Central Veins in Brain Lesions Visualized With High-Field Magnetic Resonance Imaging

A Pathologically Specific Diagnostic Biomarker for Inflammatory Demyelination in the Brain

Niraj Mistry, MA; Jennifer Dixon, PhD; Emma Tallantyre, PhD; Christopher Tench, PhD; Rasha Abdel-Fahim, MBBCh; Tim Jaspan, FRCR; Paul S. Morgan, PhD; Peter Morris, PhD; Nikos Evangelou, FRCP

Importance: There is no single test that is diagnostic for multiple sclerosis (MS), and existing diagnostic criteria are imperfect. This can lead to diagnostic delay. Some patients require multiple (sometimes invasive) investigations, and extensive clinical follow-up to confirm or exclude a diagnosis of MS. A diagnostic biomarker that is pathologically specific for the inflammatory demyelination in MS could overhaul current diagnostic algorithms.

Objective: To prospectively assess the diagnostic value of visualizing central veins in brain lesions with magnetic resonance imaging (MRI) for patients with possible MS for whom the diagnosis is uncertain.

Design: Prospective longitudinal cohort study. The reference standard is a clinical diagnosis that is arrived at (after a mean follow-up of 26 months) by the treating neurologist with a specialist interest in MS. The 7-T MRI scans were analyzed at baseline, by physicians blinded to the clinical data, for the presence of visible central veins.

Setting: Academic MS referral center.

Participants: A consecutive sample of 29 patients referred with possible MS who had brain lesions detected on clinical MRI scans but whose condition remained undiagnosed despite expert clinical and radiological assessments.

Exposure: Seven-Tesla MRI using a T2*-weighted sequence.

Main Outcomes and Measures: The proportion of patients whose condition was correctly diagnosed as MS or as not MS, using 7-T MRI at study onset, compared with the eventual diagnosis reached by treating physicians blinded to the result of the MRI scan.

Results: Of the 29 patients enrolled and scanned using 7-T MRI, so far 22 have received a clinical diagnosis. All 13 patients whose condition was eventually diagnosed as MS had central veins visible in the majority of brain lesions at baseline. All 9 patients whose condition was eventually not diagnosed as MS had central veins visible in a minority of lesions.

Conclusions and Relevance: In our study, T2*-weighted 7-T MRI had 100% positive and negative predictive value for the diagnosis of MS. Clinical application of this technique could improve existing diagnostic algorithms.

teria counteract the inherent lack of specificity with which MRI depicts MS lesions.

In a significant minority of cases, however, diagnosing MS can be challenging, especially in the early stages, in late-onset disease, and in the absence of a typical history. This is a problem mainly encountered in MS referral centers. The International Panel stipulates that their criteria for diagnosis of MS should be applied only when patients have experienced a typical clinically isolated syndrome (CIS) (or progressive paraparesis, cerebellar syndrome, or cognitive syndrome in the case of suspected primary progressive MS), thereby reinforcing specificity by improving “pre-test” probability of eventual MS. The presence of oligoclonal bands in cerebrospinal fluid at the time of initial presentation cannot always be relied on; study results vary widely, but only 46% to 75% of newly presenting patients have oligoclonal bands, and oligoclonal bands can be present in conditions other than MS. If MRI could have enhanced histopathological specificity for white matter lesions, future diagnostic criteria for MS could be simplified.

Many neurologists consider early treatment of MS, even following a CIS, to be beneficial. Despite this, initial misdiagnosis, long referral delays, and long diagnostic delays are widespread.

The histopathological precedent that most MS lesions are centered on a vein was elegantly demonstrated long ago, and it is consistent with the hypothesis that autoreactive T cells enter brain parenchyma from the systemic circulation and induce local destruction of myelin. Of all pathological features that define CNS demyelinating diseases and distinguish them from other predominantly white matter diseases, the perivenous demyelination identified by microscopy is the most specific. Standard T2-weighted 1.5-T MRI of the brain, in conjunction with additional susceptibility-weighted imaging MR venography, has previously been used to show the relationship between MS lesions and blood vessels. Although this technique can be used to detect an MS lesion and a blood vessel in close proximity to each other, its failure to demonstrate them simultaneously using a single-image acquisition makes exact spatial relationships difficult to determine.

Ultrahigh-field in vivo MRI can be used to provide enhanced spatial resolution and strong T2* contrast (owing to the paramagnetic properties of deoxyhemoglobin, veins become especially hypointense in T2*-weighted images). Ultrahigh-field strength, 7-T T2*-weighted MRI has previously been used to detect central veins in the majority of lesions in patients known to have MS, and it is superior to susceptibility-weighted imaging at visualizing relevant sizes of veins in varying orientations. Applying the same 7-T MRI technique has been shown to accurately distinguish patients known to have MS (in whom >40% of lesions appeared to have central veins) from patients known to have ischemic (ie, microangiopathic) incidental white matter MRI-detected hyperintensities (in whom <40% of lesions appeared to have central veins).

The real usefulness of a diagnostic biomarker depends on its accuracy at the time of the patient’s initial presentation, rather than its ability to distinguish established cases of MS from cases known to not have MS. The present study aimed to prospectively assess the value of a single 7-T T2*-weighted MRI brain scan for predicting an eventual diagnosis of MS in patients for whom the question of inflammatory demyelination has been raised but for whom a diagnosis of their condition could not initially be determined despite experienced clinical and radiological assessments.

Figure 1. Patient flow diagram summarizing 7-T T2*-weighted magnetic resonance imaging (MRI) study design. All 29 patients underwent the index test, which was a single 7-T MRI brain scan. The test result was positive if more than 40% of visible brain lesions appeared perivenous and negative if less than 40% of visible brain lesions appeared perivenous. The reference standard is a clinical diagnosis that is arrived at (after a mean follow-up of 26 months) by the treating neurologist with a specialist interest in multiple sclerosis (MS). In one patient, the 7-T brain scan could not be interpreted because it was degraded by a movement artifact. The reference standard has so far been inconclusive in 7 patients, who remain under clinical follow-up.

**METHOD**

**PARTICIPANTS**

Patients referred to the neurology department of the Nottingham University Hospitals NHS Trust in England were considered for enrollment in our study if a neurologist specializing in MS was unable to diagnose whether the patient’s condition was...
MS or not without further paraclinical testing and/or clinical follow-up. Prior to enrollment, a participant must have had at least 1 MRI brain scan of satisfactory diagnostic quality, which was then interpreted by an experienced neuroradiologist with whom the treating neurologist had discussed the clinical details.

Recruited patients comprised 2 groups. One group was composed of patients who had experienced a typical CIS (or sustained deterioration consistent with progressive MS) but had MRI findings inconsistent or insufficient to support a diagnosis of MS. The other group was composed of patients with neurological presentations not conforming to typical CIS (or sustained deterioration consistent with progressive MS), for whom subsequent MRI raised neuroradiological suspicions of demyelinating disease. Our study population consisted of a consecutive series of participants defined by the inclusion and exclusion criteria who were prospectively enrolled before the index test (7-T high-field MRI) was performed. After the index test, patients were followed up prospectively to allow for the reference standard of clinical diagnosis to be achieved, by the accrual of further clinical events and/or additional clinical investigations.

Potential participants were excluded if they did not wish to undergo additional MRI of the brain. All participants gave informed consent, and our study had been approved by the local research ethics committee.

**TEST METHODS**

The reference standard was the eventual diagnosis arrived at by the treating neurologists with a specialist interest in MS who were blinded to the results from the 7-T MRI analysis. The diagnosis, as is standard practice, was reached by using the clinical history of the patient and the results of the examination and paraclinical tests, in accordance with the criteria of the International Panel on Diagnosis of MS available at the time.

The index test was a single T2*-weighted 7-T MRI brain scan performed and analyzed in advance of any further investigations arranged by the treating neurologists. Images were acquired using a Philips Achieva 7T system (Philips Medical Systems) equipped with whole-body gradients, a 16-channel head-only parallel imaging sensitivity encoding (SENSE) receiver coil, and a head-only volume transmit coil (Nova Medical, Inc.). A 3-dimensional gradient echo sequence was acquired using 200 transverse slices acquired in 4 stacks, each stack overlapping by 10 slices (192×164×85 mm³ field of view; 0.5-mm isotropic voxels; echo time, 20 milliseconds; repetition time, 150 milliseconds; and flip angle, 14°). A parallel imaging SENSE factor of 2 (right-left direction) and an echoplanar imaging factor of 3 were used; the acquisition time was 8.8 minutes.

A neurology research fellow blinded to all clinical information analyzed the anonymized MRI data, guided by an experienced neuroradiologist. Analysis was restricted to the supratentorial brain volume because, at the time of our study, the 7-T receiver coil array yielded a suboptimal signal to noise ratio infratentorially. Lesions were classed as perivenous if they appeared to have 1 or more central veins. On 7-T MRI scans, a central vein was considered to be present if its hypointensity appeared at the center of the surrounding hyperintense lesion infratentorially. A perivenous lesion percentage “cutoff” of 40% was chosen to predict a diagnosis of MS (>40%) or non-MS (<40%) based on the findings of previous work.

**STATISTICAL METHODS**

The Fisher exact test was used to compare the proportion of perivenous lesions and the occurrence rate of specific vein-lesion morphologies between the MS and non-MS groups. We estimated the accuracy of the index test by calculating the proportion of agreement with the reference standard.

Although the data were anonymized, there was potential for unblinding based on whether the lesions had an anatomical distribution characteristic of MS. To assess the vein-lesion clas-
sification reproducibility and to determine whether the vein-lesion classification had been influenced by such unblinding, tightly cropped images of randomly selected lesions (without anatomical context or orientation information) were classified according to perivenous status by a second observer who was blinded to the original results. This was done for 20 lesions seen in 3 orthogonal planes. A Cohen \( \kappa \) coefficient of agreement between the 2 observers was calculated.

**RESULTS**

Twenty-nine patients were recruited between May 13, 2009, and February 10, 2012 (comprising 21 women and 8 men) whose median age was 50.7 years (range, 30.6-74.5 years). All patients underwent a single T2*-weighted 7-T MRI brain scan (ie, the index test). Seven patients had not yet received a clinical diagnosis from their neurologist. This is summarized in Figure 1. The median follow-up period (since the index test) is currently 26 months (range, 4-37 months). None of the patients received disease-modifying therapies during the study period. All those who eventually received a diagnosis of MS had minimal or no disability.

Of the 22 patients who received a clinical diagnosis, 13 received a diagnosis of MS, and 9 were diagnosed as having microangiopathic white matter lesions (ie, definitely not MS). All 13 patients who eventually received a diagnosis of MS had central veins visible in more than 40% of brain lesions (median, 97% [range, 70%-100%]). All 9 patients who were diagnosed as not having MS had central veins visible in less than 40% of brain lesions (median, 25% [range, 9%-33%]) (Figure 2). This difference in the proportion of perivenous lesions between the MS group and the non-MS group was highly significant (\( P < .001 \)). Examples of lesions from each group are shown in Figure 3. Lesions in the MS group often had a characteristic morphology when seen using 7-T T2*-weighted MRI, as shown in Figure 4. A cross-tabulation of the index test results vs clinical MRI find-
diagnostically. For those with a non-MS diagnosis, risk factors for small vessel ischemic lesions are given in parentheses.

For those with a non-MS diagnosis, risk factors for small vessel ischemic lesions are given in parentheses. To be used in the absence of a typical CIS; therefore, DIS and DIT assessments listed in absence of CIS have the caveat that they could not have been used. In this prospective study, we found that a single 7-T T2*-weighted MRI scan can be used to accurately diagnose inflammatory demyelination and predict MS at follow-up. We have found, and presented previously, that, by using an optimized T2*-weighted sequence on a clinical 3-T scanner, one can also detect the presence of perivenous white matter lesions. The number of individuals enrolled in our study is perhaps too low to draw any definite conclusions. Further follow-up of this preliminary study’s cohort will be required to corroborate eventual diagnoses owing to the limitations of the reference standard; in reality, the definite diagnosis is often only established after many years, and, in some ways, only an expert histopathological examination can be definitive. If confirmed in a large prospective cohort using 3-T clinical scanners in multiple centers, the diagnosis of inflammatory demyelination and MS could be simplified.

The conventional MRI characteristics of MS lesions are nonspecific. For this reason, the International Pan...
el’s 2010 MS diagnostic criteria only apply in cases with typical CIS (or a year of sustained progression for primary progressive MS) and cannot be used for white matter lesions found incidentally, when the MRI was performed for another indication. Even in the context of a typical CIS, existing diagnostic MRI criteria for dissemination in space are imperfect (with sensitivity of 71.9% and a specificity of 77.2%). In cases without a typical CIS history, or with nontypical MRI findings, diagnostic dilemma and delay can have an effect on a patient’s emotional well-being, as well as diverting further resources into additional tests and clinical assessments.

Patients commonly find lumbar puncture to be an unpleasant experience, and it is often diagnostically unhelpful. A CNS tissue biopsy has been the only specific way to identify demyelinating plaques in vivo. T2*-weighted MRI enables the simultaneous visualization of hyperintense MS lesions and their central veins, which appear contrastingly hypointense owing to the paramagnetic properties of deoxyhemoglobin. To our knowledge, this is the first noninvasive, pathologically specific, single in vivo test for detecting inflammatory demyelinating CNS plaques. Even so, it has not been tested for distinguishing MS from other rarer causes of inflammatory demyelination; therefore, clinical acumen and appropriate paraclinical testing would still be required to distinguish other causes (such as acute disseminated encephalomyelitis or neuromyelitis optica) from MS.

In our cohort, using 7-T T2*-weighted MRI analysis to dichotomize patients (according to whether more or less than 40% of their lesions were perivenous) was a reliable way to predict an eventual clinical diagnosis, with 100% positive and negative predictive value for MS. The visibility of small veins is impaired if the image signal to noise ratio is poor (eg, when a movement artifact degrades image quality). The interpretation of images degraded by movement could result in false negatives. In our study, only one attempt was made to acquire a T2*-weighted scan for each participant. Were such a technique to be used clinically in the future, image acquisition could be repeated in the event of poor initial scan quality. To conclude, for the current cohort of patients in whom conventional methods left initial diagnostic doubt, a single early 7-T T2*-weighted MRI had 100% positive and negative predictive value for MS.

Accepted for Publication: October 11, 2012.

Published Online: March 25, 2013. doi:10.1001/jamaneurol.2013.1405

Correspondence: Nikos Evangelou, FRCP, Division of Clinical Neurology, University of Nottingham, Queen’s Medical Centre, C Floor, South Block, Derby Road, Nottingham NG7 2UH, England (nikos.evangelou@nottingham.ac.uk).

Author Contributions: Dr Evangelou had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Dixon, Tallantyre, Morgan, Morris, and Evangelou. Acquisition of data: Mistry, Dixon, Abdel-Fahim, Morgan, Morris, and Evangelou. Analysis and interpretation of data: Mistry, Tallantyre, Tench, Abdel-Fahim, Jaspan, Morgan, Morris, and Evangelou. Drafting of the manuscript: Mistry, Morris, and Evangelou. Critical revision of the manuscript for important intellectual content: Dixon, Tallantyre, Tench, Abdel-Fahim, Jaspan, Morgan, Morris, and Evangelou. Statistical analysis: Mistry, Tench, and Evangelou. Obtained funding: Morris and Evangelou. Administrative, technical, and material support: Dixon, Jaspan, Morgan, and Morris. Study supervision: Tallantyre, Jaspan, Morgan, Morris, and Evangelou.

Conflict of Interest Disclosures: Dr Mistry reports that he has been taken to scientific conferences at the expense of Bayer Schering Pharma, Merck Serono, and Novartis; these companies paid for the cost of his travels, accommodations, and registrations.

Funding/Support: This study was funded by the UK Multiple Sclerosis Society (grant 919) and the Medical Research Council (grant G0901321).

Role of the Sponsor: The sponsor of the study did not participate in the design and conduct of the study; in the collection, analysis, and interpretation of the data; or in the preparation, review, or approval of the manuscript.

REFERENCES