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Inclusion of the Symbol Digit Modalities Test in a revised assessment of 'no evidence of disease activity-4 (NEDA-4)' in Latin-American patients with multiple sclerosis

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ABSTRACT

Background: : In relapsing-remitting multiple sclerosis (RRMS), no evidence of disease activity-3 (NEDA-3) is defined as the absence of: (1) relapses; (2) disability progression; (3) MRI activity (new/enlarged T2 lesions and/or gadolinium-enhanced T1 lesions). NEDA-4 status is defined as meeting all NEDA-3 criteria plus having an annualized percentage brain volume change (a-PBVC) >-0.4%. In individual patients, brain volume assessment is confounded with normal aging, methodological limitations and fluid-shift related fluctuations in brain volume. Cognitive impairment has been proposed as another component that should be integrated into therapeutic algorithms for RRMS. We aim to determine the proportion of patients failing to meet NEDA-4 criteria and to appraise whether the Symbol Digit Modalities Test (SDMT) is capable of replacing a-PBVC as one of the components of NEDA-4. We hypothesize that NEDA-4 has the potential to capture the impact of DMT therapies in RRMS.

Methods: : Forty-five patients were prospectively followed 1 and 2 years after their baseline assessment at the University of Chile Hospital. SIENA software was used to assess a-PBVC.

Results: : At baseline, the patients had a mean age of 33.0 years (range 18–57), disease duration of 1.9 years (0.4–4), Expanded Disability Status Scale score of 1.3 (0–4), and 67% were female. The majority had RRMS (91% while 9% had clinically isolated syndrome (CIS)). Seventy-three percent were on the so-called first line DMTs such as interferons (53%), glatiramer acetate (13%), teriflunomide (9%), and 18% were on fingolimod. There was a serial decline in the proportion of NEDA: after 1 and 2 years of follow-up 60% and 47% met NEDA-3 status, and 38% and 27% met NEDA-4, respectively. At the last follow-up 21% remained on interferons, 47% were now on fingolimod, 4% on alemtuzumab and 2% on natalizumab. At year 1 and year 2, with the replacement of a-PBVC by SDMT, 53% and 40% of patients achieved a putative NEDA-4 status, respectively.

Conclusion: : Brain volumetric MRI has yet to be translated into clinical practice and SDMT may qualify as the fourth component of NEDA-4 definition. NEDA-4 has the potential to capture the impact of DMT therapies in RRMS earlier in the disease course of RRMS.

1. Introduction

Combined disease status assessments are increasingly explored to evaluate the overall impact of disease modifying treatments (DMTs) in relapsing-remitting multiple sclerosis (RRMS). During 2018–2019 a number of studies with real-world clinical data on No Evidence of Disease Activity-3 (NEDA-3) have been published (Table 1). NEDA-3 is defined as the absence of: (1) relapses; (2) disability progression; (3) MRI activity (new/enlarged T2 lesions and/or gadolinium-enhanced T1 lesions). However, individual components of NEDA-3 are somewhat impractical and their exact definitions vary in routine clinical practice for assessing ongoing disease activity (Hegen et al., 2018).

Disease activity follow-up may be improved by considering quantitative magnetic resonance imaging (qMRI). In the present study, structural image evaluation, using normalization, of atrophy (SIENA) (Smith et al., 2001) was used to explore

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Table 1
Studies reporting NEDA-3 and NEDA-4 outcomes.

Reference	*Prospective Retrospective*	*Real world (RW) vs. Clinical trials (CT)*	*N (>20)*	DMT	Time Point, years	% reaching NEDA-3	% reaching NEDA-4 (*N*)
Nygaard et al., 2015	Prospective	RW	72	I-GA-F-N*	1	54	nr
Huhn et al., 2019	Retrospective	RW	306	EMA**	1	45	nr
Rojas et al., 2019	Prospective	RW	87	interferon beta	1	63	nr
Perumal et al., 2019	Retrospective	CT	187	natalizumab	1	56	nr
Weisntock et al., 2018	Retrospective	RW	586	fingolimod	1,3	58	37 (325)
Zivadinov et al., 2018	Retrospective ***	RW	192	fingolimod	1,6	56	nr
Zivadinov et al., 2018	Retrospective ****	RW	398	fingolimod	1,6	64	nr
(Kappos et al., 2016)	Retrospective	CT	783	Fingolimod	2	31	20 (706)
Yokote et al., 2018	Retrospective	RW	22	RCW (I-F-N) *	2	64	22
Kim et al., 2019	Retrospective	RW	152	Interferon-beta	2	38	nr
Huhn et al., 2019	Retrospective	RW	159	EMA**	2	29	nr
Rojas et al., 2019	Prospective		87	interferon beta	2	45	nr
Perumal et al., 2019	Retrospective	CT	120	natalizumab	2	74	nr
Frau et al., 2019	Prospective	RW	90	alemtuzumab	2	44	nr
Prosperini et al., 2018	Retrospective	RW	40	alemtuzumab	3	45	nr
Rojas et al., 2019	Prospective	RW	87	interferon beta	3	39	nr
Huhn et al., 2019	Retrospective	RW	84	EMA	3	21	nr

* I: interferons; GA: glatiramer acetate; F: fingolimod; N: natalizumab.
** EMA: European Medicines Agency approved therapies.
*** from eight academic centers.
**** from 25 private centers; nr: not reported.

annualized percentage brain volume change (a-PBVC) in RRMS and to investigate the addition to NEDA-3 of a fourth criterion—no pathological a-PBVC —proposed by Kappos et al. (2016). During normal aging, a-PBVC has been estimated as $> -0.4\%$ (Anderson et al., 2007; De Stefano et al., 2016). NEDA-4 status is defined as meeting all NEDA-3 criteria plus having an a-PBVC of $> -0.4\%$ (Kappos et al., 2016).

Brain volumetric MRI has yet to be translated into clinical practice. In individual patients, brain volume assessment is confounded with normal aging, methodological limitations and fluid-shift related fluctuations in brain volume. In particular, concerns exist regarding the biological validity of the proposed cut-off value of -0.4% to discriminate the pathological brain volume loss in RRMS as this value was obtained from a longitudinal MRI dataset that included only 35 healthy controls (De Stefano et al., 2016). Despite the small sample, this figure is the most accepted and has been widely used as an outcome measure in clinical trials.

Cognitive impairment has been proposed as another component to assess evidence of disease activity and for being integrated into therapeutic algorithms for RRMS (Stangel et al., 2015). The Symbol Digit Modalities Test (SDMT) is a fast-neurocognitive tool and the measure of choice for MS in assessing cognitive speed. This test is the only one with established clinically meaningful change of 4 points or 10% in magnitude for cognitive screening and assessing efficacy of treatment in MS (Benedict et al., 2017; Kalb et al., 2018; Strober et al., 2019).

NEDA-4 outcomes have exclusively been reported from *post-hoc* analyses from RCT (Kappos et al., 2010); *to our knowledge there are no prospective real-world studies* presenting data on NEDA-4, let alone in Latin-American (LATAM) populations. Table 1 shows that only two studies have reported NEDA-4 outcomes, both retrospective and in patients using fingolimod. It is noticeable that much discussion on NEDA-4 has taken place in the absence of prospective real-world data. To address these issues our prospective and observational study investigates for first time a real-world experience of calculating serial NEDA-4 outcomes.

Less than 0.04% of the literature on MS is focused on LATAM MS patients (Khan et al., 2015). It was estimated that 2.221.180 persons had MS Wallin et al., 2019 ("Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016.," 2019), corresponding to a prevalence of 30.1 per 100,000 inhabitants. MS epidemiology in LATAM is scarce. Argentina and Uruguay have the highest prevalence of MS with rates of 25.6 and 20.6 per 100,000 inhabitants, respectively (Cristiano and Rojas, 2017). Both countries had an important Caucasian migratory flow. On the other hand, in Chile mestizo population predominates (Caucasian and Amerindian natives classically without African immigrants) (Fuentes et al., 2014). A national register study found a small incidence and prevalence when compared to the global data, with values of 0.89 (95% CI 0.75–1.05) and 4.48 (95% CI 4.15–4.81) per 100,000 inhabitant, respectively, (Diaz et al., 2012).

We present prospectively collected clinical data from LATAM Chilean RRMS patients in early disease stages, at a single center and during the routine clinical assessment. We aim to determine the proportion of patients failing to meet one or more NEDA-4 criteria after 1 and 2 years of follow-up and the contribution of each NEDA-4 component to this. We hypothesize that NEDA-4 has the potential to capture the impact of DMT therapies in RRMS and that considering NEDA-4 status, clinicians may select a second-line DMT earlier in the disease course to control subclinical disease activity of RRMS. We have also appraised whether SDMT is capable of replacing a-PBVC as one of the components of NEDA-4 in routine clinical practice.

2. Materials and methods

2.1. Patient assessment

Forty-five adult patients with RRMS according to the revised McDonald criteria (Polman et al., 2011) were followed at the University of Chile Hospital. This observational study was integrated into routine clinical practice and therefore the treating neurologists were free to make any therapeutic change. Between January 2016 and March 2019, patients were scheduled to undergo clinical and MRI assessments at baseline screening, and at months 12 and 24. For both the baseline and follow-up assessments, the clinical data and MRI scans were acquired within 1 week of each other. Patients were assessed for the first time when relapse free and at least 90 days after their last relapse. All RRMS patients were on DMT (Table 2). According to the recommendations made by the Ministry of Health of Chile, interferons, glatiramer acetate and teriflunomide are considered as fist line DMTs, and fingolimod, alemtuzumab and natalizumab are second line DMTs. Patients were excluded if they had a clinical disease duration of ≥ 4 years and an EDSS score of ≥ 4. Due to the observational nature of the study, no further inclusion criteria were defined.

Table 2
Patients demographic characteristics and evaluation at baseline, 1-year and 2-year follow-up.

Characteristics	*n*: 45		
Baseline age, years, mean (SD)	33.0 (10.5)		
Female, *n* (%)	30 (67)		
Mean disease duration of RRMS since diagnosis (SD), years	1.9 (0.4–4)		
Expanded Disability Status Scale score, mean (range), baseline and follow-up	Baseline	Year 1	Year 2
	1.3 (0–4)	1.3 (0–4.5)	1.4 (0–5.5)
Brief International Cognitive Assessment for Multiple Sclerosis, mean (SD), baseline and follow-up	120 (27)	123 (30)	127 (31)
Symbol Digit Modalities Test	43(13)	42 (13)	46 (15)
California Verbal Learning Test 2	54 (10)	54 (10)	54 (12)
Brief Visual Spatial Memory Test-Revised	23 (7)	23 (7)	26 (10)
Disease-modifying therapy, *n* (%)			
Interferon	23 (53)	16 (35)	8 (21)
Fingolimod	8 (18)	13 (29)	21(47)
Glatiramer acetate	6 (13)	6(13)	5 (11)
Teriflunomide	4 (9)	4 (9)	4 (9)
Natalizumab	0	1 (2)	1 (2)
Alemtuzumab	0	1 (2)	2 (4)
Without (CIS)	4 (9)	4(9)	4 (9)
Relapses before 1st visit, *n* (%) one	31 (65)		
two or more	17 (35)		
T2 lesions, *n* (%), baseline and follow-up. <10	13 (29)	12 (27)	9 (20)
11–50	28 (62)	28 (62)	31(67)
>50	4 (9)	5(11)	5 (11)
Gadolinium-enhanced T1 lesions, *n* (%), baseline and follow-up.	4 (9)	5 (11)	4 (9)
Proportion of patients who failed to meet NEDA-4 criteria	Year 1	Year 2	
Relapses	20% (9/45)	33% (15/45)	
EDSS progression	16% (7/45)	11% (5/45)	
New T2 lesions	11% (5/45)	7% (3/45)	
Gadolinium-enhanced T1 lesions	9% (4/45)	13% (6/45)	
a-PBVC $\leq -0.4\%$	52% (23/45)	49% (22/45)	
Proportion of patients achieving NEDA-3 status	60% (27/45)	47% (21/45)	
Proportion of patients achieving NEDA-4 status	38% (17/45)	27% (12/45)	
Proportion of patients achieving NEDA-4 status using SDMT decreased by 4 points or more.	53% (24/45)	40% (18/45)	
Proportion of patients with SDMT decreased 4 points or more.	16% (7/45)	20% (8/45)	
Correlations between clinical outcome NEDA-4 status using a-PBVC and SDMT change during the 24-month follow-up period	$r = 0,37$	$p = 0.01$	

The following definitions were used for the individual components of NEDA-4 taken from Kappos et al. (2016). Relapse: the appearance of a new or worsening of a previously stable neurological abnormality, present for at least 24 h and occurring in the absence of fever or infection, confirmed within 7 days of symptom onset. Focal MRI activity: new or enlarged T2 lesions and/or gadolinium-enhanced T1 lesions. Disability progression: an increase in the EDSS score of at least 0.5 points from the baseline score. a-PBVC $\leq -0.4\%$ is considered an abnormal cerebral atrophy rate .

Neuropsychological status was assessed using the Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS) (Benedict et al., 2012) and scores were assessed relative to normative data in a Hispanic population (Vanotti et al., 2016). At 12 and 24 months worsening of at least 4 points of the SDMT was considered as clinically meaningful.

2.2. MRI acquisition

Brain MRI was performed at baseline and follow-up on the same MRI system using the same imaging protocol (same pulse sequences and spatial resolution). MRI images were acquired on a 1.5 T Siemens MRI scanner. Axial T1-weighted images of the whole brain were obtained using a 3D inversion-recovery prepared spoiled gradient-echo (IR-SPGR) sequence. The following parameters were used in this volumetric sequence: field of view of 250×234 mm; matrix of 256×240 mm; repetition time of 12 ms; echo time of 5.68 ms; excitation flip angle of 15º; isotropic voxel size of $0.98 \times 0.98 \times 0.98$ mm. Patients underwent a second and third MRI brain scan within two years of follow-up.

Two neuroradiologists blinded to clinical data independently assessed the MRI scans of every patient. In a pilot stage of the study, which included the 45 baseline MRI examinations, the inter-rater reliability for the neuroradiologists was calculated using Cohen's kappa coefficient. Kappa values for the T2 lesion number categories were 0.909 for less than 10 lesions, 0.836 for 11–49 lesions and 0.730 for 50 lesions or more than. In case of disagreement in the independent evaluation, a joint evaluation of the examination was made, where a consensus was reached to define the number of T2 lesions. No MRI images included in this study showed any structural abnormalities other than atrophy-related changes and demyelinating lesions. New lesions at follow up (T2 lesions and gadolinium-enhancing lesions) were evaluated by eye and were defined as hyperintensities > approximately 3 mm on T2-weighted/FLAIR scans or showing gadolinium enhancement on T1-weighted scans. The enlargement of T2 lesions from baseline to follow-up was also evaluated by eye. The number of T2 lesions per patient scan was divided into three categories: less than 10; 11 to

Table 3
Quantitative MRI volumetric data in RRMS: normalized brain tissue volume and annualized PBVC.

	Baseline (B)	Follow-up 1 (F1)	Follow-up 2 (F2)	*p* value
Annualized-PBVC mean% ± SD (range)		0.45 ± 0.68 (2.4 − −0.67)	0.48 ± 0.57 (2.98− −0.8)	0.86
Normalized brain volume, mL, mean ± SD (range)	1565 ± 51 (1432–1668)	1557 ± 56(1455–1655)	1553 ± 48 (1466−1553)	0.011* (B vs F2)
Peripheral gray matter, mL, mean ± SD (range)	584 ± 30 (518–643)	579 ± 34 (502–652)	578 ± 29 (514−641)	0.049 (B vs. F2)
Gray matter, mL, mean ± SD (range)	750 ± 32 (680–813)	744 ± 36 (662–807)	744 ± 34 (675−830)	0.047* (B vs. F2)
White matter, mL, mean (range)	816 ± 34 (728–893)	812 ± 35 (741–876)	808 ± 31(745−864)	0.015* (B vs.F2)

49; and 50 or more (Arnold et al., 2015).

2.3. MRI analysis

All images were converted to NIFTI format using MRIcron software (http://people.cas.sc.edu/rorden/mricron/dcm2nii.html). Cross-sectional whole brain volumes and brain tissue volumes were estimated using SIENAX (Smith et al., 2002). The longitudinal SIENA processing algorithm has already been validated and described in detail (Smith et al., 2002). The processing went as follows: (1) Brain extraction: segmentation of brain from nonbrain tissue for each scan, followed by skull extraction. (2) Registration: registration of the segmented brain from the second (follow-up) scan to that of the first (baseline) scan using a linear transformation. The two skull images are used as normalizing factors to constrain the scale and skew. (3) Tissue type segmentation: white matter (WM) and gray matter (GM) tissues are treated as one tissue and the cerebrospinal fluid as another tissue. (4) Change analysis: detection of the edge of the brain on the registered baseline and follow-up image. At each edge point the displacement between the baseline brain edge and follow-up brain edge is determined. Finally, the mean displacement of brain surface at each edge point is converted to a global percentage change in brain volume by considering the baseline brain volume. Subjects were included in the study if they had three MRI scans of adequate quality and the brain extraction step in SIENA functioned correctly. One patient was excluded because of the presence of a frontal arachnoid cyst.

2.4. Statistical analyses

Statistical analysis of the clinical data was performed using Statistical Package for Social Sciences, version 22 (IBM). The results are presented as the means ± SDs. In all cases, a two-sided p of < 0.05 was considered significant. Comparisons between groups were assessed using a t-test. After calculating the cross-sectional values of WM and GM, repeated measures design was used to compare WM and GM values at different time points (paired sample t-test). The point–biserial correlation coefficient was used to investigate relationships between the main dichotomous clinical outcomes (NEDA-4 vs. EDA status) and changes of clinical and MRI variables (tissue partition MRI-derived measures) during the 24-month follow-up period. Logistic regressions were tested between the main clinical outcome (dependent variable: NEDA-3, NEDA-4 at year one and two) and baseline characteristics of this cohort (age, disease duration, baseline treatment (first-line an second line DMTs), type of health insurance, SDMT, and MRI variables). a-PBVC was calculated by dividing the PBVC values by the interscan interval in years. Clinical scores were annualized by dividing the unit change between the assessments by the assessment interval in years. To assess the contribution of the four different components of the NEDA-4 measure, hierarchical analysis of patients was performed according to individual disease activity criteria using the following hierarchy: relapses, disability progression, MRI activity and accelerated a-PBVC or patients with SDMT decreased by 4 points or more (Kappos et al., 2016). In this analysis, patients who had an event for one outcome were removed from evaluation for any other outcomes from that point on (Figs. 1 and 2).

2.5. Protocol approval and patient consent

Prior to inclusion, patients provided informed written consent for participation in the study. The study was conducted in accordance with international standards of good clinical practice (ICH guidelines and the Declaration of Helsinki). The project was approved by the local research ethics committees of the University of Chile Hospital, Santiago, Chile.

3. Results

3.1. Clinical findings (Table 2)

3.1.1. Baseline

Forty-five patients were followed up with three clinical and MRI assessments. 91% (41/45) had relapsing-remitting MS (RRMS) and 9% (4/45) clinically isolated syndrome (CIS). At baseline, the patients had a mean age of 33.0 years (18–57), disease duration of 1.9 years (0.4–4), EDSS score of 1.3 (0–4), and female 67%. Seventy-three percent of patients were on first-line DMT (interferons (53%), glatiramer acetate (13%), teriflunomide (9%)), 18% were on fingolimod because of intolerance to interferons or used as first DMTs. CIS (9%) patients were without DMT.

3.1.2. First follow-up (at year 1, Fig. 1)

20% (9/45) of the patients had at least one relapse, 16.0% (7/45) had disability progression, 11.0% (5/45) had new T2 lesions, and 9.0% (4/45) had gadolinium-enhanced T1 lesions. Sixty percent (27/45) achieved NEDA-3. An a-PBVC $\leq -0.4\%$ was observed in 52.0% (23/45) (mean: 0.45% ± 0.68) (Fig. 3). Including a-PBVC (threshold of -0.4%), the proportion of patients achieving NEDA-4 was 38% (17/45). Thirty-three percent (15/45) were now on second-line DMT: 29% (13/45) on fingolimod, alemtuzumab 2% (1/45) and natalizumab 2% (1/45).

3.1.3. Second follow-up (at year 2, Fig. 2)

Thirty-three percent (15/45) had at least one relapse, 11% (5/45) had disability progression, 7.0% (3/45) had new/enlarged T2 lesions, and 13.0% (6/45) had gadolinium-enhanced T1 lesions. 47% (21/45) of patients achieved NEDA-3. An a-PBVC $\leq -0.4\%$ was observed in 49% (22/45) (mean: 0.48% ± 0.57) and 27% (12/45) achieved NEDA-4 (Fig. 3). Fifty-three percent (24/45) were now on second-line DMTs: fingolimod 47% (21/45), alemtuzumab 4% (2/45) and natalizumab 2% (1/45).

3.1.4. Cognitive measures (Table 2)

At baseline, fifty-three percent of patients performed badly on the SDMT (mean ± SD: 43 ± 13). At **1 year and 2 year**, 16% (7/45) and 20% (8/45) of patients had a SDMT decreased 4 points or more, respectively. At year 1 and year 2, with the inclusion of SDMT in the hierarchical analysis, 53% and 40% of patients achieved a putative NEDA-4 status, respectively, (Figs. 1 and 2).

3.1.5. Tissue partition MRI-derived measures (Table 3)

Baseline qMRI volumes were within normal limits. From baseline to 1.8 years after baseline, white matter volume mean decreased from 816 ml ± 34 to 808 ml ± 31 ($p = 0.015$), peripheral gray matter decreased from 584 ml ± 30 to 578 ml ± 29 ($p = 0.049$), and whole brain volume decreased from 1565 ml ± 51 ml to 1553 ml ± 48 ($p = 0.011$).

3.1.6. Correlations and baseline predictors of NEDA

There was a significant relationship between the changes in SDMT over the 24-month follow-up period and NEDA-4 status (r: 0.37 and $p < 0.01$). Logistic regressions were tested between the main clinical outcome (NEDA status) and baseline characteristics of this cohort (age, disease duration, baseline treatment, type of health insurance, SDMT, WM and GM) and none was a significant predictor of NEDA-4 outcome.

4. Discussion

This longitudinal study showed a serial decline in the proportion of patients with no evidence of disease activity as defined by the concepts of NEDA-3 and NEDA-4 using a-PBVC; after 1 and 2 years of follow-up 60% and 47% met NEDA-3 status and 38% and 27% met NEDA-4,

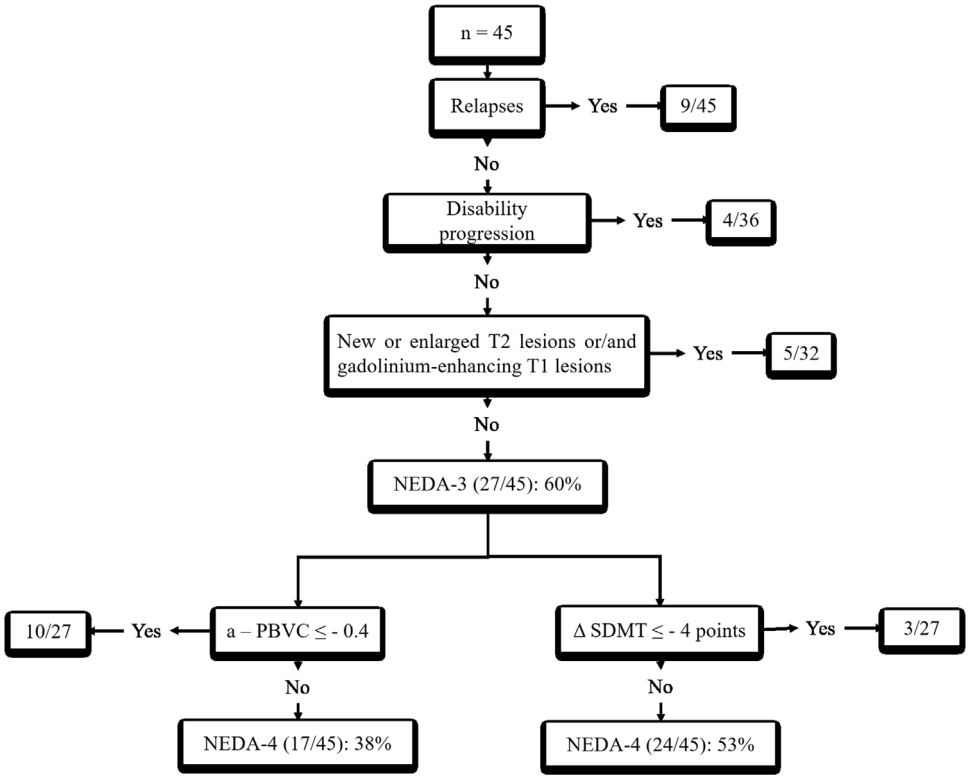

Fig. 1. Hierarchical analysis of individual disease activity criteria at year 1.

respectively. At baseline, 53% of the patients were on interferons and at the 2-year follow-up 21% remained on interferons. Based on NEDA-3 criteria, the treating neurologist replaced the use of interferons by fingolimod, natalizumab and alemtuzumab as second line therapies.

The three components of NEDA-3 may not be suitable for the determination of timely treatment failure in routine clinical practice (Schmidt et al., 2018). The components of NEDA-3 reflect the ongoing disease status imperfectly, and their variability in terms of definitions and acquisition limits their effectiveness as outcome measures. The use of relapses as outcome measures also has major limitations. Relapses

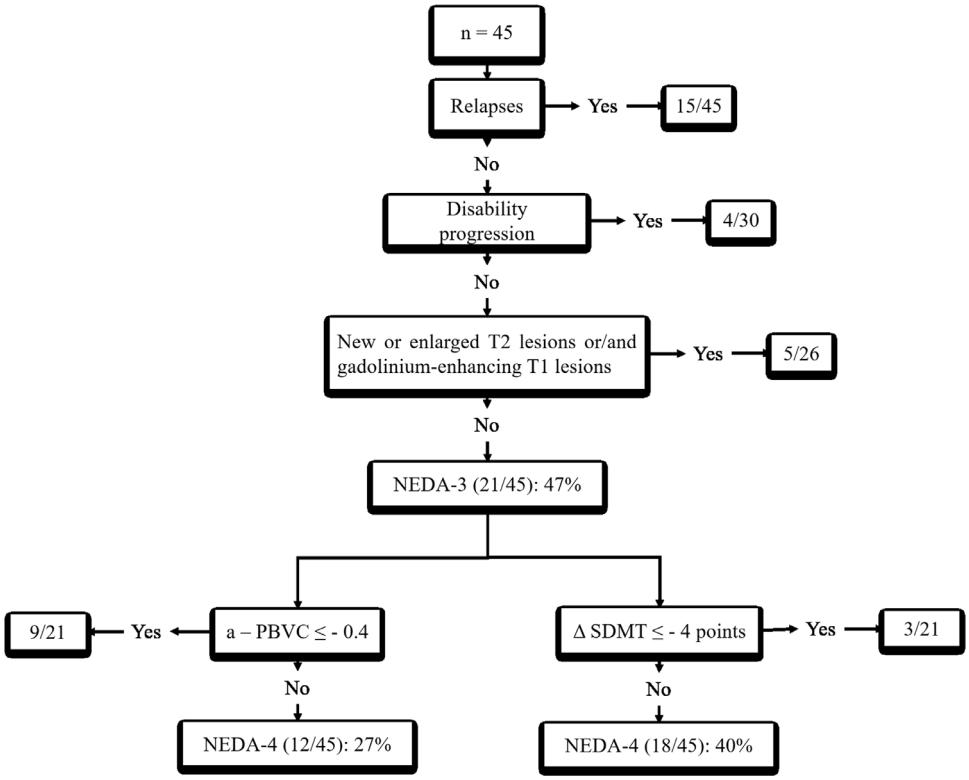

Fig. 2. Hierarchical analysis of individual disease activity criteria at year 2.

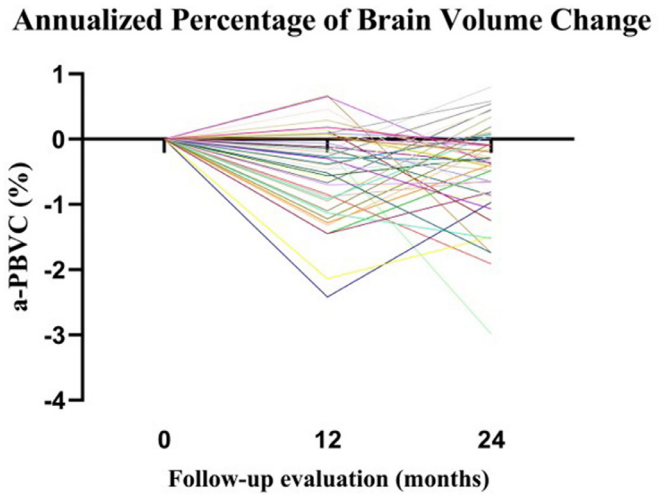

Fig. 3. 'Spaghetti' plot reporting with different colours the annualized-percentage of brain volume change (a-PBVC) for each patient.

are relative rare events (Hegen et al., 2018); in a pivotal clinical trial untreated MS patients showed an annual relapse rates of 0.4 (0.34–0.47) (Kappos et al., 2010). Particularly in early stages of the disease the number of relapses may therefore underestimate the ongoing pathological changes and overestimate the efficacy of DMTs. In clinical practice, the detection of new or enlarged T2 lesions is limited by technical and methodological factors. Manual counting of T2 lesions is imprecise, and the number of new T2 lesions is typically specified only approximately, or as >10 when many are present (Arnold et al., 2015). Moreover, the cortical lesion burden is poorly visualized by most routine MRI protocols (Geurts et al., 2012).

Cognitive assessment and other biomarkers such as neurofilament light chain (NfL) and spinal cord atrophy may qualify as additional components of NEDA definition, providing information on neurodegenerative aspects of MS in a similar way as PBVC. There is growing support for the use of cognition as an endpoint in disease modifying clinical trials. In the early stages of MS, cognitive impairment is already present in at least 50% of Chilean MS patients (Oliva et al., 2018). This frequency is concordant with other clinical reports (34%–65% (Kalb et al., 2018)). Thus, cognitive impairment is a key domain to be included when choosing an outcome measure in MS. Considering that SDMT is the most sensitive test to MS cognitive disorders (Benedict et al., 2017), this work included patients who had a deterioration of four or more points on SDMT in a potential composite endpoint. The sequential addition of SDMT results in more patients achieving NEDA-4 status at one and two years of follow-up (53% and 40% of patients achieved a putative NEDA-4 status, respectively) than those reaching NEDA-4 using a-PBVC. SDMT increased the sensitivity of NEDA-3 to detect clinical deterioration. The inclusion of neuropsychological outcomes in NEDA-4 has already been proposed (Stangel et al., 2015), but prospective studies with enough statistical power are required to elucidate whether SDMT is a more accurate and realistic component to be used in a composite assessment in MS.

NfL belong to neuronal cytoskeleton and can be assessed in different compartments, including blood, where it reaches from central nervous system when there is cell death (Bergman et al., 2016). High levels of NfL on CSF were reported on RRMS patients and a significant decline was determined after therapeutic interventions using DMTs such as natalizumab, fingolimod and rituximab (Bergman et al., 2016). Sormani et al. have proposed a cut-off of blood NfL of 22.7 pg/mL as the optimum level discriminating patients with a disability progression at year 2 (AUC = 72%, sensitivity = 76%, specificity = 67%). 20% (n = 42/214) patients achieved NEDA-NfL at month 24 (Sormani et al., 2018). Thus, blood NfL may provide information on neurodegenerative aspects of MS, and is simpler to assess (Bonnan et al., 2017).

The spinal cord assessment related to the lesions and atrophy, which may be of clinical significance as spinal cord pathology is a major contributor to RRMS disability. Indeed, the rate of spinal cord atrophy is greater than that of brain atrophy (1.78% versus 0.5% per year) (Moccia et al., 2019; Tur et al., 2018). Spinal cord atrophy-related measures are typically calculated using semi-automated segmentation-based methods, which are subject to inter-rater variability. Future directions of research to fully automated analysis methods, including segmentation of gray matter and intramedullary lesions will facilitate the use of spinal cord atrophy in the clinical and research arenas (Moccia et al., 2019).

A strength of this study is the prospectively collected clinical data, with a high-quality control standard. Throughout the duration of the study, the patients underwent the same MRI protocol on the same MRI scanner at a single site. When the patients are prospectively recruited in this way, through a single center, the risks of data variability may be substantially reduced.

This study using PBVC has a number of limitations. In this clinical series one question arise: should the treating neurologist consider switching therapy to potentially more effective drugs in patients who have not achieved NEDA-4 status? This topic is controversial, particularly regarding patients who have accelerated a-PBVC only (22% in this study). The two-year follow-up period in the present study seems to be clinically meaningful for switching the initial DMT owing to disease activity. A one-year follow up period may overestimate a-PBVC because of the resolution of the early anti-inflammatory effect of DMTs and steroids (pseudoatrophy) and a-PBVC would need to be assessed considering this caveat. Thus, a two-year period has been suggested as a more robust approach when measuring a-PBVC for overcoming the confounding factor of pseudoatrophy (Rotstein et al., 2015).

Confounding factors in determining the rate of a-PBVC require to be considered, such as, alcohol (Bartsch et al., 2007), mild traumatic brain injury (MacKenzie et al., 2002), smoking, genetics, diabetes mellitus (Enzinger et al., 2005), hydration/dehydration (Kempton et al., 2009), treatment-related changes in brain water and inflammatory cell content (pseudoatrophy) can cause changes in brain size. Moreover brain volume seems to fluctuate throughout the day, decreasing from morning to evening (Nakamura et al., 2015). Various sources of error related to image acquisition can affect MRI atrophy quantification: image artefacts due to head motion, poor signal-to-noise ratio, partial head coverage, imperfect patient repositioning in a longitudinal study and image acquisition with non-identical scan parameters. Even small changes could be argued to be an artefact caused by, for example, cardiac pulsations. To date these factors make it difficult to use individualised longitudinal brain volume assessment in a clinical setting since physiological variability and measurement errors may be added to the biological variations related to the disease.

Another factor that should be considered for assessing accuracy of brain volume measurements is the influence that WM lesions in the brain of MS patients can have in the measurement of tissue specific brain volumes (Battaglini et al., 2012). Particularly, lack of lesion filling can affect brain volume estimates with some softwares, however due to the way SIENA works by analysing changes in the brain surface CSF/boundary it is less likely to be affected by MS lesions. Indeed a study specifically investigating the effect of lesion filling with different softwares (Storelli et al., 2018) reported "Filling of WM lesions on T1-weighted studies with intensities similar to those of WM is used to improve volume estimations. The results from FSL-SIENA were not significantly affected by WM lesion filling ($P > 0.05$); while GM atrophy results for Advanced Normalization tools (ANTs), MSmetrix, and Statistical Parametric Mapping (SPM) ($P < 0.05$) were significantly influenced."

Identifying subclinical signs of disease activity is imperative to prevent the neurodegenerative aspects of RRMS and reduce progression to irreversible disability. The frequency of conversion from RRMS to a

secondary progressive multiple sclerosis (SPMS) increases with duration of disease (12% at 5 years; 41% at 10 years) (Cottrell et al., 1999). Assessing a-PBVC early during the course of the disease could help identify groups of people with RRMS who may benefit from particular types of therapies before the progression to SPMS, when patients seem to receive no benefit from DMTs. Although accelerated a-PBVC may be a predictor of disability progression and cognitive decline in the long term, a period of two year of disease course is still too short for predicting disease course (De Stefano et al., 2014; Horakova et al., 2009).

5. Conclusion

The current diagnostic criteria and the follow-up tools of disease progression in RRMS lack relevance to the neurodegenerative aspects and concentrate mainly on the inflammatory process. a-PBVC may be a cornerstone of measurement of neurodegenerative components of disease progression RRMS, which should lead to improvement in treatment strategies and patient outcomes. However, while current methods provide sufficient precision for cohort studies, they are not adequate for confidently assessing changes in individual patients. Advances in imaging and processing techniques are needed in order to enable neurologists to probe a-PBVC along with the clinical endpoints in RRMS, and ultimately to improve treatment. SDMT may replace a-PBVC as the fourth component of NEDA-4 definition. It is possibly that the utilization of the endpoint such as NEDA has significant shortcoming if it does not include cognition (Strober et al., 2019)

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Conflict of interest

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CRediT authorship contribution statement

Carlos Guevara: Conceptualization, Methodology, Validation, Formal analysis, Investigation, Writing - original draft, Supervision, Funding acquisition. **Eduardo Villa:** Validation, Formal analysis, Investigation, Writing - original draft. **Violeta Diaz:** Investigation, Writing - original draft. **Cristian Garrido:** Investigation, Conceptualization. **Melissa Martinez:** Investigation, Conceptualization. **Patricia Orellana:** Investigation, Conceptualization. **Pablo Alarcón:** Investigation, Conceptualization. **Carlos Silva-Rosas:** Investigation, Conceptualization. **Gareth J Barker:** Methodology, Validation, Writing - original draft. **Matthew J Kempton:** Methodology, Validation, Writing - original draft. **José de Grazia:** Methodology, Validation, Writing - original draft.

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