% (12) Native Americans and 2% (2) zambos.

Table 3. Baseline characteristics of included patients.

Variable	$n = 101$
Mean age (years)	35.5 ± 5
Women (*n*, %)	74 (73%)
Mean follow-up (years)	7.3 ± 3.2
Clinical syndrome	
Optic neuritis (*n*, %)	25 (25)
Brainstem (*n*, %)	20 (20)
Polyregional (*n*, %)	41 (40.5)
Spinal cord (*n*, %)	15 (14.5)
Abnormal brain MRI (*n*, %)	93 (92)
One spinal cord lesion (*n*, %)	15 (14.6)
$\geq$2 spinal cord lesions (*n*, %)	16 (16)
OBs in CSF (*n*, %)	83 (82)
Fulfilled criteria of MS during follow-up (*n*, %)	86 (85)

MRI: magnetic resonance imaging; OBs: oligoclonal bands; CSF: cerebrospinal fluid; MS: multiple sclerosis.

Sensitivity, specificity, positive predictive value, negative predictive value and accuracy ratios with 95% confidence intervals were calculated (Table 4).

High sensitivity (84%) as well as specificity (80%) was observed in this cohort of patients. It is important to highlight that when these criteria were applied to non-European descendants (mestizos, natives and zambos) the accuracy was still as high (sensitivity 77% and specificity 72%) as that observed in European descendants.

The Argentinean population is the result of intermixing of various groups, including Amerindians, Spanish, Africans and a large European immigrant population that arrived between 1870 and 1950.[19]

According to this, the results observed in the paper from Argentina, in an attempt to validate the new diagnostic criteria in an ethnic/genetic population different from the one analysed in the international validation study, are of capital importance. Further studies including other areas of LATAM are needed in order to validate these new MS criteria in the region.

Conclusion

LATAM is one of the most diverse regions in the world and a multiethnic and multicultural background characterises its population. As epidemiological and clinical characteristics of MS may vary according to environmental and genetic factors, it appears crucial to delineate the characteristics of MS in LATAM in order to achieve a better understanding of the disease behaviour in the region.

Regarding genetic factors, LATAM populations are very heterogeneous, and while Argentina and Uruguay have the largest Caucasian influence, mestizos racially constitute numerous LATAM

Table 4. Application of McDonald 2010 diagnostic criteria stratified by ethnicity.

Ethnicity	Sensitivity (CI 95%)	Specificity (CI 95%)	PPV (CI 95%)	NPV (CI 95%)
European descent	82 (78–86)	75 (72–78)	96 (91–98)	38 (35–41)
Mestizos	79 (76–83)	80 (77–84)	95 (91–97)	31 (28–35)
Natives	71 (68–74)	60 (58–64)	71 (68–75)	60 (57–64)
Non-European descent[a]	77 (75–79)	72 (68–75)	94 (88–97)	38 (35–43)

[a]Includes mestizos, natives and zambos.
CI: confidence interval; PPV: positive predictive value; NPV: negative predictive value.

inhabitants. These differences may partially explain the higher risk of MS in the southern part of the continent compared with the central region. There are many inflammatory, infectious and nutritional diseases typically seen in LATAM countries that can mimic MS and they must be rigorously excluded before establishing the diagnosis of MS. Although CSF analysis is not mandatory for the diagnosis of MS according to McDonald criteria 2010, the presence of OBs is, at least in this part of the world, useful additional information in the diagnosis workup. We should consider including CSF analysis in our region in order to achieve accurate diagnosis.

These differences and probably many others may have an impact on the applicability of these criteria, modifying their sensibility, specificity and accuracy in the region. Considering that only two studies from South America addressed the reliability of MS diagnostic criteria, more studies performed in different countries and regions of LATAM including diverse ethnic groups are urgently needed to really validate these criteria in our latitudes.

Conflicts of interest

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