

Comparison of the Diagnostic Performance of the Central Vein Sign and CSF Oligoclonal Bands Supporting the Diagnosis of Multiple Sclerosis

Christopher Martin Allen,^{1,*} Margareta A. Clarke,^{1,*} Hari V. Pai,¹ Marija Cauchi,^{2,3} Jonathan Hawken,⁴ Zin M. Htet,⁴ Kimberley Allen-Philbey,^{5,6} Bader Mohamed,^{5,6} Deborah Fitzsimmons,⁷ Roshan Das Nair,^{1,8,9} Paul Morgan,^{1,10} Christopher Partlett,¹¹ Rob A. Dineen,^{1,10} Klaus Schmierer,^{5,6} Emma Clare Tallantyre,⁴ and Nikos Evangelou¹

Neurol Open Access 2025;1:e000017. doi:10.1212/WN9.0000000000000017

Correspondence

Dr. Evangelou
nikos.evangelou@
nottingham.ac.uk

Abstract

Background and Objectives

The central vein sign (CVS) describes the presence of venules within multiple sclerosis (MS) brain lesions, visible on T2*-weighted MRI. In the upcoming revision of the MS diagnostic criteria, the simplified “rule of 6” (i.e., finding 6 lesions with a central venule) can support the diagnosis of MS as an alternative to lumbar puncture (LP). We evaluated whether a T2*-weighted MRI scan is more sensitive than oligoclonal bands (OCBs) for diagnosing MS at presentation with a typical clinically isolated syndrome (CIS). We also compared the tolerability of LP and the additional MRI.

Methods

Participants requiring an LP to meet the 2017 McDonald diagnostic criteria for MS were enrolled in this multicenter, prospective, diagnostic superiority study from 3 UK neuroscience centers. A six-minute T2*-weighted sequence was used to assess the CVS using 2 definitions: a 40% threshold of all eligible lesions and the rule of 6. These were compared with OCBs, using the clinical diagnosis at 18 months as the reference standard.

Results

Of 113 participants, 99 (mean age: 38, female: 73%) have completed all study activities: 80 were diagnosed with MS, 10 remained CIS, 8 had alternative diagnoses, and 1 remained without a diagnosis. No significant difference in diagnostic sensitivity was detected between 40% CVS threshold (90% [CI 81%–96%]) and OCB testing (84% [CI 74%–91%]) ($p = 0.332$). The rule of 6 had a sensitivity of 91% (CI 83%–96%). Side effects were reported by 75% following LP compared with 9% following MRI. All participants preferred their MRI scan over their LP.

Discussion

CVS and OCB testing is equally sensitive in supporting the diagnosis of MS in cases of typical CIS. CVS assessed using the 40% threshold, and the simpler rule of 6 produces equivalent diagnostic performance. Compared with OCB testing, CVS testing seems safer and better tolerated by patients. Further studies are needed to evaluate CVS specificity, particularly outside of typical CIS cases, as studied here.

Classification of Evidence

This study provides Class IV evidence that CSF OCBs and the CVS are equally sensitive in supporting a diagnosis of MS in patients presenting with CIS.

*These authors contributed equally to this work as joint first authors.

¹Mental Health and Clinical Neurosciences Academic Unit, School of Medicine, University of Nottingham; ²Division of Psychological Medicine and Clinical Neurosciences, Cardiff University; ³Department of Neurosciences, Mater Dei Hospital, Malta; ⁴Division of Psychological Medicine and Clinical Neuroscience, School of Medicine, Cardiff University; ⁵The Blizard Institute, Centre for Neuroscience, Surgery and Trauma, Queen Mary University of London; ⁶Clinical Board Medicine (Neuroscience), Barts Health NHS Trust; ⁷Swansea Centre for Health Economics, Swansea University; ⁸Institute of Mental Health, Nottinghamshire Healthcare NHS Foundation Trust; ⁹Health Division, SINTEF, Trondheim, Norway; ¹⁰NIHR Nottingham Biomedical Research Centre, University of Nottingham; and ¹¹Nottingham Clinical Trials Unit, School of Medicine, Faculty of Medicine and Health Sciences, University of Nottingham.

The Article Processing Charge was funded by the authors.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Copyright © 2025 The Author(s). Published by Wolters Kluwer Health, Inc. on behalf of the American Academy of Neurology.

e000017(1)

RELATED ARTICLE

Editorial

Rethinking Multiple Sclerosis Diagnosis: Can the Central Vein Sign Replace Lumbar Puncture?

Page e000021

MORE ONLINE

Class of Evidence

Criteria for rating therapeutic and diagnostic studies

NPub.org/coe

Supplementary Material

Glossary

CIS = clinically isolated syndrome; **CVS** = central vein sign; **FLAIR** = fluid-attenuated inversion recovery; **LP** = lumbar puncture; **MS** = multiple sclerosis; **NAIMS** = North American Imaging in Multiple Sclerosis; **OCB** = oligoclonal band; **ROC** = receiver operating characteristic; **SWI** = susceptibility-weighted.

Introduction

Making a diagnosis of multiple sclerosis (MS) can be challenging due to other conditions that mimic the symptoms, examination findings, and investigation results seen in MS. Diagnostic uncertainty can therefore arise, and patients frequently wait months, sometimes years, before the diagnosis is confirmed and treatment can start.¹ Diagnostic delays can affect disease outcomes because early diagnosis and treatment are important in preventing irreversible long-term disability.^{2,3} However, the main trade-off against early diagnosis is the risk of misdiagnosis because there is currently no definitive diagnostic test for MS.¹

CSF oligoclonal bands (OCBs) unmatched in serum support the diagnosis of MS in patients with a typical clinically isolated syndrome (CIS) using the 2017 McDonald diagnostic criteria.⁴ This has led to an increase in diagnostic sensitivity compared with previous iterations of the criteria.⁵ Although the majority of people with established MS have unpaired OCB (88%–99%), their sensitivity is lower in newly presenting patients (55%–68%).^{6,7} OCBs are also not specific for MS, being present in other inflammatory or infectious conditions.⁸ Lumbar puncture (LP), required to collect CSF, is often painful and may cause iatrogenic morbidity, most commonly post-LP headaches.^{9,10} As a result, LPs are associated with additional health care costs such as hospitalization for monitoring, an anesthetist performing a blood patch, and time off work.^{10,11}

The currently proposed modified diagnostic criteria introduce the central vein sign (CVS) as an imaging biomarker that can support the diagnosis of MS.¹² The CVS is the presence of a vein or venule in the center of each lesion.¹³ Research from the past 2 decades, initially using ultra-high-field (7T) and subsequently lower field (1.5 and 3T), high-resolution T2*-weighted (T2*), and susceptibility-weighted (SWI) MRI, has shown that the presence of the CVS in white matter lesions is highly specific to MS, able to differentiate it from other neuroinflammatory diseases.^{14–22} Initial studies used a threshold of 40% of lesions with a central vein,²¹ and later, the simplified “rule of 6” was introduced which requires finding 6 lesions with a central vein to differentiate MS from non-MS.²² The rule of 6 has now been incorporated into the latest proposed diagnostic criteria; patients with a typical history, evidence of dissemination in space, and 6 lesions with a central vein will be eligible to be diagnosed with MS. Alternatively, in the absence of evidence of dissemination in space, those with evidence of dissemination in time and 6

lesions with a central vein or unmatched OCB can be diagnosed with MS.¹²

We aimed to explore the diagnostic utility of the CVS in comparison with OCB in a cohort of patients with typical CIS to determine whether LP could be replaced by an MRI scan. The primary research question of this prospective, diagnostic superiority study was is CVS testing with T2* MRI more sensitive than OCB testing for the diagnosis of MS in patients presenting with typical CIS? The secondary objectives addressed the following¹: what is the specificity of the 2 diagnostic tests in patients with CIS?² What is the sensitivity and specificity of the rule of 6?³ What are the side effects and tolerability of LP and MRI in the diagnostic pathway of MS?

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

DECISive (DiagnosE using the CVS, clinical trials reference: NCT05533905) was a prospective, multicenter, pragmatic, single-group, rater-blinded, diagnostic accuracy study. The study was approved by a research ethics committee (19/LO/1499), and written informed consent was obtained from all participants before enrolment in the study. The study is reported in accordance with the STARD guidelines.²³

Study Design and Participants

Eligible participants aged 18–65 presented with a typical CIS⁴ for diagnostic evaluation of MS at 3 UK neuroscience centers (Queen’s Medical Centre, University Hospital of Wales, and The Royal London Hospital) in which LP was undertaken to assess whether patients met the revised 2017 McDonald diagnostic criteria for MS.⁴ Exclusion criteria included participants who were unable to communicate in English, unable or unwilling to provide informed consent, and/or those who already fulfilled the diagnosis of MS. Consecutive patients who met the eligibility criteria were approached after their consultation with a neurologist, and those who consented to participate were enrolled before their LP, which was undertaken as per standard of care at each study site. The investigations were to take place as soon as possible after enrolment into the study, and the order of the LP and MRI was not fixed. Any additional clinical investigations, such as blood tests for aquaporin-4 or myelin oligodendrocyte glycoprotein antibodies, or visual evoked potentials, were performed at the discretion of the clinical team.

MRI Protocol Acquisition

The study MRI was performed either as a separate research test or added to a clinical MRI before the injection of a gadolinium contrast agent (if applicable). The following 2 sequences were acquired on a 3T scanner (Philips Achieva in Nottingham, Siemens Magnetom Prisma in Cardiff, and Siemens Magnetom Verio in London): three-dimensional (3D) T2* gradient echo, sagittal acquisition, $0.6 \times 0.6 \times 0.6$ mm voxel size, $230 \times 230 \times 180$ mm field of view, effective echo time 25 ms, repetition time of 55 ms, parallel imaging factor 2, 10-degree flip angle, echo planar imaging factor or multiecho options if available, scan duration of 6 minutes or less, 3D fluid-attenuated inversion recovery (FLAIR), sagittal acquisition to match 3D T2* location, $1 \times 1 \times 1$ mm voxel size, $230 \times 230 \times 180$ mm field of view, manufacturer specific optimized acquisition settings, parallel imaging factor of 2, fat-saturation prepulse, and a scan duration of around 6 minutes.

Image Analysis

The treating neurologist did not view the T2* sequence or attempt to interpret the images, and they were not reported by a local radiologist. The MRI data acquired at each site were anonymized and transferred for blinded central review by 3 independent, blinded raters: M.A. Clarke, C.M. Allen, and H.V. Pai, neurology trainees at the time of the study, read the literature related to the CVS and were trained by R. Dineen, a professor of neuroradiology, who in addition to his research experience, assesses the CVS for clinical purposes. Training involved theoretical instruction on the imaging marker, followed by hands-on image interpretation with expert guidance. Proficiency was assessed through independent image interpretation and comparison with the RD readings. M.A. Clarke is a post-doctoral MS researcher who has been researching the CVS for 9 years. The images were split between the 3 raters and assessed independently. A proportion of scans was assessed by all raters to calculate interrater agreement.

Each FLAIR scan was assessed in 3D Slicer Version 4²⁴, and all distinct lesions, which measured at least 3 mm in 1 plane, were manually marked with fiducial coordinates. The fiducial coordinates were then used to identify lesions on the corresponding T2* scan, which used for the assessment of the CVS. The North American Imaging in MS (NAIMS) Cooperative radiologic definition of a central vein was used (Table 1).¹³ Example CVS-positive lesions are shown in Figure 1. The CVS was positive when $\geq 40\%$ of eligible lesions had a visible central vein. The cutoff value was selected before opening enrolment, following a recent prospective assessment of the CVS in cases of diagnostic uncertainty, which used the same MRI sequence and field strength as DECISive.²⁵ We also tested the performance of the rule of 6, which was met either if ≥ 6 CVS positive lesions were detected or if there were fewer than 6 lesions in total, $\geq 50\%$ of eligible lesions displayed the CVS.²²

Tolerability Analysis

All DECISive participants were invited to provide retrospective feedback on their experience of the LP and MRI scan

once the 2 tests had been performed but before the clinical diagnoses were known. This was collected using a five-point Likert scale rating the overall experience ("1—very poor" to "5—excellent"). Participants were asked if either had caused any immediate or delayed problems. To further explore participants' experiences, interviews took place using maximum variation sampling. The interviews were conducted by a person with MS, following training from the DECISive study team.

Clinical Follow-Up

Usual clinical follow-up provided the source of study follow-up assessment data. At 18 months, electronic and physical health records were accessed by the local research team.

Index Tests and Reference Standard

The analysis sample included participants who underwent both investigations of interest (CSF OCB by LP and CVS assessment on T2* MRI). The index tests were CSF OCB unmatched in serum, a positive CVS (40% or more lesions with a central vein detected on T2* MRI) and a positive rule of six. The reference standard was clinical diagnosis 18 months after recruitment. Since a positive CSF result can fulfil the 2017 McDonald criteria without further evidence of clinical or radiologic activity (thus inherently biasing the comparison between the CVS and OCB), we also tested the performance of both tests against a clinical diagnosis based on new lesions and/or a second relapse (previously termed *clinically definite MS*).

Statistical Analysis

Sensitivity, specificity, predictive values, and likelihood ratios of all tests were calculated, including 95% CIs. We used MedCalc v23.05 to calculate receiver operating characteristic (ROC) for all the index tests. If a participant attempted a test but a definitive test result was not available, it was assumed to be negative. The sensitivity of the tests was compared using the McNemar test for paired proportions. Interrater agreement was assessed by comparing the percentage agreement between the blinded raters in diagnoses according to the CVS, using the 40% threshold and the rule of 6, in a sample of 5 randomly selected patients.

Data Availability

Anonymized data not published within this article will be made available on reasonable request from any qualified investigator.

Results

Participant Demographic and Clinical Characteristics

A total of 113 participants were recruited over 30 months (7 November 2019 until 6 May 2022) across 3 participating sites (Figure 2). Fourteen participants withdrew from the study leading to a cohort of $n = 99$ whose demographic and clinical characteristics are given in Table 2. An alternative diagnosis

Table 1 NAIMS Cooperative CVS Criteria

Central vein eligibility criteria	Central vein exclusion criteria
Assessed on T2*	Assessed on FLAIR
Appears as a thin hypointense line or small hypointense dot	Infratentorial lesion location
Can be visualized in at least 2 perpendicular MRI planes, and appears as a thin line in at least 1 plane	Lesion merges with another lesion (confluent lesions)
Has a small apparent diameter (<2 mm)	Lesion is < 3 mm in diameter in any plane
Is positioned centrally in the lesion	Assessed on T2*
Runs partially or entirely through the lesion	Lesion is poorly visible (owing to motion or other MRI-related artifacts)
	Lesion has multiple distinct veins

Abbreviations: CVS = central vein sign; FLAIR = fluid-attenuated inversion recovery; NAIMS = North American Imaging in Multiple Sclerosis.

was reached in 8 participants: these included migraine (n = 2), non-MS inflammatory disorder (n = 1), idiopathic transverse myelitis (n = 1), chronic small vessel ischemic disease (n = 1), ischemic optic neuropathy (n = 1), fibromyalgia (n = 1), and radiologically isolated syndrome (RIS) (n = 1). One patient remained without a clinical diagnosis. The median interval between the LP and T2* MRI tests was 12 weeks (IQR 3–29). The LP was performed before the research MRI in 74 participants, the MRI was performed before the LP in 15 participants, and 10 had the LP and the research MRI on the same day.

Diagnostic Superiority, Sensitivity, and Specificity Analyses

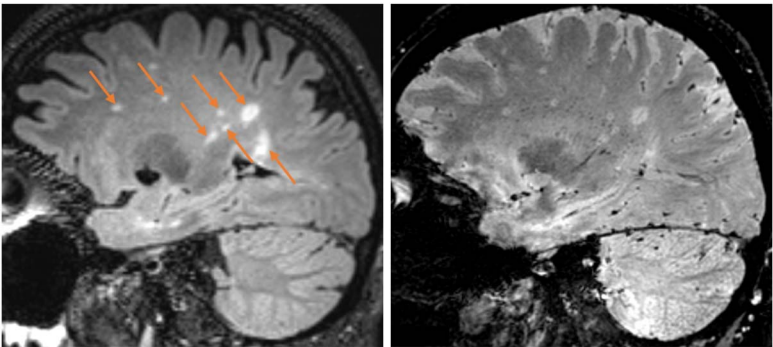
The comparison of sensitivities of the CVS and OCB testing in the MS vs non-MS group (excluding RIS and CIS) did not show superiority of the CVS assessment, as given in Table 3. Sensitivity of the CVS using the 40% threshold was 90% (CI 81%–96%), and OCB sensitivity was 84% (CI 74%–91%), McNemar test for paired proportions $p = 0.332$. The sensitivity of CVS assessment using the rule of 6 was 91% (CI 83%–96%). There were 6 discordant results for CVS assessment using the 40% threshold, and the rule of 6; 5 were

people in the MS group: 3 participants did not reach the 40% threshold (results ranged from 32% to 38% of lesions with a central vein) while fulfilling the rule of 6 and 2 fulfilled the 40% threshold (40% and 44% of eligible lesions with a central vein) without fulfilling the rule of 6. One person with RIS also fulfilled the rule of 6 without satisfying the 40% threshold (21% of eligible lesions with a central vein).

OCB achieved 100% (CI 50%–100%) specificity, while specificity for CVS using the 40% threshold and the rule of 6 were both 57% (CI 18%–90%) (Table 4). Three patients with alternative conditions had a positive CVS according to the 40% threshold and the rule of 6. The diagnoses were fibromyalgia (50% of eligible lesions with a central vein), ischemic optic neuropathy (60% of eligible lesions with a central vein), and cerebrovascular disease (50% of eligible lesions with a central vein). The diagnostic accuracy of OCB, CVS using the 40% threshold, and CVS rule of 6 were 85% (CI 76%–92%), 87% (CI 79%–94%), and 89% (CI 80%–94%), respectively.

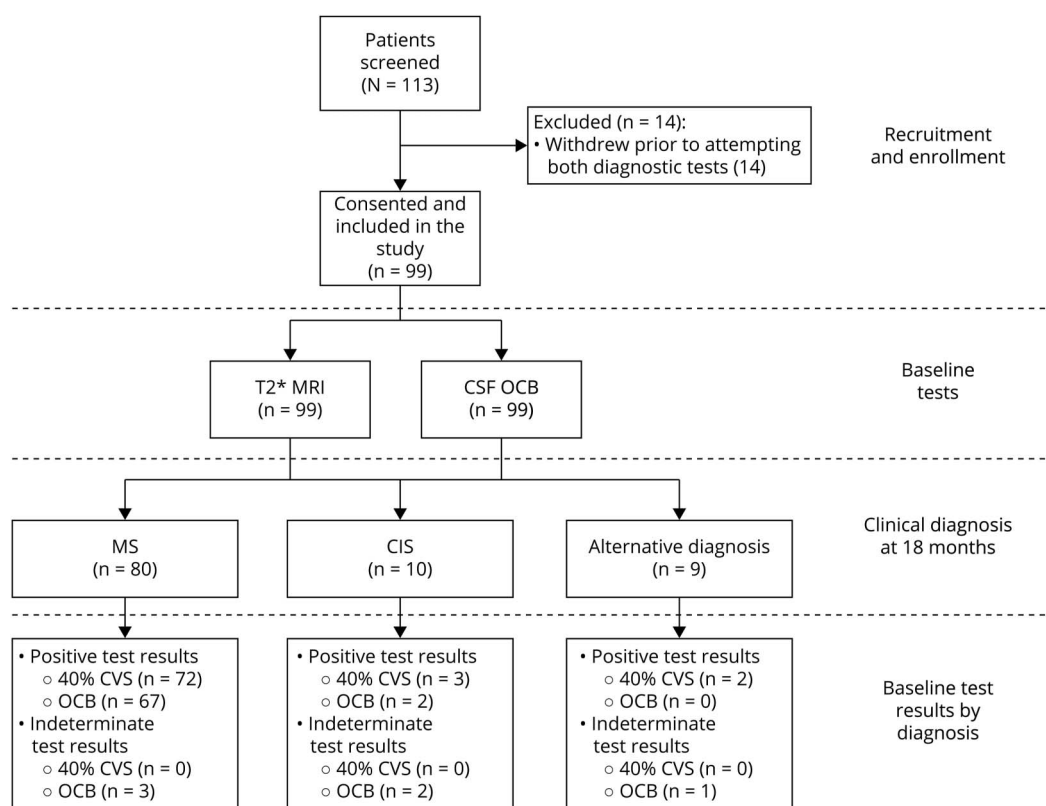
Information regarding new MRI lesions and/or clinical relapses in the 18 months of follow-up was available for 76

Figure 1 Example of Multiple Sclerosis Lesions With a Central Vein



Sagittal fluid-attenuated inversion recovery (FLAIR) of MS lesions (marked by orange arrows) and the corresponding slice of the T2* image showing the lesions each have a central vein.

Figure 2 DECISive Study Flow Diagram



participants. When comparing the diagnostic sensitivity of the CVS 40% threshold and OCB testing against clinically definite MS (evidence of new lesions and/or relapses), the CVS sensitivity was 96% (CI 86%–99%) and OCB sensitivity was 79% (CI 65%–90%), the McNemar test for paired proportions $p = 0.039$. The sensitivity of the rule of 6 was 94% (CI 83%–99%). A cross tabulation of all the index tests (CSF OCB, CVS using the 40% threshold, and rule of 6), the reference standard (clinical diagnosis at 18-month follow-up), and the alternative reference standard (clinically defined MS at 18 months) are presented in eTables 1 and 2. A ROC curve of all the index tests is shown in eFigure 1.

Interrater Agreement

The three-way interrater agreement was 100% meaning all raters independently agreed on the CVS result using both the 40% threshold and rule of 6. The 5 assessed cases included 4 participants who had a central vein in more than 40% of eligible lesions; all of them were given a clinical diagnosis of MS. One participant did not reach the 40% threshold, and their clinical diagnosis remains unknown. This participant also had negative OCB.

Tolerability Analysis

For the MRI scan, the mean Likert tolerability score was 4.4 (good), SD 0.7, and for LP, it was 3.4 (fair), SD 1.2 (comparison with the Wilcoxon signed-rank test $Z = -4.4$, $p < 0.001$). Immediate or delayed problems were reported by 74

participants following their LP and 9 following their MRI scan. Headache was reported by 33% and back pain by 27%, which were the commonest problems following the LP, which necessitated up to a fortnight off work or usual caring responsibilities in 15% of study participants. The MRI scans occasionally caused brief dizziness or claustrophobia, but there were no reports of time off work.

Seventeen participants took part in interviews (9 female, mean age 45 years [SD 13 years]). All expressed a preference for their MRI scan over their LP. The most striking difference between the 2 tests, at any time point, was the burden experienced during the LP. Many participants also reported considerable anxiety before their LP caused by sharing of negative accounts through social networks or online.

Classification of Evidence

This study provides Class IV evidence that CSF oligoclonal bands and the central vein sign are equally sensitive in supporting a diagnosis of MS in patients presenting with CIS.

Discussion

Diagnostic LP, known to be associated with iatrogenic morbidity, has been used by many centers aiming to expedite the diagnosis of MS as per the 2017 modified diagnostic criteria.⁴ Our results demonstrate that the CVS, including the rule of 6,

Table 2 Baseline Characteristics of Participants Included in the Study

Baseline characteristics	Diagnosis of MS (N = 80)	Diagnosis of CIS (N = 10)	Alternative diagnosis (N = 9)	Total (N = 99)
Mean age at enrolment, y (SD)	38 (12)	40 (13)	39 (12)	38 (12)
Sex				
Female, n (%)	60 (75)	8 (80)	6 (67)	74 (75)
Male, n (%)	20 (25)	2 (20)	3 (33)	25 (25)
Ethnicity				
White, n (%)	68 (85)	8 (80)	8 (89)	84 (85)
Asian, n (%)	6 (8)	0	1 (11)	7 (7)
Black, n (%)	3 (4)	0	0	3 (3)
Mixed, n (%)	1 (1)	1 (10)	0	2 (2)
Other, n (%)	2 (3)	0	0	2 (2)
Not provided, n (%)	0	1 (10)	0	1 (1)
Past or current tobacco use, n (%)	36 (46)	7 (70)	1 (11)	44 (45)
Hypertension, n (%)	5 (6)	1 (10)	4 (44)	10 (10)
Diabetes, n (%)	4 (5)	1 (10)	1 (11)	6 (6)
Other medical comorbidities, n (%)	2 (3)	4 (40)	4 (44)	31 (31)
Family history of MS (%)	8 (10)	0	0	8 (8)
Mode of presentation				
GP, n (%)	15 (19)	4 (40)	4 (40)	23 (23)
Emergency admission, n (%)	18 (23)	3 (30)	1 (11)	22 (22)
Ophthalmology, n (%)	21(26)	1 (10)	3 (30)	25 (25)
Other, n (%)	26 (33)	2 (20)	1 (10)	29 (29)
Suspected additional relapse(s), n (%)	18 (23)	1 (10)	2 (22)	21 (21)
Clinical brain MRI before enrolment, n (%)	71 (89)	8 (80)	9 (100)	88 (89)
Number of lesions				
None, n (%)	0	2 (25)	0	2 (2)
1, n (%)	2 (3)	1 (13)	1 (11)	4 (5)
2–3, n (%)	7 (10)	1 (13)	2 (22)	10 (11)
4–9, n (%)	30 (42)	2 (25)	3 (33)	35 (40)
10+, n (%)	27 (38)	1 (13)	1 (11)	29 (33)
Unknown, n (%)	5 (7)	1 (13)	2 (22)	8 (9)
Clinical spine MRI before enrolment, n (%)	36 (45)	7 (70)	4 (44)	47 (47)
Number of lesions				
None, n (%)	9 (25)	3 (43)	3 (75)	15 (32)
1, n (%)	8 (22)	2 (29)	0	11 (23)
2–3, n (%)	16 (44)	1 (14)	1 (25)	18 (38)
4–9, n (%)	2 (6)	0	0	2 (4)
10+, n (%)	0	0	0	0

Continued

Table 2 Baseline Characteristics of Participants Included in the Study (*continued*)

Baseline characteristics	Diagnosis of MS (N = 80)	Diagnosis of CIS (N = 10)	Alternative diagnosis (N = 9)	Total (N = 99)
Unknown, n (%)	1 (3)	1 (14)	0	2 (4)
Time from symptom onset to enrolment, wk (IQR)	18 (9–42)	19 (14–38)	34 (13–45)	19 (10–43)
Site of enrolment				
Nottingham, n (%)	48 (60)	3 (30)	3 (33)	54 (55)
Cardiff, n (%)	24 (30)	7 (70)	4 (44)	35 (35)
London, n (%)	8 (10)	0 (0)	2 (22)	10 (10)

Abbreviations: CIS = clinically isolated syndrome; GP = general practitioner; MS = multiple sclerosis.

has equivalent sensitivity to OCB testing using a prospective, multicenter study of participants presenting with typical CIS. Our study also included a tolerability analysis, which demonstrated higher tolerability of the additional MRI compared with LP. Also in our study, T2* scans were performed as a separate research intervention; however, a T2* sequence (or a similar sequence such as SWI) that takes minutes to acquire can easily be added on to standard MRI brain protocols when MS is suspected. This includes different scanner vendors and field strengths.^{18,20,26} Although the image analysis for this study was performed offline by trained image raters rather than radiologists using clinical PACS reporting systems, we do not foresee any major barriers to clinical translation of this approach. The level of agreement between raters in our study shows that with training and experience, it is possible to achieve consistent results when assessing the CVS. Radiologists and neurologists can also readily interpret the simplified rule of 6 without having to assess all lesions.

One of the fundamental issues with diagnostic accuracy studies in MS is the lack of a diagnostic gold standard to use against any proposed test. Except in rare cases, biopsy is not a feasible approach, so relying on clinical diagnoses in our study led to 2 different diagnostic standards being used, determined by OCB status. Only OCB negative cases required

proof of further radiologic or clinical disease activity. OCB showed higher specificity than CVS assessment in this study, perhaps due to this bias. In addition, clinical follow-up of only 18 months limited the accuracy of the final clinical diagnosis. The most likely outcome is that some participants whose final study diagnosis remains CIS will go on to be given a diagnosis of MS in the next 5 years, when evidence of further radiologic or clinical disease activity is detected. However, study duration could not be increased without affecting the timeliness of the study findings to influence clinical care and going beyond the acceptable duration of the study's funder.

We also applied a different reference standard of clinically definite MS to a subset where this information was available: those with evidence of new MRI lesions and/or relapses during the follow-up period. Although this comparison remained biased as those with OCB were often commenced on disease-modifying treatment following their clinical diagnosis, which suppresses this activity. Using this standard, we were able to demonstrate a significantly higher diagnostic sensitivity of the CVS compared with OCB testing, but OCB specificity remained higher than CVS assessment. This study was conducted in experienced MS centers, and only 8 patients were given an alternative diagnosis at the end of the follow-up period. This inherently underpowered our study to reliably assess specificity due to the study only recruiting those with typical CIS. Further studies are needed to evaluate CVS specificity, particularly outside of typical CIS cases, as studied here.

Recently, Toljan et al. compared OCB with CVS reporting similar sensitivity of the rule of 6 and OCB (71% vs 75%, respectively) with increased specificity of the CVS compared with OCB (86% vs 76%).²⁷ We are encouraged by the result showing high specificity of the CVS in a study which intentionally enrolled MS and non-MS cases. In another study by the same group,²⁸ the rule of 6 showed 65% sensitivity and 98% specificity in correctly classifying patients with MS. We believe that differences in the target population (people with typical CIS requiring only a positive LP to be diagnosed with

Table 3 Comparison of the Sensitivity of the Central Vein Sign and Oligoclonal Band Testing

		CVS correctly diagnosed MS		Total, (%)
		Yes	No	
OCB correctly diagnosed MS	Yes	61	6	67/80 (84)
	No	11	2	13/78 (17)
Total, (%)		72/80 (90)	8/80 (10)	80

Abbreviations: CVS = central vein sign; MS = multiple sclerosis; OCB = unmatched oligoclonal bands.
p value from the McNemar test: *p* = 0.332.

Table 4 Diagnostic Accuracy Measures for the Central Vein Sign and Oligoclonal Band Testing

Test performance	CVS	Rule of 6	OCB
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)
Sensitivity	90.0 (81.2–95.6)	91.3 (82.8–96.4)	83.8 (73.8–91.1)
Specificity	57.1 (18.4–90.1)	57.1 (18.4–90.1)	100.0 (59.0–100.0)
Predictive values for MS			
Positive predictive value	96.0 (91.1–98.3)	96.1 (91.2–98.3)	100.0 (94.6–100.0)
Negative predictive value	33.3 (16.6–55.6)	36.4 (18.0–59.8)	35.0 (24.7–47.0)
Likelihood ratios for MS			
Positive likelihood ratio	2.1 (0.9–5.0)	2.13 (0.9–5.0)	—
Negative likelihood ratio	0.2 (0.1–0.4)	0.2 (0.1–0.4)	0.2 (0.1–0.3)

Abbreviations: CVS = central vein sign; MS = multiple sclerosis; OCB = unmatched oligoclonal bands.

MS in our study, and people with T2 lesions and suspicion of MS in the 2 other studies) led to the differences in reported sensitivity and specificity. CVS assessment requires NAIMS CVS eligible supratentorial lesions. Typical CIS presentations include optic neuritis and partial transverse myelitis, and patients may have no lesions eligible for CVS interpretation at their first presentation. The range assessed in DECISive was 0–37. Although there is no evidence of a difference in performance between the CVS 40% threshold and the rule of 6 in DECISive, combining high-quality diagnostic studies would create a larger data set to assess the reliability of CVS interpretation with high and low lesion counts.

The proposed changes to the McDonald criteria specify that a positive LP or finding 6 lesions with a central vein can confirm a diagnosis of MS. With increasing recognition of MS misdiagnosis,²⁹ the desire to reach a diagnosis earlier (even in RIS), and our findings of a unanimous preference for an additional MRI scan over an LP, we encourage the widespread adoption of susceptibility-based imaging for MS diagnosis. CVS assessment should be particularly helpful in older patients or those presenting with vascular risk factors.

Our study was affected by the coronavirus pandemic. Initially, both diagnostic tests were planned to take place within 8 weeks of each other, to minimize the risk of bias. However, due to lack of MRI scanner capacity and recurrent periods of lockdowns, the CVS assessment took place at a systematically later timepoint for some while LPs continued as usual as they were classed as routine clinical care. Considering that the CVS presence is not related to timing of assessment,³⁰ we do not think this affected our results. However, there were participants who withdrew consent because of the pandemic, which lowered the final power of the primary analysis.

This multicenter study supports the use of CVS at centers that have a 3T MRI scanner and radiologists reporting through the rule of 6. Some patients may still require diagnostic LP, for

example, to rule out viral infection in cases of partial transverse myelitis. However, we expect that the overall number of patients requiring diagnostic LP will reduce, thereby reducing the burden for patients and costs of health care services. Building on these findings, a future economic analysis can formally assess the costs and consequence of implementing the CVS.

DECISive has shown that the sensitivity of the CVS is comparable with testing for OCB at first presentation with typical CIS in a pragmatic prospective multicenter study which aimed to replicate its performance in routine clinical practice. CVS with a threshold of 40% and the rule of 6 produced equivalent diagnostic performance, suggesting this could easily be implemented in clinical practice in centers with a 3T MRI scanner.

Acknowledgment

The authors thank all the study participants and our study research team, who helped recruit and scan patients for this study.

Author Contributions

C.M. Allen: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. M.A. Clarke: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. H.V. Pai: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. M. Cauchi: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J. Hawken: major role in the acquisition of data. Z.M. Htet: major role in the acquisition of data. K. Allen-Philbey: major role in the acquisition of data. B. Mohamed: major role in the acquisition of data. D. Fitzsimmons: drafting/revision of the manuscript for content,

including medical writing for content; study concept or design. R. Das Nair: drafting/revision of the manuscript for content, including medical writing for content; study concept or design. P. Morgan: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C. Partlett: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. R.A. Dineen: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. K. Schmierer: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. E.C. Tallantyre: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. N. Evangelou: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

Study Funding

This study was funded by NIHR Research for Patient Benefit (PB-PG-0418-20044).

Disclosure

C.M. Allen has received grant income from the National Institute for Health and Care Research (NIHR). M.A. Clarke is a 2023ECTRIMS postdoctoral research fellow. R. das Nair has received research grants from the UK NIHR, the UKMS Society, and Progressive MS Alliance; and has received speakers' bureau fees from Biogen, Novartis, and Merck. P.S. Morgan has received honoraria and travel funding to speak at educational meetings from Janssen; and research support from the UK National Institute of Health Research and General Electric Healthcare. R.A. Dineen has received research support from the UK National Institute of Health Research. K. Schmierer is a member of the MAGNIFY-MS steering committee and the MS Global Advisory Network (Merck KGaA); is Chief Investigator of ChariotMS, supported by the National Institute of Health Research EME programme, the MS Society of Great Britain and Northern Ireland, the National MS Society (US), Barts Charity, and Merck KGaA; has received further research support from Biogen, Roche, Novartis, and Sandoz; has received speaking honoraria from and/or served in an advisory role for Biogen, Merck, Novartis, Roche, Sanofi-Genzyme, and T.G. Therapeutics; and has received remuneration for teaching activities from Medscape and MS Academy. E.C. Tallantyre has received honoraria for consulting work from Biogen, Janssen, Merck, Novartis, and Roche; and has received travel grants to attend or speak at educational meetings from Biogen, Merck, Roche, Takeda, and Novartis. N. Evangelou has served as a member of advisory boards for Biogen, Merck, Novartis, and Roche; and has received grant income from the United Kingdom Multiple Sclerosis Society, the Medical Research Council, the Patient-Centered Outcomes Research

Institute, and the National Institute for Health Research. All other authors have no relevant disclosures. Go to Neurology.org/OA for full disclosures.

Publication History

Received by *Neurology*® Open Access January 7, 2025. Accepted in final form March 27, 2025. Submitted and externally peer reviewed. The handling editor was Amy Kunchok, MBBS, MMed, FRACP, PhD.

References

- Solomon AJ, Arrambide G, Brownlee WJ, et al. Differential diagnosis of suspected multiple sclerosis: an updated consensus approach. *Lancet Neurol*. 2023;22(8):750-768. doi:10.1016/s1474-4422(23)00148-5
- Comi G, Radaelli M, Soelberg Sørensen P. Evolving concepts in the treatment of relapsing multiple sclerosis. *Lancet*. 2017;389(10076):1347-1356. doi:10.1016/s0140-6736(16)32388-1
- Fernández Ó. Is there a change of paradigm towards more effective treatment early in the course of apparent high-risk MS? *Mult Scler Relat Disord*. 2017;17:75-83. doi:10.1016/j.msard.2017.07.003
- Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162-173. doi:10.1016/s1474-4422(17)30470-2
- Filippi M, Preziosa P, Meani A, et al.; MAGNIMS Study Group. Performance of the 2017 and 2010 revised McDonald criteria in predicting MS diagnosis after a clinically isolated syndrome: a MAGNIMS study. *Neurology*. 2022;98(1):e1-e14. doi:10.1212/WNL.00000000000013016
- Schwenkenbecher P, Sarikidi A, Wurster U, et al. McDonald criteria 2010 and 2005 compared: persistence of high oligoclonal band prevalence despite almost doubled diagnostic sensitivity. *Int J Mol Sci*. 2016;17(9):1592. doi: 10.3390/ijms17091592
- Dobson R, Ramagopalan S, Davis A, Giovannoni G. Cerebrospinal fluid oligoclonal bands in multiple sclerosis and clinically isolated syndromes: a meta-analysis of prevalence, prognosis and effect of latitude. *J Neurol Neurosurg Psychiatry*. 2013;84(8):909-914. doi:10.1136/jnnp-2012-304695
- Freedman MS, Thompson EJ, Deisenhammer F, et al. Recommended standard of cerebrospinal fluid analysis in the diagnosis of multiple sclerosis: a consensus statement. *Arch Neurol*. 2005;62(6):865-870. doi:10.1001/archneur.62.6.865
- Scotton WJ, Mollan SP, Walters T, et al. Characterising the patient experience of diagnostic lumbar puncture in idiopathic intracranial hypertension: a cross-sectional online survey. *BMJ Open*. 2018;8(5):e020445. doi:10.1136/bmjopen-2017-020445
- Davis A, Dobson R, Kaninia S, et al. Change practice now! Using atraumatic needles to prevent post lumbar puncture headache. *Eur J Neurol*. 2014;21(2):305-311. doi:10.1111/ene.12307
- Jabbari A, Alijanpour E, Mir M, Bani Hashem N, Rabiea SM, Rupani MA. Post spinal puncture headache, an old problem and new concepts: review of articles about predisposing factors. *Caspian J Intern Med*. 2013;4(1):595-602.
- Montalban X. Revised McDonald cCriteria 2023. *40th Congress of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)*. 2024.
- Sati P, Oh J, Constable RT, et al.; NAIMS Cooperative. 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. *Nat Rev Neurol*. 2016;12(12):714-722. doi:10.1038/nrneurol.2016.166
- Tallantyre EC, Brookes MJ, Dixon JE, Morgan PS, Evangelou N, Morris PG. Demonstrating the perivascular distribution of Ms lesions in vivo with 7-tesla MRI. *Neurology*. 2008;70(22):2076-2078. doi:10.1212/01.wnl.0000313377.49555.2e
- Mistry N, Dixon J, Tallantyre E, et al. Central veins in brain lesions visualized with high-field magnetic resonance imaging: a pathologically specific diagnostic biomarker for inflammatory demyelination in the brain. *JAMA Neurol*. 2013;70(5):623-628. doi: 10.1001/jamaneurol.2013.1405
- Tallantyre EC, Morgan PS, Dixon JE, et al. A comparison of 3T and 7T in the detection of small parenchymal veins within MS lesions. *Invest Radiol*. 2009;44(9):491-494. doi:10.1097/rli.0b013e3181b4c144
- Tan IL, Van Schijndel RA, Pouwels PJW, et al. MR venography of multiple sclerosis. *AJNR Am J neuroradiology*. 2000;21(6):1039-1042.
- Clarke MA, Pareto D, Pessini-Ferreira L, et al. Value of 3T susceptibility-weighted imaging in the diagnosis of multiple sclerosis. *AJNR Am J neuroradiology*. 2020;41(6):1001-1008. doi:10.3174/ajnr.A6547
- Hammond KE, Metcalf M, Carvajal L, et al. Quantitative in vivo magnetic resonance imaging of multiple sclerosis at 7 Tesla with sensitivity to iron. *Ann Neurol*. 2008;64(6):707-713. doi:10.1002/ana.21582
- Samaraweera APR, Clarke MA, Whitehead A, et al. The central vein sign in multiple sclerosis lesions is present irrespective of the T2* sequence at 3 T. *J Neuroimaging*. 2017;27(1):114-121. doi:10.1111/jon.12367
- Tallantyre EC, Dixon JE, Donaldson I, et al. Ultra-high-field imaging distinguishes MS lesions from asymptomatic white matter lesions. *Neurology*. 2011;76(6):534-539. doi: 10.1212/WNL.0b013e31820b7630
- Mistry N, Abdel-Fahim R, Samaraweera A, et al. Imaging central veins in brain lesions with 3-T T2*-weighted magnetic resonance imaging differentiates multiple sclerosis from microangiopathic brain lesions. *Mult Scler*. 2016;22(10):1289-1296. doi:doi:10.1177/1352458515616700

23. Bossuyt PM, Reitsma JB, Bruns DE, et al.; STARD Group. Stard 2015: an updated list of essential items for reporting diagnostic accuracy studies. *BMJ*. 2015;351:h5527. doi:10.1136/bmj.h5527
24. Fedorov A, Beichel R, Kalpathy-Cramer J, et al. 3D slicer as an image computing platform for the quantitative imaging network. *Magn Reson Imaging*. 2012;30(9):1323-1341. doi:10.1016/j.mri.2012.05.001
25. Clarke MA, Samaraweera APR, Falah Y, et al. Single Test to ARrive at Multiple Sclerosis (STAR-MS) diagnosis: a prospective pilot study assessing the accuracy of the central vein sign in predicting multiple sclerosis in cases of diagnostic uncertainty. *Mult Scler*. 2020;26(4):433-441. doi:10.1177/1352458519882282
26. Maggi P, Absinta M, Grammatico M, et al. Central vein sign differentiates Multiple Sclerosis from central nervous system inflammatory vasculopathies. *Ann Neurol*. 2018;83(2):283-294. doi:10.1002/ana.25146
27. Toljan K, Daboul L, Raza P, et al. Diagnostic performance of central vein sign versus oligoclonal bands for multiple sclerosis. *Mult Scler*. 2024;30(10):1268-1277. doi:10.1177/13524585241271988
28. Daboul L, O'Donnell CM, Amin M, et al. A multicenter pilot study evaluating simplified central vein assessment for the diagnosis of multiple sclerosis. *Mult Scler*. 2024;30(1):25-34. doi:10.1177/13524585231214360
29. Kaisey M, Solomon AJ, Luu M, Giesser BS, Sicotte NL. Incidence of multiple sclerosis misdiagnosis in referrals to two academic centers. *Mult Scler Relat Disord*. 2019;30:51-56. doi:10.1016/j.msard.2019.01.048
30. Sinnecker T, Clarke MA, Meier D, et al.; MAGNIMS Study Group. Evaluation of the central vein sign as a diagnostic imaging biomarker in multiple sclerosis. *JAMA Neurol*. 2019;76(12):1446-1456. doi:10.1001/jamaneurol.2019.2478