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Abstract

Aim: To compare the sensitivity, specificity and accuracy of the 2010 and 2017 revisions of the McDonald criteria in a Croatian cohort of patients with a clinically isolated syndrome (CIS).
Methods: Prospectively collected data from 113 patients were retrospectively analyzed. Sensitivity, specificity and accuracy for both criteria were calculated regarding conversion to clinically definite multiple sclerosis (Poser CDMS) or multiple sclerosis (MS) (defined as fulfilment of clinical or MRI evidence for dissemination in space and the development of a second relapse and/or ≥ 1 new T2 lesions on the follow-up MRIs) during a two-year follow-up. Survival analysis was performed to estimate the cumulative risk of patients developing Poser CDMS. Binary logistic regression model was used to determine which variables are statistically significant predictors for the conversion to MS.
Results: The 2017 revision had higher sensitivity (85 vs. 30% and 85 vs. 41%) and lower specificity (33 vs. 63% and 63 vs. 85%) compared to the 2010 revisions, for conversion to Poser CDMS and MS, respectively. Patients who did not meet the 2017 McDonald criteria had a higher chance of conversion-free survival for Poser CDMS than those who met the 2017 McDonald criteria (p=0.037). Results of the multivariate regression analysis revealed that patients who at baseline fulfilled 2017 revisions of the McDonald criteria have the increased likelihood of conversion to MS (Exp(B) 9.68, 95%CI 3.62 – 25.90, p<0.00001).
Conclusion: This study provides new information about the application of the 2017 revisions of the McDonald criteria in a Croatian cohort of patients with typical CIS.

Key words: multiple sclerosis, McDonald criteria, dissemination in time, dissemination in space, CSF-specific oligoclonal IgG bands, symptomatic lesions

Highlights

- During the 2-year follow-up, the 2017 revision had higher sensitivity and lower specificity compared to the 2010 revisions, for conversion to Poser CDMS and MS, respectively.
- During the 2-year follow-up, patients who did not meet the 2017 McDonald criteria had a higher chance of conversion-free survival for Poser CDMS than those who met the 2017 McDonald criteria.
- During the 2-year follow-up, patients who at baseline fulfilled 2017 revisions of the McDonald criteria have the increased likelihood of conversion to MS.

Introduction

Multiple sclerosis (MS) is a chronic, demyelinating, immune-mediated disorder of the central nervous system with progressive neuroaxonal degeneration (1). Although significant advances in the diagnosis and treatment of MS have been made, there is still a considerable delay between the onset of MS-characteristic symptoms and establishing the diagnosis and treating MS (2). The delay in the diagnosis and treatment can have devastating consequences on a person with MS (pwMS), as substantial evidence exists arguing that early treatment is more effective than treatment later in the disease course (3,4).

Over the years there have been several attempts to modify the criteria in order to establish the diagnosis of MS earlier and more easily (5, 6,7,8,9). Compared to the 2010 revisions, following changes have been made in in the recently published 2017 revisions to the McDonald criteria: 1) Cortical and juxtacortical lesions can be used in fulfilling MRI criteria for dissemination in space (DIS); 2) Symptomatic and asymptomatic MRI lesions can be considered in the determination of DIS or dissemination in time (DIT), and 3) In a patient with a typical CIS and fulfilment of DIS criteria, presence of CSF-specific IgG oligoclonal bands allows a diagnosis of MS (9).

As for any newly developed criteria, appropriate use and performance of the criteria across patient populations are essential. Therefore, the aim of this study was to compare the sensitivity, specificity, predictive value and accuracy of the 2010 and 2017 revisions of the McDonald criteria in a Croatian cohort of patients with a CIS, in order to evaluate the performance of the aforementioned criteria in the diagnosis of MS.

Methods

Patients

Patients were recruited from the database of BACIS project (10) in which consecutive patients with CIS were recruited into a two-year prospective clinical and neurophysiological follow-up from October 2014 until April 2016. All patients signed informed consent and the study was approved by Ethical Committees of the University Hospital Center Zagreb and the University of Zagreb, School of Medicine.

Baseline variables

For the purpose of the present study, data from all 128 patients participating in BACIS project were analyzed and only patients with available following data were included: definite diagnosis of CIS, a complete neurological examination, CSF analysis for the presence of CSF-specific oligoclonal IgG bands, visual evoked potentials, a baseline brain MRI obtained less than 3 months from the clinical onset, at least 1 follow-up brain MRI obtained in the second year of follow-up, completed two-year follow-up. Additionally, baseline cervical spinal cord MRI was analyzed when available.

A CIS is defined as an acute or subacute episode of neurological dysfunction due to inflammatory demyelination that lasts more than 24 hours and occurs in the absence of fever, infection or encephalopathy (11). CIS episodes were further divided into optic neuritis, transverse myelitis, brainstem/cerebellar syndromes, hemispheral syndromes (hemiparesis or homonymous hemianopia) and multifocal presentations. The presence of CSF-specific oligoclonal IgG bands was detected using isoelectric focusing and immunofixation. All the baseline brain MRIs were performed on 1.5 T scanners. Axial T2-weighted, fluid-attenuated

inversion recovery (FLAIR), and post-gadolinium T1-weighted sequences with 5 mm images were analyzed for the presence of lesions. Axial T2 cervical spinal cord sequence was analyzed only during the baseline visit, if available.
Baseline scans were scored for DIS and DIT according to the revised McDonald criteria from 2010 and 2017 (Table 2). Following this, we determined for each patient whether they met the criteria for the diagnosis of MS according to the revised McDonald criteria from 2010 and 2017, while taking into account clinical, MRI and CSF data.

Two-year follow-up variables
Two sets of analyses were performed to compare the 2010 and 2017 McDonald criteria.
The first analysis took into account patients who converted to MS during a two-year follow-up. Conversion to MS was defined if the patient who fulfilled clinical or MRI evidence for DIS, during the two-year follow-up fulfilled DIT, which was defined as the presence of one or both of the following parameters (3):

1. the patient developed a second relapse
2. ≥ 1 new T2 lesions on any of the follow-up MRIs

If an individual had a second relapse in the form of optic neuritis or transverse myelitis, a relevant MRI scan was not available, therefore a difference between clinical and MRI results was present.
The second analysis took into account only those patients who converted to clinically definite multiple sclerosis (Poser CDMS) according to the Poser criteria (i.e. experienced a second relapse) during the two-year follow-up, regardless of MRI findings.
For both analyses the MS relapse was defined as an occurrence of new or worsening neurological symptoms attributable to MS that met the following criteria: symptoms must persist for >24 hours and should not be attributable to confounding clinical factors (e.g. fever, infection, injury, adverse reactions to medications), symptoms should be preceded by neurological stability for at least 30 days, symptoms should be accompanied by new objective neurological worsening determined with EDSS/Functional Systems Score (FSS) assessment.
All follow-up MRIs were performed on 1.5 T scanners with the same sequences analyzed and compared with the baseline scans.
For both analysis, all patients who fulfilled either 2010 or 2017 criterion at baseline were considered as positive cases for that specific criterion and patients not meeting that criterion were considered as negative cases.
Patients who converted to MS or Poser CDMS and fulfilled 2010 or 2017 criteria were considered as true positive (TP). Patients who did not convert to MS or Poser CDMS and did not fulfill 2010 or 2017 criteria were considered as true negative (TN). Patients who converted to MS or Poser CDMS but did not fulfill 2010 or 2017 criteria were considered as false negative (FN). Patients who did not convert to MS or Poser CDMS but fulfilled 2010 or 2017 criteria were considered as false positive (FP). The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of the two versions of the McDonald's criteria were determined, separately for each analysis.

Primary outcomes
The primary outcomes were to determine sensitivity, specificity, predictive value and accuracy of the 2010 and 2017 revisions of the McDonald criteria and to compare the performance of both criteria in the diagnosis of MS.

Secondary outcomes

Secondary outcomes were to estimate the cumulative risk and hazard ratio of patients developing Poser CDMS using the 2010 and 2017 McDonald criteria during a two-year follow-up.

Furthermore, in order to examine the influence of the sex, age and 2010 or 2017 revisions to the McDonald criteria on the likelihood that patients will develop conversion to MS, a multivariate logistic regression model was used.

Statistical analysis

McNemar test was used to determine if there is a difference in dichotomous dependent variables (2010 McDonald criteria and 2017 McDonald criteria, McDonald criteria and frequency of conversion to MS/Poser CDMS). Survival analysis was performed in the form of Kaplan-Meier curves in order to estimate the cumulative risk of patients developing Poser CDMS, and in the form of the Cox regression model with the time to conversion to Poser CDMS as an outcome, in order to obtain hazard ratio (HR) adjusted for sex and age, for different versions of McDonald criteria.

Binary logistic regression model was used to determine which variables (sex, age, 2010 McDonald criteria or 2017 McDonald criteria) are statistically significant predictors for the conversion to MS.

Statistical analysis was performed using the IBM SPSS software, version 20. Two-tailed p values <0.05 were considered as statistically significant.

Results

Patients, baseline, and two-year follow-up variables

Altogether 113 patients with complete data were available for the analysis. Baseline patient characteristics are presented in Table 1. At the baseline visit, 39 (35%) and 83(74%) fulfilled the 2010 and 2017 revision of the McDonald criteria, respectively. Out of 44 patients who did not fulfill the 2010, but fulfilled the 2017 revision of the McDonald's criteria, 43 (98%) fulfilled the 2017 revision because of the presence of CSF-specific oligoclonal IgG bands, 6 (14%) because of the presence of symptomatic brainstem lesions and 9 (20%) because of the presence of symptomatic cervical spinal cord lesions (one patient could fulfill the 2017 revision of the McDonald's criteria due to more than 1 criteria).

None of the patients received disease modifying therapy until the occurrence of the second relapse. During the two-year follow up, 73 (65%) developed ≥1 new T2 lesion on one of the follow-up MRIs, while 40 (35%) developed a new relapse. Conversion to MS occurred in 86 (76%) and in Poser CDMS in 40 (35%) patients.

Primary outcomes

Sensitivity, specificity, predictive value and accuracy of the 2010 and 2017 revisions of the McDonald criteria for conversion to MS and Poser CDMS are presented in Table 3.

In order to compare the criteria, we used the McNemar test and all results are presented in Table 4. At the baseline visit, significantly more patients fulfilled 2017 revisions of the McDonald criteria than 2010 revisions of the McDonald criteria (83 vs. 39, $p<0.001$). A significant proportion of patients who converted to MS during the two-year follow-up (51

patients, 59% of all patients that converted to MS), did not fulfill 2010 revisions to the McDonald criteria at baseline (p<0.001). Only 31% (12 out of 39) patients who fulfilled 2010 revisions of the McDonald criteria did convert to Poser CDMS, but 62% (46 out of 74) patients who did not fulfill the 2010 criteria, also did not convert to Poser CDMS. Most of the patients who fulfilled 2017 revisions to the McDonald criteria at baseline converted to MS (88%, 73 out of 83). However, only 41% (34 out of 83) patients who fulfilled 2017 revisions to the McDonald criteria at baseline converted to Poser CDMS.

Secondary outcomes

Kaplan-Meier curves used to estimate the cumulative risk of patients developing Poser CDMS using the 2010 and 2017 McDonald criteria are shown in Figure 1. Patients who did not meet the 2017 McDonald criteria had a higher chance of conversion-free survival than those who met the 2017 McDonald criteria (figure 1, p=0.037), while for 2010 McDonald criteria there was no statistically significant difference in the survival distribution between two conditions. Results of the Cox regression analysis showed that adjusted hazard ratios for 2010 revisions to the McDonald criteria (HR=0.814, p=0.552) and 2017 revisions to the McDonald criteria (HR=2.333, p=0.056) were not statistically significant. Also, hazard ratios for sex and age were not statistically significant (all p values > 0.05).

The multivariate logistic regression model for the 2010 criteria was not statistically significant $\chi^2(3) = 6.931$, p=0.074. On the other hand, the multivariate logistic regression model for the 2017 criteria was statistically significant, $\chi^2(3) = 22.276$, p<0.0001 and it correctly classified 79.6% of cases. Results of the multivariate regression analysis revealed that patients who at baseline fulfilled 2017 revisions of the McDonald criteria have the increased likelihood of conversion to MS (Exp(B) 9.68, 95%CI 3.62 – 25.90, p<0.00001), while sex and age were not statistically significant predictors (p=0.832 and p=0.784).

Discussion

In this study we evaluated the performance of the 2010 and 2017 McDonald criteria in a cohort of patients who had a typical CIS in terms of Poser CDMS conversion at 2 years. We have found that both criteria had similar accuracy, with 2010 McDonald criteria having low sensitivity and moderate specificity, and 2017 McDonald criteria having high sensitivity and low specificity.

When we compared the 2010 and 2017 revisions of the McDonald criteria relating to the conversion to MS, a significant proportion of patients who converted to MS during the two-year follow-up, did not fulfill 2010 revisions to the McDonald criteria at baseline. Opposite to this, most of the patients who fulfilled 2017 revisions to the McDonald criteria at baseline converted to MS. Contrary, no difference was observed related to conversion to Poser CDMS. Similar to our observation, no difference was observed in previous studies when comparing the 2005 and 2010 revisions of the McDonalds criteria (12,13). It has to be emphasized that these differences depend on the duration of the follow-up, with longer follow-up yielding better congruence of the criteria (13). Furthermore, diagnosis of MS could be made in significantly higher number of patients and significantly faster with the 2017 criteria compared to 2010 criteria. The main reason for this is the inclusion of CSF-specific oligoclonal IgG bands in the 2017 revisions of the McDonald criteria, to substitute for the requirement of fulfilling DIT. Several studies have emphasized the importance of CSF-specific oligoclonal IgG bands in patients with CIS, with the evidence that the risk of conversion to MS substantially increases

if CSF-specific oligoclonal IgG bands are present at baseline (14,15). Another important factor in the 2017 revisions of the McDonald criteria is presence of symptomatic brainstem and spinal cord lesions. In our cohort, 6 patients did not meet 2010 revisions of the McDonald criteria because of presence of symptomatic brainstem and 9 because of presence of symptomatic spinal cord lesion. The 2017 revisions of the McDonald criteria no longer distinguish between symptomatic and asymptomatic lesions based on several studies showing that including lesions in the symptomatic region in DIS increases the sensitivity of MRI criteria for diagnosing MS without compromising specificity. (16,17)

Survival probability analyses showed that only patients who did not meet the 2017 McDonald criteria had a higher chance of conversion-free survival to Poser CDMS than those who met the 2017 McDonald criteria. In a recently published study comparing 2010 revisions of the McDonald criteria and the 2016 MAGNIMS criteria, patient not meeting both criteria had a higher chance of conversion-free survival (18). Furthermore, this study also showed that both sets of criteria according to adjusted hazard ratio, carried a significantly increased risk for conversion to Poser CDMS, while in our studies the risk was higher only for 2017 revisions of the McDonald criteria, although not statistically significant. This discrepancy could be explained with longer follow-up in the former study. However, when we performed multivariate logistic regression analysis, patients with CIS who fulfilled the 2017 revision of the McDonald criteria, had the increased likelihood of conversion to MS.

The main limitations of our study are small number of subjects, the short follow-up period and a retrospective design. However, we examined patients regularly every six-months in a prospective manner, with only 12% of the patients excluded from the analysis (either for alternate diagnosis or because they were lost to follow-up). Furthermore, there is a possibility of selection bias, because all patients were followed in a tertiary medical center. However, this is unlikely due to the organization of the neurology service in Croatia, where more than 60% of all pwMS in Croatia are being followed and more than 50% are receiving disease modifying therapy in our center. This argues that the obtain results may be applied to patients usually seen in clinical practice in Croatia or elsewhere in Europe. Thirdly, due to the MRI availability, MRI scans were acquired using different parameters (eg, slice thickness), but like previously reported, this approach allows to evaluate the MRI criteria in a situation close to a clinical setting (18).

In conclusion, this study provides new information about the application of the 2017 revisions of the McDonald criteria in a Croatian cohort of patients with typical CIS. While, we found no difference in the accuracy between 2010 and 2017 revisions related to conversion to Poser CDMS, the 2017 revisions of the McDonald criteria had higher accuracy when looking conversion to MS including MRI findings, allowing making the diagnosis of MS in a significant proportion of patients with CIS during the 2-year follow-up. These findings may assist in treatment decisions, as identification of patients with a higher probability of conversion to MS is associated with different treatment approaches compared to patients with lower probability of conversion.

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Table 1. Baseline characteristics

	Patients with CIS (N=113)
Demographic	
Age at onset	32.1±8.7
Sex	
Male	80 (70.8%)
Female	33 (29.2%)
Clinical	
EDSS at baseline	1.0 (0-3.5)
Type of CIS	
Monofocal	109 (96.5%)
Optic Neuritis	34 (30.1%)
Incomplete transverse myelitis	36 (31.9%)
Brainstem/cerebellar	27 (23.9%)
Hemispheral	12 (10.6%)
Multifocal	4 (3.5%)
Presence of oligoclonal IgG bands	94 (83.2%)
Meeting 2017 McDonald criteria because of oligoclonal IgG bands	43 (38.1%)
Neurophysiological	
Prolonged VEP latencies on the right eye	3 (2.7%)
Prolonged VEP latencies on the left eye	21 (18.6%)
MRI	
Presence of lesions	110 (97.3%)
Number of lesions	11 (0-76)
Presence of gadolinium-enhancing lesions	43 (38.1%)
Cervical spinal cord MRI available	85 (75%)
Presence of cervical spinal cord lesions (% of available MR scans)	48 (56%)
Not meeting 2010 McDonald criteria because of presence of symptomatic brainstem lesion	6 (5.3%)
Not meeting 2010 McDonald criteria because of presence of symptomatic spinal cord lesion	9 (8%)

EDSS – expanded disability status scale, CIS – clinically isolated syndrome, VEP – visual evoked potentials

Table 2. Differences in MRI dissemination in space and dissemination in time criteria between 2010 and 2017 McDonald's criteria.

	2010 McDonald's criteria	2017 McDonald's criteria
Dissemination is space	≥1 T2 lesion in at least 2 of 4 area of CNS: periventricular juxtacortical infratentorial* spinal cord*	≥1 T2 lesion in at least 2 of 4 area of CNS: periventricular cortical/juxtacortical infratentorial spinal cord
Dissemination in time	Simultaneous presence of asymptomatic gadolinium-enhancing and nonenhancing lesions.	Simultaneous presence of gadolinium-enhancing and nonenhancing lesions.

*In a subject with brainstem or spinal cord type of CIS, the symptomatic lesion is excluded from the count.

Table 3. Sensitivity, specificity, predictive value and accuracy of the 2010 and 2017 revisions to the McDonald criteria.

Conversion to MS									
	TP	FP	TN	FN	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Accuracy (95% CI)
2010	35	4	23	51	0.41 (0.30-0.52)	0.85 (0.66-0.96)	0.90 (0.77-0.96)	0.31 (0.26-0.36)	0.51 (0.42-0.61)
2017	73	10	17	13	0.85 (0.76-0.92)	0.63 (0.42-0.81)	0.88 (0.82-0.92)	0.57 (0.42-0.70)	0.80 (0.71-0.87)
Conversion to Poser CDMS									
2010	12	27	46	28	0.30 (0.17-0.47)	0.63 (0.51-0.74)	0.31 (0.20-0.44)	0.62 (0.56-0.68)	0.51 (0.42-0.61)
2017	34	49	24	6	0.85 (0.70-0.94)	0.33 (0.22-0.45)	0.41 (0.36-0.46)	0.80 (0.64-0.90)	0.51 (0.42-0.61)

MS – multiple sclerosis, CDMS – clinically definitive multiple sclerosis, TP – true positive, TN – true negative, FP – false positive, FN – false negative

Sensitivity = TP/(TP+FN)

Specificity = TN/(TN+FP)

PPV (positive predictive value) = TP/(TP+FP)

NPV (negative predictive value) = TN/(TN+FN)

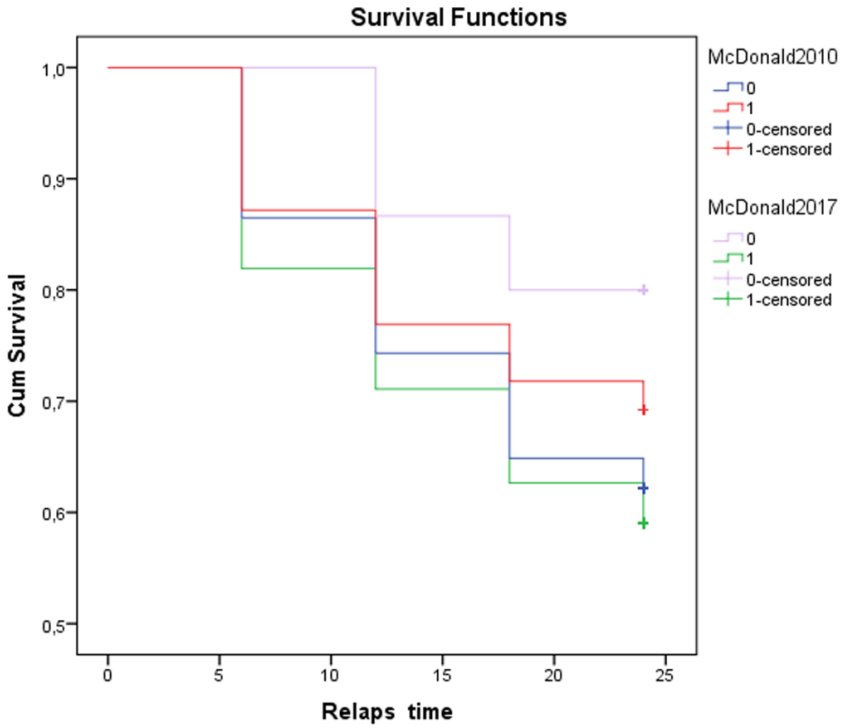
Accuracy = (TP+TN)/(TP+FP+TN+FN)

Table 4. Comparison between 2010 and 2017 revisions of the McDonald criteria using the McNemar test.

		Negative	Positive	P value
		McDonald 2017		
McDonald 2010	Negative	30	44	<0.001
	Positive	0	39	
		Conversion to MS		
McDonald 2010	Negative	23	51	<0.001
	Positive	4	35	
		Conversion to MS		
McDonald 2017	Negative	17	13	0.678
	Positive	10	73	
		Conversion to Poser CDMS		
McDonald 2010	Negative	46	28	1.000
	Positive	27	12	
		Conversion to Poser CDMS		
McDonald 2017	Negative	24	6	<0.001
	Positive	49	34	

Figures

Figure 1. Kaplan-Meier curves showing the survival probability estimates of not developing clinically definite multiple sclerosis two years from disease onset considering 2010 and 2017 McDonald criteria.



	0 month	6 months	12 months	18 months	24 months
2010 criteria					
negative	74	64	55	48	46
positive	39	34	30	28	27
2017 criteria					
negative	30	30	26	24	24
positive	83	68	59	52	49