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Composite Marker of Cognitive Dysfunction and Brain Atrophy is Highly Accurate in Discriminating Between Relapsing-Remitting and Secondary Progressive Multiple Sclerosis

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: With the advent of numerous new-generation disease-modifying drugs for multiple sclerosis (MS), the discrimination between relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS) has become a problem of high importance. The aim of our study was to find a simple way to accurately discriminate between RRMS and SPMS that is applicable in clinical practice as a composite marker, using the linear measures of magnetic resonance imaging (MRI) and the results of cognitive tests.

Material/Methods: We included 88 MS patients in the study: 43 participants had RRMS and 45 had SPMS. A battery consisting of 11 tests was used to evaluate cognitive function. We used 11 linear MRI measures and 7 indexes to assess brain atrophy.

Results: Four cognitive tests and 3 linear MRI measures were able to distinguish RRMS from SPMS with the AUC >0.8 based on ROC analysis. Multiple logistic regression models were constructed to identify the best set of cognitive and MRI markers. The model, using the Rey Auditory Verbal Learning Test (RAVLT), Digit Symbol Substitution Test (DSST), and Huckman Index, showed the highest predictive ability: AUC=0.921 ($p<0.001$). We constructed a simple remission-progression index from the same 3 variables, which discriminated well between RRMS and SPMS: AUC=0.920 ($p<0.001$), maximal Youden Index=0.702, cut-off=1.68, sensitivity=79.1%, and specificity=91.1%.

Conclusions: The composite remission-progression index, using the RAVLT test, DSST test, and MRI Huckman Index, is highly accurate in discriminating between RRMS and SPMS.

MeSH Keywords: Demyelinating Autoimmune Diseases, CNS • Magnetic Resonance Imaging • Multiple Sclerosis • Multiple Sclerosis, Chronic Progressive • Multiple Sclerosis, Relapsing-Remitting • Neuropsychological Tests

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Background

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system, which is characterized by clinical relapses and remissions and by progression of disability over time [1]. MS most often presents with a series of relapses and remissions as relapsing-remitting multiple sclerosis (RRMS), but then evolves over a variable period of time into a slowly progressive form of neurological dysfunction termed secondary progressive multiple sclerosis (SPMS) [2]. The reasons for this change in clinical presentation are not fully understood [2]. The defining feature of RRMS is the presence of stable periods of remission without progression of disability between relapses. The tracking of clinical presentation and the disability level, which is usually evaluated by the expanded disability status scale (EDSS), is the most common way to differentiate between RRMS and SPMS [3]. However, the clinical presentation does not always allow clear separation, and it is often difficult to distinguish the point of conversion from RRMS to SPMS [3]. The disability periodically increases and, at least partially, decreases during relapses of MS. The distinction is even more complicated by the fact that the patients with SPMS may continue to have relapses for several years. The defining feature of SPMS is the absence of stable remissions without progression of disability, regardless of whether the relapses still occur. The absence of more accurate independent diagnostic markers with longitudinal follow-up can lead to a lag-time of several years before a well-substantiated diagnosis of SPMS may be established [2].

Developing discriminating markers that can distinguish between the different clinical phenotypes of MS is an important goal to ensure that appropriate treatment is prescribed in a timely manner [3]. Furthermore, such markers may provide new insights into the pathological basis of progressive MS and lead to development of effective treatments for prevention of disability [3].

Although CNS magnetic resonance imaging (MRI) and various cognitive function tests have helped in the diagnosis of MS, they alone do not discriminate very well between the relapsing-remitting and secondary progressive forms in MS. Conventional MRI is a routine clinical test for the diagnosis and therapeutic follow-up of MS patients, but the effectiveness and specificity of MRI alone in distinguishing RRMS from SPMS is limited when inflammation and demyelination are the prevailing pathological basis of the disease and when axonal loss and neurodegeneration become key contributing factors in disability progression [1]. Therefore, numerous attempts have been made to find useful markers using other approaches, such as searching for new markers or combining ones that are already in use. A wide variety of studies have examined the ability of various methods to distinguish RRMS from SPMS, including cerebrospinal fluid (CSF) and blood biomarkers [4,5], metabolomic biofluid analysis [3], contingent negative variation [6], NMR/PLS-DA analysis of serum metabolite [3], high-performance liquid chromatography-coupled mass spectrometry (HPLC) [2], MR spectroscopy (MRS) [7], and circulating miRNAs [8]. None of these methods, however, are able to achieve satisfactory levels of differentiation of SPMS from RRMS and are not always available to apply in clinical practice.

Because patients with relapsing-remitting MS are more likely to respond to immunomodulatory disease-modifying treatment than those with a progressive MS course, there is great need to accurately diagnose the secondary progressive form of MS. Also, new drugs for treatment of secondary progressive form of MS are currently emerging [8]. These previously unavailable therapies can be very effective but possess many adverse effects; therefore, diagnostic error can be very harmful.

The aim of our study was to evaluate the ability of commonly used cognitive function tests and linear MRI measures to differentiate between the 2 most common clinical forms of MS (RR *vs.* SP). Based on these data, we constructed an optimal logistic regression model consisting of the cognitive function tests (behavioral markers) and MRI measurement variables (structural markers) that display the best AUC of ROC curves for differentiating RRMS from SPMS. We used the obtained results to build a remission-progression index that is easy to use in everyday clinical practice for the above-mentioned task.

Material and Methods

The study was performed at the Center for Neurology and the Center for Radiology of Vilnius University Hospital "Santariskiu Klinikos" during the period 2015–2016. The study participants were recruited using the Electronic Multiple Sclerosis Patients' Monitoring System, which allows constant longitudinal follow-up of physical, neurological, clinical, laboratory, MRI, treatment, and disability data of MS patients. Only MS patients with longitudinally documented and unequivocal RRMS and SPMS were enrolled in the study. All MS patients with uncertain clinical subtype (RRMS or SPMS) were excluded from the study.

The study protocol was approved by the Lithuanian Bioethics Committee. All participants signed an informed consent before the start of study procedures.

Inclusion and exclusion criteria

Principal inclusion and exclusion criteria for MS patients were:

1) The age of participants – 18 years and more;
2) MS diagnosis was established according to the revised McDonald criteria 2010;

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Table 1. Classification of the brain MRI lesions.

Variants of MRI classification*	1	2	3	4
T2W	0	1–2	3–8	9+
Infratentorial	0	1+		
Juxtacortical	0	1+		
Periventricular	0	1–2	3+	
T1W „black holes“	0	1–2	3+	

3) The participants should not have any concomitant diseases causing neurological physical disability, psychiatric disorders, or diseases affecting cognitive functions;
4) The participants should not be treated at least for 1 month prior to inclusion in the study with any medications affecting cognitive functions (e.g., antidepressants, anxiolytics, antipsychotics, H_2 blockers, opioids, and anticholinergics);
5) MS patients should not be treated at least for 2 weeks prior to inclusion in the study with high doses of intravenous methylprednisolone and/or plasma exchange and at least for 6 months did not receive long-term oral prednisolone therapy;
6) Brain MRIs for MS patients were performed not earlier than 2 weeks before cognitive examination. Demyelinating focal lesions had to fulfill radiological Barkhof criteria for MS radiological diagnosis.

Any conditions not fulfilling inclusion criteria were considered as exclusion criteria.

Neurological examination was performed and laboratory investigations were made to exclude other neurological and other somatic diseases. General physical disability of MS patients was evaluated by use of the EDSS scale.

Cognitive testing instruments

To assess cognitive function, a cognitive test battery consisting of 11 cognitive tests and subtests was applied:
1) Working memory and attention were assessed by the Digit Span Forwards Test (DSf) and Digit Span Backwards Test (DSb);
2) Speed of psychomotor reactions and attention were tested by using the Digit Symbol Substitution Test (DSST);
3) Attention concentration and mental flexibility were tested by the Trail Making Test-A, (TMT-A) and Trail Making Test-B (TMT-B);
4) Executive function (pattern fluency similar to verbal fluency tests) and attention were evaluated by the Five Point Test (FPT);
5) Verbal memory and verbal learning were evaluated by the Rey Auditory Verbal Learning Test (RAVLT);
6) Verbal delayed recall and recognition were tested by a variant of the RAVLT Words Recognition Test;
7) Verbal fluency was evaluated by the Letter Fluency Test (LFT-P,A,S) and Category Fluency Test (CATflT);
8) Visual constructive memory was tested using the Rey-Osterrieth Complex Figure Test (ROCFT);
9) Logical memory was evaluated by the Short Story Test (Story);
10) Semantic memory was assessed by the Word Pair Association Test (WPA);
11) Conceptual reasoning and executive function were tested by the Cognitive Estimation Test, Axelrot Miles (Cog ET).

MRI scans

Magnetic resonance imaging was performed using a 1.5 Tesla scanner Magnetom Symphony (Siemens, Germany). MRI examinations included the following sequences: T1 (repetition time 526 ms, echo time 14 ms), T2 (repetition time 4110 ms, echo time 105 ms) and fluid-attenuated inversion recovery (FLAIR) T2 (repetition time 9000 ms, echo time 122 ms). Slice thickness was 5 mm. A radiologist who was blinded to the patient's MS diagnosis and clinical data rated brain lesions and calculated linear measures of brain atrophy. T2W and T1W lesion load was calculated and classified according to the scheme, taking into account the amount and localization of T2W and T1W lesions (Table 1).

Linear MRI parameters for measuring brain atrophy were applied: width of third ventricle, bicaudatus index, bifrontal index, Huckman Index, index of frontal atrophy, Evans index and index of corpus callosum (Table 2).

Statistical analysis

Data were analyzed with SPSS 17.0 (version for Windows) and SAS 9.2 (version for Windows). For quantitative data, descriptive statistics are presented as Mean ±SD. For categorical data, frequencies are reported. For quantitative variables, we used the *t* test or Mann-Whitney U test for comparing 2 groups. To avoid the possible influence of age, RRMS and SPMS groups were also compared according to cognitive function and MRI

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Table 2. Brain MRI linear measures of atrophy and indexes.

No.	Linear measure	The definition of the linear measure	Index (if several linear measures are included)	Ratio of measures
1	E	The width of third ventricle	The width of third ventricle	E
2	D	Min distance between *nuclei caudati*	Bicaudatus index	D/I
3	I	Max distance between lateral brain limits at the level of nuclei caudati	Bicaudatus index	D/I
4	F	Max distance between lateral ventricles posterior horns	Bifrontal index	F/C
5	C	Max distance between lateral ventricles anterior horns	Bifrontal index	F/C
	C	Max distance between lateral ventricles anterior horns	Huckman index	C+D
	D	Min distance between *nuclei caudati*	Huckman index	C+D
	C	Max distance between lateral ventricles anterior horns	Index of frontal atrophy	C/O
6	O	Max distance between lateral brain dimensions (lateral horns) in the same level	Index of frontal atrophy	C/O
7	G	Distance between third ventricle and *sulcus Sylvii*	G	G/H
8	H	Max distance between lateral brain dimensions in the same level	H	G/H
	C	Max distance between lateral ventricles anterior horns	Evans index	C/A
9	A	Max brain dimension	Evans infex	C/A
10	L	Dimension of anterior part of *corpus callosum*	L/K Index of *corpus callosum*	L/K
11	K	Total sagital dimension of *corpus callosum*	L/K Index of *corpus callosum*	L/K

Max – maximal; Min – minimal; A – Max brain dimension; C – Max distance between lateral ventricles anterior horns; O – Max distance between lateral brain dimensions (lateral horns) in the same level; D – Min distance between nucleus caudatus; I – Max distance between lateral brain dimensions in the same level (*nucleus caudatus*); E – the width of third ventricle; F – Max distance between lateral ventricles posterior horns; G – distance between third ventricle and *sulcus Sylvii*; H – Max distance between lateral brain dimensions in the same (III ventr.- *sulcus Sylvii*) level.

measurements by means of covariance analysis (ANCOVA). Comparing 2 groups with respect to categorical variables, the chi-square test or Fisher's exact test were used. ROC analysis was applied to determine the predictors most suitable to discriminate between RRMS and SPMS. Then, we constructed numerous multiple logistic regression models to determine which one of the combined cognitive function and MRI measurements markers had the best predictive ability to discriminate between RRMS versus SPMS. The level of significance was set at 0.05. One-sided p values were not used.

Results

Demographical characteristics

The study included 88 patients, of whom 43 (48.9%) had RRMS and 45 (51.1%) had SPMS. Demographic characteristics of both groups are presented in Table 3. The groups did not differ according to education and MS anamnesis, but differed with respect to all other factors. Regarding the number of lesions on the MRI scans, it is important to note that the groups were not significantly different; however, the SP group tended to have more T2W lesions (Table 4).

Comparison of RRMS and SPMS groups according to cognitive function and MRI measurements

Since our main goal was to find the cognitive function tests and MRI measurements which were appropriate to discriminate between RRMS and SPMS, we compared groups with respect to cognitive function and MRI measurements. Comparisons were made in 2 ways: using the *t* test (or Mann-Whitney test) and by means of covariance analysis (Table 5). The latter was done to account for possible age and education influence, which were included as additional covariates into the model.

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Table 3. Demographic and clinical characteristics of the study participants.

Variable	RR (n=43)	SP (n=45)	P value
Age in years	33.65±9.23	47.82±7.72	<0.001
Male/female	15 (34.9%)/28 (65.1%)	16 (35.6%)/29 (64.4%)	0.947 ns
Duration of education in years	14.31±2.67	13.09±2.67	0.026
MS anamnesis*	2 (4.7%)	4 (8.9%)	0.677 ns
EDSS (total)	2.84±1.36	4.91±1.32	<0.001
MS duration in months	90.53±68.74	222.11±91.78	<0.001

* The patient has relatives with MS.

Table 4. Radiological characterization of MRI scans.

	RR (n=43)	AP (n=45)	P value
T1W			
0	13 (31.7%)	6 (13.3%)	0.114
1–2	12 (29.3%)	15 (33.3%)	
3+	16 (39.0%)	24 (53.3%)	
T2W			
0	0 (0.0%)	0 (0.0%)	
1–2	5 (11.6%)	1 (2.2%)	0.063
3–8	14 (32.6%)	9 (20.0%)	
9+	24 (55.8%)	35 (77.8%)	

Discriminative ability of cognitive tests results and MRI atrophy measurements

Taking into account the results of comparisons presented in Table 3, we calculated the area under receiver operator curve (AUC) for the variables that significantly differed between groups. Values of corresponding AUCs are presented in Table 6. For brevity, we report only the values that exceed 0.8. DSST had the best overall predictive ability and also the best predictive ability among cognitive function tests. The bicaudatus ratio had the best predictive ability among MRI measurements.

It is usually the case that models involving several variables perform better than the single variables do. We aimed to build a model involving as many variables as possible, presented in Table 6, while maintaining the p value of the variables in the model below 0.05 and avoiding multicollinearity. For these reasons and practical applicability of the model, we aimed to include both cognitive test results and linear measurements of magnetic resonance imaging (MRI). Taking into account these factors, we have determined that the best was the model presented in Table 7.

The best multivariate logistic regression model included the 3 analytes (2 cognitive function tests results: the sum of the recalled words in the first 5 attempts to learn the word list of the RAVLT test and DSST; and 1 MRI measurement: Huckman Index) as independent variables and the clinical MS forms (relapsing-remitting *vs.* secondary progressive) as the dichotomous target variable. We obtained a model that included the 3 analytes as predictors for the MS clinical form. With the obtained binary logistic regression model, we can calculate the probability for a patient to be diagnosed with progressive MS. The probability for a specific patient to be diagnosed with the progressive form is given in the model by the coefficient on the constant term 4.109 and the 3 individual coefficients:

$$\ln(p/(1-p))=\beta_0+\beta_1 X_1+\beta_2 \beta_2+\beta_3 X_3$$

For instance, for a patient with values of RAVLT (1–5 sum)=26, DSST=15, and Huckman Index=46.40, the model assigns a 0.93818=93.818% probability of having a progressive form. Huckman Index with odds ratio (OR) OR >1 (Table 7) is a risk factor for having a progressive clinical form of MS, while the sum of the recalled words in the first 5 attempts to learn the word list of the RAVLT test and DSST result with OR <1 are

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Table 5. Comparison of RRMS and SPMS groups according to Cognitive tests results and MRI atrophy measurements*.

Cognitive function test/MRI measurement Mean ±SD	RRMS (n=43)	SPMS (n=45)	P value (1)	P value (2)
Index of frontal atrophy	0.30±0.03	0.37±0.19	<0.031	<0.226 ns
Index of Evans	0.25±0.03	0.28±0.03	<0.001	<0.001
Huckman index	47.00±6.63	55.30±7.85	<0.001	<0.001
Bicaudatus index	0.12±0.02	0.16±0.03	<0.001	<0.001
Width of third ventricle	4.65±1.64	7.28±1.92	<0.001	<0.001
Bifrontal index	1.86±0.23	1.86±0.22	0.396 ns	0.174 ns
Index of corpus callosum	0.16±0.02	0.13±0.03	0.063 ns	0.670 ns
DSF	4.88±0.98	5.20±3.47	0.566 ns	0.151 ns
DSB	3.90±0.85	3.42±1.01	0.019	0.371 ns
DSST	45.05±13.53	23.40±13.43	<0.001	<0.001
TMTA	49.51±25.54	99.11±86.58	<0.001	0.023
TMTB	135.49±26.39	238.059±26.805	<0.001	0.018
FPT	23.67±9.99	15.42±8.66	<0.001	0.059 ns
ROCFT_copy	35.13±1.62	32.63±6.30	0.014	0.304 ns
LFT_D	10.26±3.40	8.07±3.86	0.006	0.144 ns
LFT_A	9.63±3.57	7.82±3.60	0.021	0.124 ns
LFT_S	10.63±3.33	8.11±3.37	0.001	0.127 ns
CATflT	19.67±4.76	15.38±4.77	<0.001	0.006
IST, *Story*	15.60±4.20	11.00±4.24	<0.001	0.004
RAVLT 1-5 SUM**	51.40±7.70	38.12±9.39	0.001	0.02
WPA_1	8.30±1.54	7.40±2.03	0.021	0.232 ns
WPA_2	8.42±1.50	7.33±2.08	0.006	<0.222 ns

* "P value (1)" corresponds to a p value obtained by t-test or Mann-Whitney test; "P value (2)" corresponds to a p value obtained by means of covariance analysis (ANCOVA) with age and education as covariates; ns – not significant; ** the sum of the recalled words in the first 5 attempts to learn the word list of the RAVLT test.

protective factors for already being in the stage of the secondary progressive clinical form of MS. The characteristics of the best multivariate logistic regression model are provided in Table 8.

Considering odds >/< 1 (i.e., a greater/less probability of having a progressive versus RRMS clinical form according to the model) as a positive/negative prognosis, the model gives a sensitivity of 90.7%, a specificity of 80.0%, a positive predictive value (PPV) of 83.7%, a negative predictive value of 84.4%, and an accuracy of 84.1% for our cohort of MS patients. Each of the analytes included in the best model by multivariate logistic regression analysis was independently analyzed by univariate regression analysis (ROC analysis) for its predictive ability to discriminate between SPMS and a RRMS patients. Cut-off values for individual variables of the regression are provided in Table 9.

For each analyte, a specific cut-off value: <45.5, DSST <29.5 and Huckman Index >46.35 could discriminate with different sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy between progressive and RR-MS patients. This multivariate logistic regression model gave the highest sensitivity and specificity. The ROC curve based on the results of multiple logistic regression analysis is provided in Figure 1.

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Table 6. Values of AUC for discrimination between RRMS and SPMS*.

Variable	AUC (SE)	95% CI	p value	Direction**
DSST	0.873 (0.038)	(0.799; 0.947)	<0.001	–
RAVLT 1-5 SUM	0.865 (0.037)	(0.792; 0.939)	<0.001	–
Bicaudatus index	0.864 (0.038)	(0.789; 0.938)	<0.001	+
Width of third ventricle	0.846 (0.042)	(0.764; 0.928)	<0.001	+
TMA	0.816 (0.045)	(0.728; 0.905)	<0.001	+
TMB	0.814 (0.045)	(0.725; 0.903)	<0.001	+
Huckman index	0.802 (0.047)	(0.709; 0.894)	<0.001	+

* For each variable AUC with standard error is reported (AUC (SE)); p value shows, whether corresponding AUC significantly differs from 0.5; ** falling into SPMS group was treated as event; "+" means that greater values of variable indicate SPMS whereas "–" means that greater values of variable indicate RRMS.

Table 7. Summary of the best multivariate logistic regression model.

Variable	β (SE)*		p value	OR (95% CI)	
RAVLT 1-5 SUM	–0.114	(0.50)	0.024	0.893	(0.809; 0.985)
DSST	–0.069	(0.029)	0.017	0.993	(0.809; 0.988)
Huckman index	0.120	(0.046)	0.01	1.127	(1.03; 1.234)
Constant	1.413	(3.243)	0.663	4.109	

* Regression coefficient and standard error (β (SE)).

Table 8. Characteristics of the best multivariate logistic regression model.

AUC (95% CI)*	Sensitivity	Specificity	Accuracy	Youden's index
0.921 (0.866; 0.976)	90.7%	80.0%	84.1%	0.707

* AUC significantly differed from 0.5 (p<0.001); standard error for the AUC was equal to 0.029.

Table 9. Cut-off values for individual variables of the regression.

Variable	Cut-off	Sensitivity	Specificity	Youden's index
RAVLT 1-5 SUM	45.5	79.1%	75.6%	0.546
DSST	29.5	93.0%	73.3%	0.664
Huckman index	46.35	55.8%	95.6%	0.514

Remission-progression index

For the purposes of everyday clinical practice, the above-mentioned logistic regression formula is not practical. The formula is too computationally complex for a practitioner to apply it in daily practice for differentiating the 2 clinical forms of MS. Therefore, we constructed a simple, arithmetically computable index, in which the ability to distinguish RRMS from SPMS is only slightly lower than of the above-mentioned binary logistic regression, and it is easy to use this "remission-progression index" in everyday clinical practice. The remission-progression (RP) index can be calculated using the simple arithmetic formula:

Remission-Progression Index
=(RAVLT 1–5 SUM + DSST)/Huckman Index

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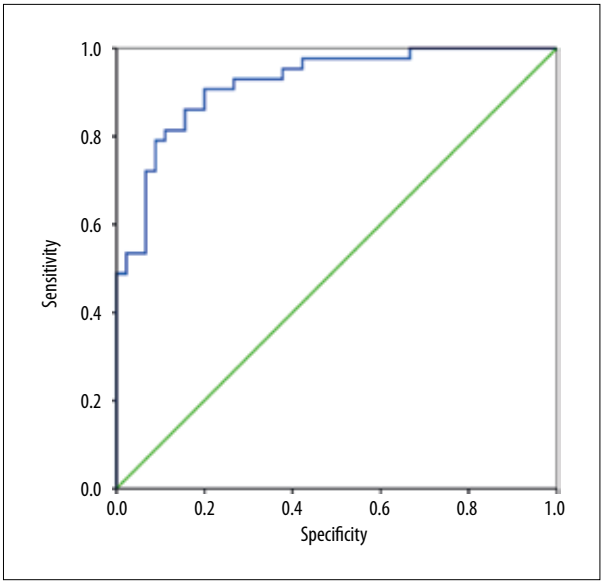

Figure 1. Receiver operating characteristics (ROC) curve of the composite marker, including RAVLT, DSST, and Huckman Index, for the discrimination of RRMS and SPMS based on the results of multiple logistic regression analysis.

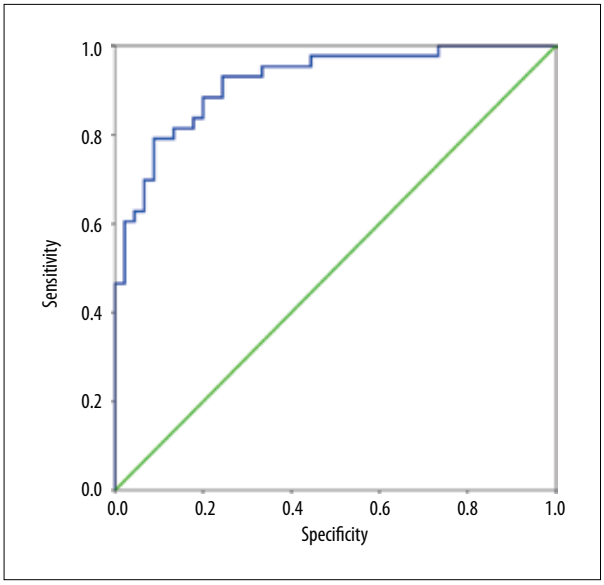

Figure 2. Receiver operating characteristics (ROC) curve of the remission-progression index, including RAVLT, DSST, and Huckman Index, for the discrimination of RRMS and SPMS.

Table 10. Characteristics of the remission-progression index.

Cut-off	AUC (95% CI)*	Sensitivity	Specificity	Youden's Index
1.68	0.920 (0.864; 0.975)	79.1%	91.1%	0.702

* AUC significantly differed ($p<0.001$) from 0.5 (Null hypothesis true ares=0.5); standard error for the AUC was equal to 0.029.

The characteristics of the remission-progression index are provided in Table 10. The ROC curve for the remission-progression index is provided in Figure 2.

Discussion

There are a significant number of biomarkers for the diagnosis of multiple sclerosis, but the same markers cannot usually be applied to distinguish between RRMS and SPMS [9–11]. The course of multiple sclerosis and the response to treatment is highly variable and there is urgent need to recognize and predict outcomes in individual MS patients that could enable more personalized treatment strategies. The number of potential biomarkers that are studied for differentiating clinical forms of MS is large, but the limited information on their independent diagnostic/prognostic value and the lack of validation in independent patient cohorts are major limits to their use in routine clinical practice [12]. We examined various neuropsychological tests (behavioral markers) and linear MRI brain atrophy measurements (structural markers), extracted the ones with the best ROC curve AUC values, and built an optimal binary logistic regression model involving cognitive function tests as well as MRI brain atrophy measurements.

Brain atrophy as an important feature of MS pathophysiological development was recognized since the earliest MRI studies of MS [13,14]. The degree of brain atrophy seems to correlate with progressing disability better than other MRI features, such as brain demyelinating lesions [13,14]. A study by Fisher et al. (2008) showed that the rate of atrophy differs between the different clinical groups of MS [15]. Our data indicate that there are significant differences in the degree of brain atrophy in different clinical MS subtypes (RR and SP), which correlates with verbal memory impairment and other neurocognitive symptoms and can also be used for subtyping the diagnosis of MS, which is in line with other reports [16]. We used linear measurements as markers of brain atrophy because they are easy to use in clinical practice, do not require volumetric analysis software, and have been evaluated as valid brain atrophy measures for use in monitoring MS progression [17].

Results in Table 6 indicate that, individually, bicaudatus ratio, the width of the third ventricle, and Huckman Index are the

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linear MRI measurements that properly classify the most cases when comparing RRMS and SPMS groups, and therefore can be used as differentiating markers. Nearly all performed linear measurements (with the exception of bifrontal index and index of corpus callosum) showed significant differences between the clinical groups. Bicaudatus ratio and the width of the third ventricle were correlated mostly with the performed cognitive tests (bicaudatus: r=–0.532 with DSST, p<0.001 and r=–0.527 with RAVLT1-5 SUM, p<0.05, width of the third ventricle: r=–0.534 with DSST, p<0.001 and r=–0.515 with RAVLT1–5 SUM, p<0.05). These results agree with the findings of a previous study by Bermel et al., which established that the bicaudatus ratio is highly related to cognitive dysfunction in MS patients and closely correlates with SDMT cognitive test results [18]. Nevertheless, it should be noted that no single indicator, neither cognitive nor MRI measures, reached an AUC above 0.9 in ROC analysis, while composite markers used in our analysis exceeded AUC 0.92.

We included the Huckman Index instead of bicaudatus ratio or width of third ventricle in our final logistic regression model and remission-progression index, because multiple logistic regression models with bicaudatus ratio or width of third ventricle produced models with at least 1 of the independent variables not statistically significant.

There clearly are significant differences in cognitive dysfunction between RRMS and SPMS patient groups (Table 5). Even though the general relationship between the progression of MS and cognitive impairment level is not universally agreed on, most studies indicate that patients with progressive subtypes of MS are more likely to exhibit cognitive impairment in general, and that cognitive dysfunction tends to progress over time [19,20]. Nearly all performed tests were able to identify significant differences between groups, but the difference was most clearly evident in DSST and RAVLT results. Both of these tests were included in our final logistic regression model and remission-progression index. The DSST is similar to the SDMT, which is included in the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) [21,22]. This supports the opinion that memory, complex attention, information-processing speed, and executive functions are the most commonly involved domains in people with MS [20].

Our multiple logistic regression model yielded 0.921 AUC value, 90.7%, sensitivity and 80.0% specificity. We have found few studies aiming to use different types of measures to construct a better-performing composite marker for clinical subtyping of MS. In comparison to a similar study by Tejera-Alhambra et al. (2015), where a model to predict clinical subtype of MS from plasma biomarkers (a combination of 4 plasma proteins: hepatocyte growth factor (HGF), eotaxin, epidermal growth factor (EGF), and macrophage inflammatory protein (MIP)-1β) was constructed, the sensitivity was 71.7% and specificity was 89.9% [4]. Another recent study by Dickens et al. (2015) tested whether it is possible to differentiate RRMS from SPMS using a combination of nuclear magnetic resonance (NMR) metabolomics and partial least-squares discriminant analysis (PLS-DA) of biofluids [3]. The results of distinguishing RRMS from SPMS were a sensitivity of –0.9 and specificity of –0.8 [3]. Other studies in MS usually compared individual biomarkers for their predictive value of disease subtyping. However, most of their predictive values were quite low [10,23–26].

In an article by Lublin et al., it was stated that "to date, there are no clear clinical, imaging, immunologic, or pathologic criteria to determine the transition point when RRMS converts to SPMS; the transition is usually gradual. This has limited our ability to study the imaging and biomarker characteristics that may distinguish this course." Even though it is difficult to determine the exact transition point at which RRMS converts to SPMS, the distinction of individual cases of RRMS and SPMS has a great significance for decisions regarding treatment selection. Our study provides further insights into the distinctive abilities of a large array of cognitive function measurements and MRI markers in MS, and offers a useful tool for differentiating RRMS from SPMS that is easy to use in clinical practice.

Conclusions

The composite remission-progression index, including the sum of the recalled words in the first 5 trials of the RAVLT test, DSST test results, and the MRI Huckman Index, is able to discriminate RRMS and SPMS with high accuracy.

Conflicts of interests

The authors have no conflicts of interest to declare.

References:

1. Obert D, Helms G, Sättler MB et al: Brain metabolite changes in patients with relapsing-remitting and secondary progressive multiple sclerosis: A two-year follow-up study. PLoS One, 2016; 11(9): e0162583
2. Jia Y, Wu T, Jelinek CA et al: Development of protein biomarkers in cerebrospinal fluid for secondary progressive multiple sclerosis using selected reaction monitoring mass spectrometry (SRM-MS). Clin Proteomics, 2012; 9(1): 9
3. Dickens AM, Larkin JR, Griffin JL et al: A type 2 biomarker separates relapsing-remitting from secondary progressive multiple sclerosis. Neurology, 2014; 83(17): 1492–99
4. Tejera-Alhambra M, Casrouge A, de Andrés C et al: Plasma biomarkers discriminate clinical forms of multiple sclerosis. PLoS One, 2015; 10(6): e0128952

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

5. Teunissen CE, Koel-Simmelink MJ, Pham TV et al: Identification of biomarkers for diagnosis and progression of MS by MALDI-TOF mass spectrometry. Mult Scler, 2011; 17(7): 838–50
6. Uysal U, Idiman F, Idiman E et al: Contingent negative variation is associated with cognitive dysfunction and secondary progressive disease course in multiple sclerosis. J Clin Neurol, 2014; 10(4): 296–303
7. Narayana PA: Magnetic resonance spectroscopy in the monitoring of multiple sclerosis. J Neuroimaging, 2005; 15(4 Suppl.): 46S–57S
8. Vistbakka J, Elovaara I, Lehtimäki T, Hagman S: Circulating microRNAs as biomarkers in progressive multiple sclerosis. Mult Scler, 2016 [Epub ahead of print].
9. Teunissen CE, Malekzadeh A, Leurs C et al: Body fluid biomarkers for multiple sclerosis – the long road to clinical application. Nat Rev Neurol, 2015; 11(10): 585–96
10. Katsavos S, Anagnostouli M: Biomarkers in multiple sclerosis: an up-to-date overview. Mult Scler Int, 2013; 2013: 340508
11. Comabella M, Montalban X: Body fluid biomarkers in multiple sclerosis. Lancet Neurol, 2014; 13(1): 113–26
12. Tejera-Alhambra M, Fernández-Paredes L, de Andrés C, Sánchez-Ramón S: Multiple Sclerosis: Where do we go from here? EMJ Neurol, 2016; 4(1): 84–95
13. Giorgio A, Battaglini M, Smith SM, De Stefano N: Brain atrophy assessment in multiple sclerosis: importance and limitations. Neuroimaging Clin N Am, 2008; 18(4): 675–86
14. Filippi M, Agosta F: Imaging biomarkers in multiple sclerosis. J Magn Reson Imaging, 2010; 31(4): 770–88
15. Fisher E, Lee JC, Nakamura K, Rudick RA: Gray matter atrophy in multiple sclerosis: A longitudinal study. Ann Neurol, 2008; 64(3): 255–65
16. Sanfilipo MP, Benedict RH, Weinstock-Guttman B, Bakshi R: Gray and white matter brain atrophy and neuropsychological impairment in multiple sclerosis. Neurology, 2006; 66(5): 685–92
17. Butzkueven H, Kolbe SC, Jolley DJ et al: Validation of linear cerebral atrophy markers in multiple sclerosis. J Clin Neurosci, 2008; 15(2): 130–37
18. Bermel RA, Bakshi R, Tjoa C et al: Bicaudate ratio as a magnetic resonance imaging marker of brain atrophy in multiple sclerosis. Arch Neurol, 2002; 59(2): 275–80
19. Rahn K, Slusher B, Kaplin A: Cognitive impairment in multiple sclerosis: A forgotten disability remembered. Cerebrum, 2012; 2012: 14
20. Amato MP, Portaccio E, Goretti B et al: Cognitive impairment in early stages of multiple sclerosis. Neurol Sci, 2010; 31(Suppl. 2): S211–14
21. Langdon DW, Amato MP, Boringa J et al: Recommendations for a Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS). Mult Scler, 2012; 18(6): 891–98
22. Parmenter BA, Weinstock-Guttman B, Garg N et al: Screening for cognitive impairment in multiple sclerosis using the Symbol digit Modalities Test. Mult Scler, 2007; 13(1): 52–57
23. Whitaker JN, Kachelhofer RD, Bradley EL et al: Urinary myelin basic protein-like material as a correlate of the progression of multiple sclerosis. Ann Neurol, 1995; 38(4): 625–32
24. Ott M, Demisch L, Engelhardt W, Fischer PA: Interleukin-2, soluble interleukin-2-receptor, neopterin, L-tryptophan and beta 2-microglobulin levels in CSF and serum of patients with relapsing-remitting or chronic-progressive multiple sclerosis. J Neurol, 1993; 241(2): 108–14
25. Giovannoni G, Lai M, Kidd D et al: Daily urinary neopterin excretion as an immunological marker of disease activity in multiple sclerosis. Brain, 1997; 120: 1–13
26. Kuhle J, Leppert D, Petzold A et al: Neurofilament heavy chain in CSF correlates with relapses and disability in multiple sclerosis. Neurology, 2011; 76(14): 1206–13
27. Lublin FD, Reingold SC, Cohen JA et al: Defining the clinical course of multiple sclerosis: The 2013 revisions. Neurology, 2014; 83(3): 278–86

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]