The McDonald criteria for dissemination in space in the differential diagnosis of multiple sclerosis and neuro-Behcet's disease

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Abstract

Background: Neuro-Behcet's disease (NBD) is similar to multiple sclerosis (MS) in multiple aspects. This study was conducted to investigate the sensitivity, specificity, accuracy, positive and negative predictive values for the 2005 revised McDonald MRI criteria for the diagnosis of MS and NBD. *Methods:* This study enrolled 28 consecutive patients with a diagnosis of NBD and 48 patients with a diagnosis of clinically definite MS, who were referred to the Nemazee Hospital, Shiraz University of Medical Sciences, between March 2009 and March 2010. Brain and spinal cord magnetic resonance imaging (MRI) were obtained. Two Radiologists, blinded to clinical diagnosis, reviewed the MRI. We investigated the sensitivity, specificity, accuracy, and positive and negative predictive values of the 2005 revision of the McDonald criteria for dissemination in space for the diagnosis of MS and NBD. *Results:* There were a total of 10 men and 38 women with a mean age of 32.76±7.5 years, with a diagnosis of MS, and 18 men and 10 women with a mean age of 26.8±5.9 years with a diagnosis of parenchymal NBD. The interobserver agreement for the diagnosis of MS using the 2005 revision of the McDonald criteria for dissemination in space with the use of the Cohen kappa scores was 0.82. The sensitivity, specificity, accuracy, and positive and negative predictive values were 80%, 61%, 71.5%, 77% and 64%, respectively.
Conclusion: The accuracy and specificity of the McDonald criteria for dissemination in space for the differentiation of MS and NBD are not optimal.

INTRODUCTION

Neuro-Behcet's disease (NBD) is very similar to multiple sclerosis (MS) in multiple aspects: predilection to present in young adults, relapsing – remitting or progressive course, visual and sensori-motor manifestations, perivascular infiltration of inflammatory cells, and abnormal evoked potentials.[1,2] As the two entities have different therapeutic approaches, an accurate diagnosis is crucial.[3]

During the last two decades, the diagnostic criteria for MS have changed several times in order to detect the disease as accurately as possible. The McDonald criteria are based on two principles: dissemination in time, and in space, for a neurologic manifestation compatible with demyelination. The McDonald criteria for the diagnosis of MS have been revised in 2005 and in 2010.[4]

This study was conducted to investigate the sensitivity, specificity, accuracy, positive and negative predictive values for 2005 revision of the McDonald criteria for diagnosis of MS and NBD. It should be kept in mind that the start of the current study took place before the release of the 2010 revision of the McDonald criteria.

METHODS

The study enrolled 28 consecutive patients with the diagnosis of NBD and 48 patients with the diagnosis of clinically definite MS who referred to the Department of Neurology of the Nemazee Hospital (teaching hospital affiliated to the Shiraz University of Medical Sciences) from March

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2009 to March 2010. The inclusion criteria for NBD were the fulfillment of the International Study Group criteria for Behcet's Disease[5] and the presence of relevant neurological syndromes confirmed by ancillary investigations such as magnetic resonance imaging (MRI), cerebrospinal fluid (CSF) analyses, electrodiagnostic studies, histopathologic analyses and the absence of other diseases that can mimic MS. Inclusion criteria for clinically definite MS was the fulfillment of the Poser criteria.[6] Exclusion criteria for both groups were: positive rheumatoid factor (RF), anti-double stranded DNA (Anti-ds DNA), antinuclear antibodies (ANA), anticardiolipin antibodies (ACLA), antineutrophil cytoplamic antibodies (ANCA), brucella agglutination tests, CSF cultures, echocardiographic findings correlating with cardiogenic embolism, diabetes mellitus, hyperlipidemia, family history of premature atherosclerosis or other major risk factors like stroke at young age, intravenous drug abuse, presence of neurologic side effects of drugs which are used in the treatment of NBD or MS, and any other clinical or paraclinical findings which were consistent with any clinical entity other than NBD or MS. Patients with non-parenchymal NBD were also excluded.

All participants in the study gave their written informed consent. This research was approved by the Ethics Committee of the Shiraz University of Medical Sciences (N0#5246).

The MRIs were performed with a 1.5T Philips Intera. Available images from 0.3T magnets were excluded from the study. The MRI sequences included axial and coronal fast spin echo (FSE) T2-weighted images (TR/TE:3631-4000/100-117, ETL:12-26), axial FLAIR (TR/TE/TI:6000-6660/100-117/1200-2000), pre- and post-contrast axial, coronal and sagittal (SE) T1-weighted (TR/TE:495-500/15-20) and, in some patients, sagittal Proton density (TR/TE:180/30). The section thickness was of 5 mm, without any gap. The contrast agents used in most of the patients were Magnevist (gadopentatedimeglumine, Bayer AG, Leverkusen, Germany) or Omniscan (gadodiamide, GE Healthcare, Buckinghamshire, UK) and in few cases Dotarem (gadotratemeglumine, Guerbet, Cedex, France), with a dose of 0.1-0.2 mM/kg of body weight. The interval between contrast injection and imaging was of 5-7 minutes.

Brain and spinal cord MRIs were obtained just after the clinical confirmation of NBD or MS. Two Radiologists with 6 and 5 years' experience in neuroradiology (RJ and ZZ), who blinded to the clinical diagnosis, reviewed the 76 available MRIs. Each Radiologist evaluated the available hard copy separately and filled in a designated questionnaire for each patient, as an assessment of the 2005 revision of the McDonald criteria for MS. The Radiologists were completely blind to the clinical diagnosis, age, sex and number of the patients in each diagnostic group. The differences were settled by consensus and the accuracy of the McDonald criteria in differentiating MS was determined by using data from the combined assessment. The validity of the McDonald diagnostic criteria for MS was assessed by comparison with the gold standard for the disease, which was defined as clinically definite MS with the Poser criteria. We calculated the number of true positives (TP; McDonald MS positive, clinically definite MS positive), true negatives (TN; McDonald MS negative, clinically definite MS negative), false positives (FP; McDonald MS positive, clinically definite MS negative), and false negatives (FN; McDonald MS negative, clinically definite MS positive) and used them to determine the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy.

Statistical analysis

Interobserver variability was assessed with the Cohen K statistic. The guideline of Landis and Koch was followed in the interpretation of the values: 0.00–0.20, slight agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.80–1.00, almost perfect agreement. All the statistical analysis were performed with the SPSS statistical software, version 11 (SPSS Inc., Chicago, Illinois).

RESULTS

There were 10 men and 38 women with a mean age of 32.76±7.5 years with a diagnosis of MS, and 18 men and 10 women with a mean age of 26.8±5.9 years, with a diagnosis of parenchymal NBD.

The mean duration of MS was 3.2±1.5 years and the mean duration of BD before progression to NBD was 5.6±2.3 years. Table 1 depicts the anatomic area of involvement in MS and NBD, according to the two observers' opinions. Table 2 reveals the percentage of positivity of separate criteria and whole criteria of the McDonald criteria for dissemination in space. Table 3 shows the sensitivity, specificity, accuracy, positive and negative predictive values for the McDonald

Table 1: Distribution of lesions in anatomic locations

	Observer 1		Observer 2	
	MS patients	**NBD patients**	**MS patients**	**NBD patients**
Cortical	17(35.4%)	6(21.4%)	12(25%)	3(10.7%)
Juxtacortical	44(91.7%)	99(68.3%)	42(87.5%)	17(60.7%)
Superficial white matter	45(93.8%)	22(78.6%)	46(95.8%)	21(75%)
Periventricular white matter	45(93.8%)	16(57.1%)	41(85.4%)	13(46.4%)
Corpus callosum	35(72.9%)	4(14.3%)	38(79.2%)	3(10.7%)
Internal capsule	13(27.1%)	5(17.9%)	7(14.6%)	5(17.9%)
Thalamus	6(12.5%)	2(7.1%)	3(6.3%)	0(0.0%)
Basal ganglia	1(2.1%)	1(3.6%)	5(10.4%)	4(14.4%)
Midbrain	21(43.8%)	8(28.6%)	18(37.5%)	8(28.6%)
Mesodiancephalic junction	2(4.2%)	5(17.9%)	1(2.1%)	6(21.4%)
Pons	16(33.3%)	5(18%)	9(18.8%)	3(10.7%)
Medulla	6(12.5%)	5(17.9%)	2(4.2%)	0(0.0%)
Cerebellar hemishphere	17(35.4%)	2(7.1%)	11(22.9%)	2(7.1%)
Cerebellar peduncle	11(22.9%)	4(14.3%)	7(14.6%)	3(10.7%)

MS, multiple sclerosis; NBD, Neuro-Behcet's disease

criteria for the diagnosis of MS in the studied population.

Overall, participating observers were able to make a correct diagnosis of MS considering the McDonald criteria for dissemination in space in 83.3% and 75.0% of MS patients, respectively. However, 35.7-42.9% of NBD patients were erroneously diagnosed as MS (false-positive findings) according to the McDonald criteria for dissemination in space by both Radiologists. Interobserver variability for the quantitative data assessments was measured, using Cohen K scores and the interobserver agreement for the diagnosis of MS using McDonald criteria for dissemination in space was 0.82 (almost perfect agreement); however, the results suggested that observer one was more sensitive while observer two was more specific.

Corpus callosal lesions were six times more prevalent in MS patients compared to NBD patients (in 76% of the MS patients, while in only 12.5% of NBD patients). Meanwhile, the basal ganglia and mesodiencephalic junction presented a slightly higher frequency of involvement in NBD patients, although the difference was only significant for mesodiencephalic lesions (P value < 0.05).

Extension of the lesion from one anatomic site to another neighboring site was reported in 19.7% and 14.3% of NBD patients, while in only 3.1% and 1% of MS patients, respectively. Another finding was the predominance in the brainstem and/or basal ganglia involvement, which, although infrequent (about 11% of NBD patients), has a high discriminative value for differentiating NBD from MS patients. This predominance was not seen in any of the MS patients. Out of all the McDonald criteria for dissemination in space, only infratentorial lesions were not significantly more prevalent in MS. All other criteria were significantly more prevalent among patients with MS (p < 0.05).

DISCUSSION

Differentiation of MS from NBD is crucial especially in geographic areas with a high

Table 2: Comparison of MRI findings between patients with multiple sclerosis (MS) and patients with neuro-Behcet's disease (NBD)

	Observer1		Observer2	
	MS patients	NBD patients	MS patients	NBD patients
At least 9 T2 hypersignalbrain and/or cord lesions if there is no Gd-enhancing lesion	41(85.4%)	16(57.1%)	39(81.3%)	11(39.3%)
	P(.012)		P(.000)	
At least three periventricular lesions	45(93.8%)	15(53.6%)	41(85.4%)	13(46.5%)
	P(<0.001)		P(0.001)	
At least one Juxtacortical lesion	44(91.7%)	19(68.3%)	42(87.5%)	17(60.7%)
	P(0.018)		P(0.010)	
At least one Infratentorial or cord lesion	27(56.3%)	13(46.4%)	22(45.8%)	9(32.1%)
	P(0.479)		P(0.334)	
At least one Enhancing T1	15(21.3%)	2(7.1%)	10(20.8%)	3(10.7%)
	P(0.021)		P(0.351)	
McDonald fulfilled	40(83.3%)	12(42.9%)	36(75%)	10(35.7%)
	P(0.001)		P(0.001)	

prevalence of both diseases. For example prevalence rate of MS and BD in Iran were about 51/100.000[7] and 80/100.000[8] respectively. Diagnosis of NBD is not a major issue in patients who fulfill the International Study Group (ISG) criteria for BD. Patients with incomplete criteria for BD, who have neurological manifestations and MRI lesions which are similar to MS, can cause a diagnostic dilemma. If history taking or physical examination are not done accurately and oral ulcers or painless genital ulcers are neglected, a patient with BD who presents with neurological manifestations could be easily misdiagnosed as MS.[9]

In current study, the accuracy of the McDonald criteria for the differentiation of MS and NBD is about 70%. In a previous study from our center, 12% of patients with NBD fulfilled the McDonald dissemination in space criteria on the MRIs obtained during their first attack. This ratio reached 71% of the patients in their last follow-up MRIs.[10]

This should be taken into account in making a diagnosis of a lifelong disease like MS, a high

Table3: Sensitivity, specificity, accuracy, positive and negative predictive values for McDonald criteria for diagnosis of multiple sclerosis

	Observer1	Observer2	Consensus
Sensitivity	83%	75%	80%
Specificity	57%	64%	61%
Accuracy	73.5%	71%	71.5%
Positive predictive value	77%	78%	77%
Negative Predictive value	66.5%	60%	64%

specificity for a test is more important than a high sensitivity. Our results are consistent with the study by Swanton et al.[11], in which the DIS component alone was less specific for clinically definite MS than "dissemination in time"(DIT) alone.

The involvement of the corpus callosum was significantly higher in patients with MS in comparison with NBD. This finding was consistent with previous studies.[12-14] In the report of Jafari et al.[15] 46 (37%) of the patients fulfilled the Barkhof criteria after their first episode of clinically isolated syndrome (CIS), of which 70% had at least one corpus callosal lesion. Only 11% of those who did not fulfilled the criteria had corpus callosal lesions. Although these lesions have multiple differential diagnoses[16], it is proposed that adding corpus callosal lesions with particular characteristics as a criterion for the diagnosis of MS may enhance the specificity of the McDonald criteria.

Wechsler et al.[17] showed that in differentiating NBD from other neurological disorders, the absence of "predominantly periventricular" white matter lesions favors the diagnosis of NBD. The most common sites of involvement in the current series were the superficial and the deep white matters. This finding was consistent with several other studies.[18,19] The current study showed that although periventricular involvement is significantly more frequent in MS, it can be seen in more than half of NBD patients. Predominantly brain stem lesion and extensive lesion were more common in NBD rather than MS. These characteristics can be used for the differential diagnosis of NBD from other diseases.

Coban et al.[20] proposed a constellation of findings for differentiating NBD from clinical definite MS and neuropsychiatric Lupus, but they did not mention their radiological criteria for MS. They reported a positive predictive value of 100% for acute NBD, 40% for chronic NBD, and 95.5% for MS. Six out of 34 patients who were diagnosed as NBD had "silent neurological involvement", which should not have been included. Due to these methodological drawbacks, the 96.5% specificity of the radiological diagnosis for NBD should be interpreted with caution.

In the absence of a definitive diagnostic test, diagnosis of MS is based a complex of clinical and investigatory findings. Thus, the true accuracy of the criteria in population-based studies remains difficult to determine, and there is an overreliance on MRI, with possible misdiagnosis.[21,22] Because of limited specificity of MRI findings, there are many studies addressing accuracy of McDonald criteria in diagnosis of MS in various settings.[11-15,21] This study is unique in that we addressed a specific differential diagnosis endemic to our region, that can masquerade MS both clinically and in MRI.

As for shortcomings, we did not categorize patients with MS to relapsing-remitting, primary progressive, secondary progressive and relapsing-progressive and patients with NBD to polyphasic and progressive subgroups. It was due to the small patient population in both groups. We did not consider the effects of the size of the lesions. If we considered lesions more than 3 mm, as Korteweg et al.[23] did, our result might have been different from the current. Gender difference was not studied as well. We used consensus method rather than selecting an Ombudsman to reduce interobserver variability.

Current study was done using 2005 revision of McDonald criteria. 2005 McDonald Criteria have been validated in Asian MS patients.[24,25] The new (2010) revision was proposed after our data collection. Meanwhile, Hsueh et al. compared the sensitivity, specificity and accuracy of 2005 and 2010 versions of McDonald Criteria. The 2010 version was more sensitive, less specific, and more accurate, but the differences were not statistically significant.[24] Using 2010 criteria for dissemination in space in the differential diagnosis of MS and NBD might have given a different results.

In conclusion, the current study showed that, although the 2005 revision of McDonald dissemination in space criteria are valuable in the diagnosis of MS, its specificity in distinguishing MS from NBD is less than optimal. Therefore, MRI alone does not seem to be an optimal investigatory tool for the differentiation of MS and NBD in a patient with relevant neurological manifestations. Presently, there is no substitute for a careful record of the patient's history and a complete physical exam for the detection of muco-cutaneous, ocular and other manifestations of general BD, in order to establish the diagnosis.

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DISCLOSURE

Conflict of interest: None

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