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A Multicenter Evaluation of the Diagnostic Performance of the Central Vein Sign Using Simplified Algorithms

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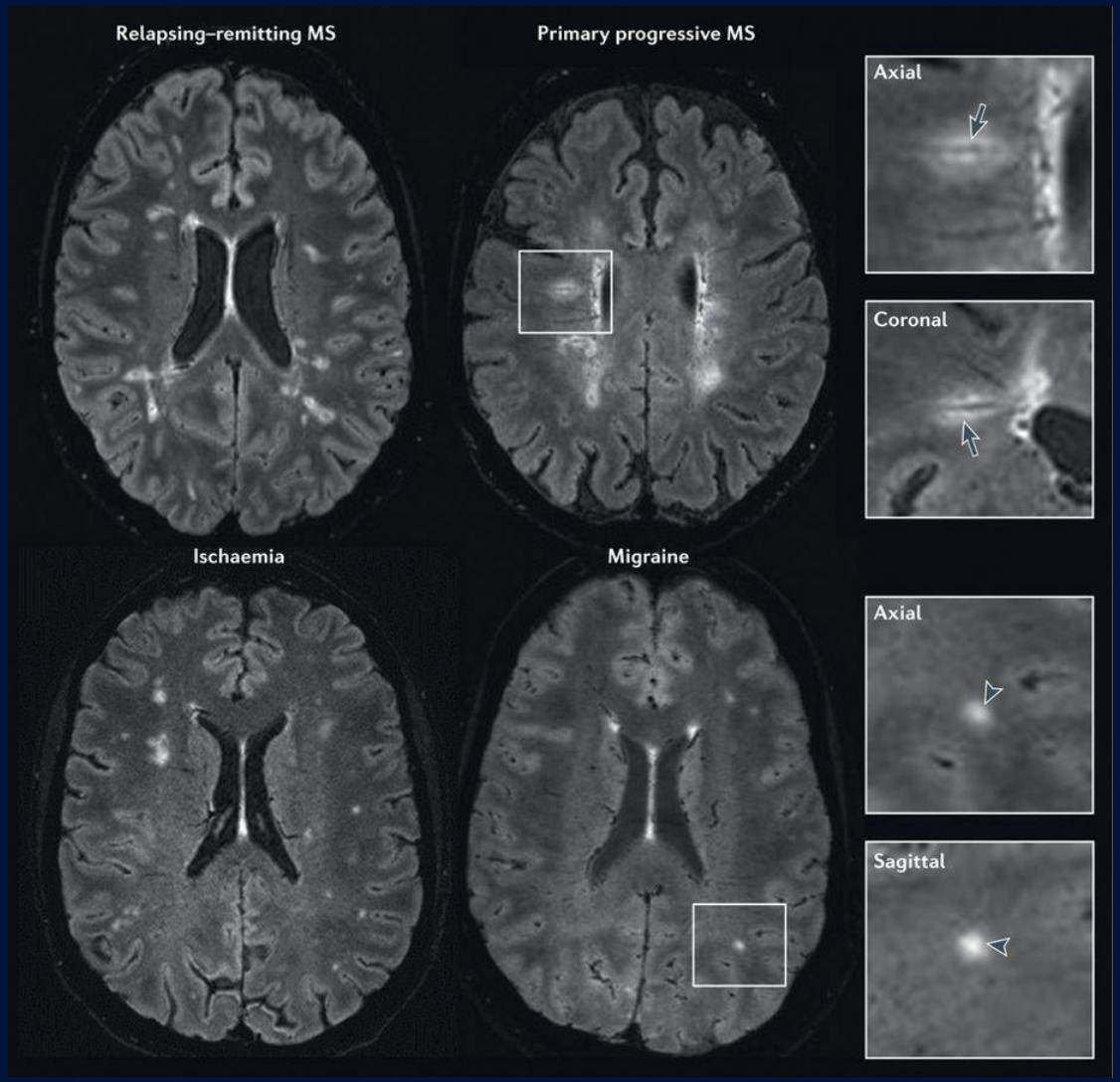
Introduction

- Limited specificity of current diagnostic criteria (McDonald 2017)[1]
- High rates of misdiagnosis (~1 in 5 MS patients are misdiagnosed)[2]
- Potential solution: a radiologic biomarker for MS – the **Central Vein Sign[3]**
- **Central Vein Sign (CVS)**
  - Visualized on susceptibility-based MR imaging sequences, including FLAIR*

    FLAIR = FLAIR x T2*-weighted*
  - Appears as a thin hypointense line or small hypointense dot
  - Must visualize in at least two perpendicular MRI planes



1. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *The Lancet Neurology* 2018;17:162-73.
2. Kaisey M, Solomon AJ, Luu M, et al. Incidence of multiple sclerosis misdiagnosis in referrals to two academic centers. *Mult Scler Relat Dis* 2019; *30*:51–6.
3. Sati, P. et al. (2016). The central vein sign and its clinical evaluation for the diagnosis of multiple sclerosis: a consensus statement from the North American Imaging in Multiple Sclerosis Cooperative. Nature Reviews Neurology *12*, 714.

Introduction

How do we measure the CVS?

- Threshold proportions of all lesions:

$$\frac{CVS\ positive\ lesions}{CVS\ positive\ lesions + CVS\ negative\ lesions}$$

  - Thresholds anywhere from 35-50% have been suggested[1,2]
  - Time-intensive process, not as readily applicable to clinical settings
- Simplified algorithms:
  - Select-3*: counting at least 3 CVS+ lesions over an entire FLAIR* scan (previously found to have a sensitivity of 0.83, specificity of 0.81)[3]
  - Though much easier to apply clinically, the ideal threshold (# of lesions to count) has not been investigated in a large cohort

Objective: evaluate the sensitivity and specificity of simplified algorithms for assessing the CVS using FLAIR* for MS diagnosis

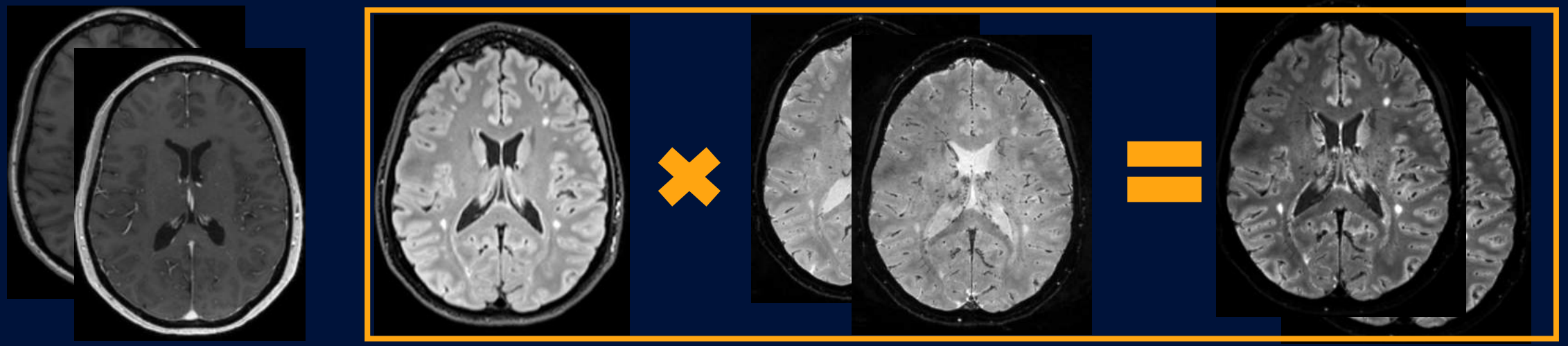
1. Maggi P et al. (2018). Central vein sign differentiates Multiple Sclerosis from central nervous system inflammatory vasculopathies: Central Vein Sign. Annals of Neurology 83, 283–294.
2. Tallantyre EC et al. (2011). Ultra-high-field imaging distinguishes MS lesions from asymptomatic white matter lesions. Neurology 76, 534–539.3.
3. Solomon AJ et al. (2018). Diagnostic performance of central vein sign for multiple sclerosis with a simplified three-lesion algorithm. Multiple Sclerosis Journal 24, 750–7.

Methods: Study Design

- Prospective multi-center observational pilot study
- 97 subjects with a clinical/radiological suspicion of MS were recruited across 10 different North American MS referral sites in 2018-2019
  - Cleveland Clinic, University of Toronto, University of Pennsylvania, University of Vermont, Johns Hopkins University, University of California San Francisco, University of Texas—Houston, Cedars Sinai Medical Center, University of Southern California, and Yale University
- Each subject had a single clinical visit which included brain MRI with gadolinium (macrocyclic chelates)
- Clinicians at each site determined if the subject met McDonald 2017 criteria after workup
- Clinicians followed up with participants as needed, and reported the diagnosis at follow-up approximately 12 months later

Methods: Image Acquisition and Analysis

- MRI Protocol was pre-specified at 3T with the following sequences obtained:



3D T1-weighted (pre- & post-contrast)

3D FLAIR

3D T2*-weighted (pre- & post-contrast)

FLAIR* (pre- & post-contrast)

- 92 post-Gd scans were analyzed for the CVS by trained raters at each institution
  - Images were uploaded to a cloud server (QMENTA)
  - Trained raters selected up to 6 lesions meeting NAIMS criteria[1] on pre- and post-contrast FLAIR* images
  - The diagnostic performance of the CVS was evaluated at thresholds of 1 CVS+ lesion (Select-1*) up to 6 (Select-6*)

1. Sati, P. et al. (2016). The central vein sign and its clinical evaluation for the diagnosis of multiple sclerosis: a consensus statement from the North American Imaging in Multiple Sclerosis Cooperative. Nature Reviews Neurology *12*, 714.

Results

97 subjects were consented and enrolled. 5 subjects were excluded from analysis due to excessive image artifacts (4) or missing post-Gd scans (1). In total, 92 subjects were included in the analysis.

	MS	Non-MS*
Number (%)	38 (41)	54 (59)
Age, mean ± SD	41 ± 12	47 ± 11
Female, no. (%)	22 (58)	45 (83)
Race, white, no. (%)	32 (84)	44 (81)
Hypertension, no. (%)	2 (5)	13 (24)
Diabetes, no. (%)	1 (3)	3 (6)
Coronary Artery Disease, no. (%)	0 (0)	1 (2)
Hyperlipidemia, no. (%)	2 (5)	10 (19)
Past tobacco use, no. (%)	9 (24)	13 (24)
Current tobacco use, no. (%)	2 (5)	3 (6)
Symptom duration (weeks), median [IQR]	53 [266] N=38	109 [271] N=43
EDSS, mean ± SD	1.3 ± 1.0	N/A
T25FW, mean ± SD	4.7 ± 1.0	5.5 ± 1.4
9-HPT (seconds), mean ± SD	22.0 ± 3.8	21.3 ± 4.1
SDMT (number correct), mean ± SD	52.0 ± 10.8	52.3 ± 12.1
CSF-specific OCB positive / number tested	18 / 23	7 / 27

**Did not meet McDonald 2017 Criteria for MS at initial evaluation*

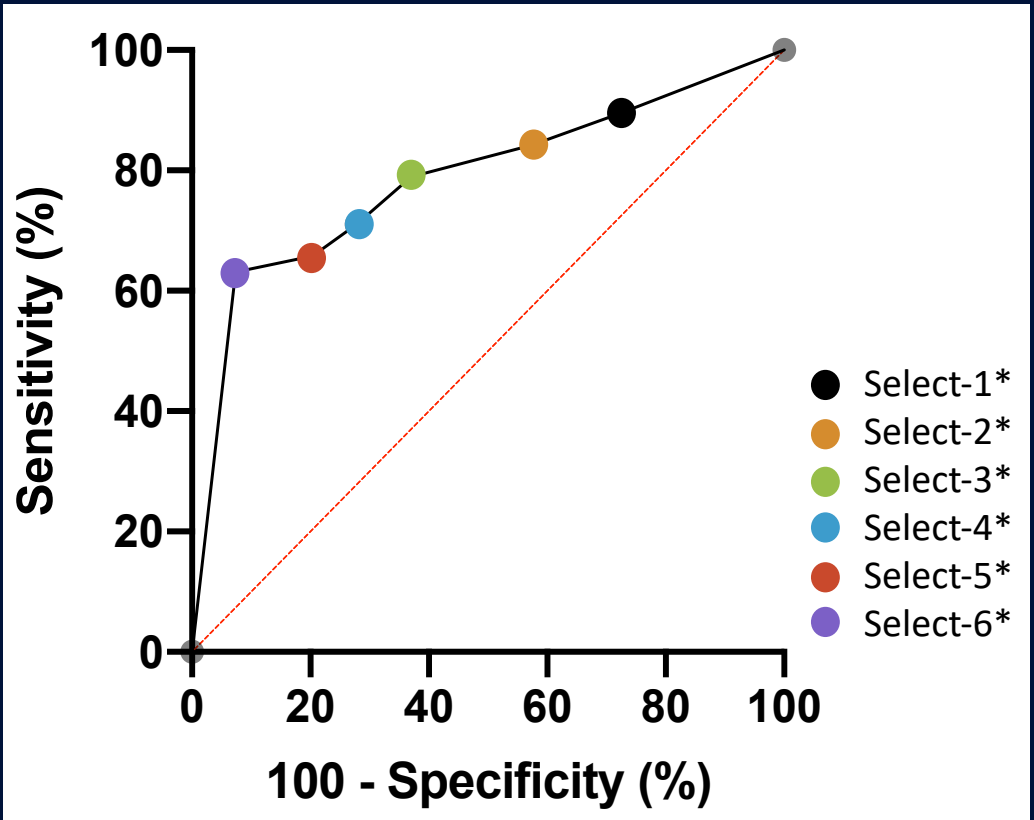
Of the MS subjects:

- 2 PPMS subjects
- 36 RRMS subjects

T25FW= Timed 25-foot walk test. EDSS= Expanded Disability Status Scale. 9-HPT= 9-Hole Peg Test. SDMT= Symbol Digit Modalities Test. CSF= Cerebrospinal fluid. OCB= oligoclonal bands

Results

ROC Curve for Diagnosing MS based on Select-n* (post-Gd)



AUROC: 0.79 (95% CI: 0.68-0.89)

	Sensitivity	Specificity	NPV	PPV
Select-1*	89%	28%	79%	47%
Select-2*	84%	43%	79%	51%
Select-3*	79%	63%	81%	60%
Select-4*	71%	72%	78%	64%
Select-5*	66%	80%	77%	70%
Select-6*	63%	93%	78%	86%

NPV= Negative Predictive Value, PPV= Positive Predictive Value

Results: 12-month Follow-up

- Categorization of participants as MS vs non-MS was unchanged in 83 participants (90%) but changed in 9 participants (10%):
  - 7 met McDonald 2017 Criteria at 12 months
  - 2 subjects who initially met McDonald 2017 Criteria were given alternative diagnoses at follow-up
  - *Would the CVS have been able to predict this change?*
    - **4/7** of interval MS cases were CVS+ by Select-3*
    - **2/2** MS cases that were later undiagnosed were CVS- by Select-3*
- AUROC unchanged at follow up at 0.79

Conclusions

Simplified CVS algorithms rated by clinical neurologists can accurately discriminate MS and non-MS cases

- Select-3*: Identified 4/7 interval MS cases -- may aid in identifying possible MS cases that would benefit from close follow-up
- Select-6*: High specificity of 93%, could be useful in differentiating MS from mimickers
- AUROC of 0.79

- Future Directions:
  - Larger longitudinal prospective study to:
    - Determine if the CVS will allow for an earlier accurate diagnosis of MS
    - Explore how best to integrate CVS findings into the diagnostic criteria
  - Exploration of automated methods of CVS assessment
  - Determine if the CVS can be helpful in follow-up of established MS patients