The Prognostic Utility of MRI in Clinically Isolated Syndrome: A Literature Review

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ABSTRACT

SUMMARY: For patients presenting with clinically isolated syndrome, the treating clinician needs to advise the patient on the probability of conversion to clinically definite multiple sclerosis. MR imaging may give useful prognostic information, and there is large body of literature pertaining to the use of MR imaging in assessing patients presenting with clinically isolated syndrome. This literature review evaluates the accuracy of MR imaging in predicting which patients with clinically isolated syndrome will go on to develop long-term disease and/or disability. New and emerging MR imaging technologies and their applicability to patients with clinically isolated syndrome are also considered.

ABBREVIATIONS: CDMS = clinically definite multiple sclerosis; CIS = clinically isolated syndrome; EDSS = Expanded Disability Status Scale; T2LV = T2 lesion volume

Multiple sclerosis is a chronic autoimmune inflammatory disease of the CNS, which may have long-term consequences on patients quality of life. In 85% of patients with MS, the first presentation is in the form of clinically isolated syndrome (CIS).[1] It is important to identify which patients presenting with CIS will go on to develop MS to expedite treatment initiation with the goal of reducing future morbidity.

MR imaging has a central role in the investigation of patients presenting with a suspected demyelinating illness. In addition to excluding other diseases, MR imaging allows clinicians to observe the pathologic processes underpinning the clinical manifestations in vivo. In individuals with established MS, MR imaging appearances are considered predictive of future disability and disease progression. However, the prognostic value of MR imaging in subjects presenting with CIS is less clear.

This review will address whether MR imaging data from subjects presenting with CIS is predictive of future disease and disability. New and emerging MR imaging technologies will also be reviewed.

MATERIALS AND METHODS

References were identified by PubMed and MEDLINE searches, between 1993 and February 2013, and further references were identified from relevant articles. The search terms "clinically isolated syndrome," "CIS," "first demyelinating event," "FDE," "multiple sclerosis," "MS," "MR imaging," and "MRI" were used. Articles were limited to English language.

Studies for inclusion were to meet the following criteria: 1) the study must address the ability of MR imaging to predict MS and/or disability in subjects with CIS, 2) MR imaging must be performed at initial presentation, 3) CIS must be statistically analyzed separately from other phenotypes. The following exclusion criteria were applied: 1) MR imaging features not included as independent or dependent variables in statistical analysis, 2) subject group with single-category symptoms only, 3) spinal cord MR imaging investigation only, and 4) pediatric studies.

A single reviewer with experience in research design and methodology performed the literature search and collated data.

Definition of CIS

CIS is defined as a monophasic presentation with suspected underlying inflammatory demyelination. Symptoms are typically of rapid onset, and last for more than 24 hours. CIS is divided into 4 categories, based on whether presentation demonstrates mono- or multifocal clinical or MR imaging features.[2] MR imaging lesions should appear typical for demyelination, may be located in the brain or spinal cord, and an alternative diagnosis should be considered less likely.[2]

Published rates of conversion from CIS to clinically definite MS (CDMS) differ according to length of study follow-up. Five studies were identified in which subjects were followed for greater than 6 years. For follow-up of 6.9, 7.2, 7.3, 14.0, and 20.0 years, total conversion rates were 48%, 60%, 85%, 68%, and 63%, respectively.[3-7]

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Conventional MR Imaging

Conventional MR imaging has a well-established role in the initial assessment of subjects with CIS. The risk of conversion to CDMS is greater in patients presenting with abnormal T2WI. Subjects with CIS subjects in the range of 50%–70% present with abnormal T2WI.[1] Two studies were identified which observed subjects for over 10 years. Fisniku et al[7] followed 107 subjects with CIS to 20.2 years; 82% with abnormal baseline MR imaging converted to CDMS, compared with 21% with normal MR imaging. In another study, 88% of subjects with abnormal MR imaging converted by 14 years, compared with 19% of those with normal scans.[6]

T2 lesion number at presentation has been associated with increased risk of conversion to CDMS.[8-17] However, a recent meta-analysis concluded that abnormal T2WI, regardless of lesion number, was associated with increased risk of conversion.[18] However, the review was limited, with nonuniform definitions of conversion to MS, and varied length of follow-up among the included studies.

In addition to T2 lesions, increased risk of conversion to MS is associated with the presence of gadolinium-enhancing lesions.[8,12-14,16,19-23] Accurate estimation of the incidence of Gd-enhancing lesions at CIS presentation is difficult because of inconsistent administration of contrast across studies. Gd-enhancing lesions may only be present in subjects with abnormal T2WI.[8,24] The presence of at least 1 Gd-enhancing lesion is predictive of time to CDMS in monofocal, but not in multifocal, presentations.[25]

The prognostic significance of T1 lesions has been infrequently addressed. Summers et al[4] found that in addition to Gd-enhancing lesions, T1 lesions were predictive of cognitive dysfunction after 7 years.

Few studies have addressed the association between conventional MR imaging measures and disability. A number of disability scales are used in subjects with CIS. The most frequently used is the Expanded Disability Status Scale (EDSS), which primarily assesses ambulation.[26] Another scale, the Multiple Sclerosis Functional Composite, addresses cognition in addition to mobility.[27,28] Baseline T2 lesion number is associated with EDSS at long-term follow-up of up to 14 years.[6,9] A recent study found that baseline Gd-enhancing lesion number was predictive of both EDSS and Multiple Sclerosis Functional Composite at 6 years. The authors also found that while baseline T2 lesion number was not associated with disability, the increase in T2 lesion number over the first year after presentation was predictive of EDSS at 6 years.[29]

Similar to subjects with MS, lesions are primarily distributed around the ventricular system in subjects with CIS.[30,31] The risk of disease progression is associated with lesion location, with periventricular,[32] callosal,[32,33] and cerebellar[34] distributions being most associated with conversion to CDMS.

Infratentorial lesion location may be associated with increased risk of disease and disability.[34,35] Since infratentorial lesions are likely to affect clinically eloquent areas, they may have greater contribution to future disability.[34] However, brain stem syndromes are represented infrequently in the literature. In a large multicenter study of 468 subjects with CIS, infratentorial lesions (including the brain stem and cerebellum) were not associated with increased risk of conversion.[12]

MR Imaging Volumetrics

Brain volume measurement is considered a surrogate marker for neurodegeneration in patients with MS.[36] It is uncertain whether neurodegeneration is present in subjects with CIS.

Techniques for MR imaging volumetrics may be 2D or 3D, and range from fully manual to fully automatic. Numerous software packages are available, including Statistical Parametric Mapping (SPM; Wellcome Department of Imaging Neuroscience, London, UK),[37] FreeSurfer (http://surfer.nmr.mgh.harvard.edu),[38,39] and the FMRIB Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl).[40,41] After removing the skull, automated segmentation algorithms are applied to MR imaging data to obtain GM,[42] WM,[43] CSF, and whole-brain volumes. In addition to absolute values, volumes may be expressed as a fraction of total intracranial volume.

Estimates of baseline lesion volumes are heterogeneous. Mean T2 lesion volume (T2LV) has been estimated to be between 2.0 mL to 6.2 mL,[21,29,44-48] whereas T1 lesion volume estimates range from 0.4 mL to 0.5 mL.[29,46,48] Gd-enhancing lesion volume has been inconsistently reported because of nonuniform use of contrast. Baseline lesion volumes have been noted to differ considerably depending on patient symptoms.[21,45]

Subjects with CIS who convert to CDMS demonstrate a greater T2LV at presentation compared with those who do not convert.[11,16,22,29,49] From multivariate regression analysis, Calabrese et al[50] found that baseline T2LV was an independent predictor of conversion to MS by 4 years. A study by Paolillo et al,[51] on the other hand, did not demonstrate either T1 lesion volume or T2LV to be associated with conversion; however, in that study, follow-up was limited to 18 months.

T2LV is associated with the development of future disability. An early study by Brex et al[6] found that baseline T2LV was associated with EDSS at 14 years, with the increase in T2LV over the first 5 years also being associated with disability at follow-up. Similarly, other studies have found that the rate of increase in T2LV in the first year is associated with greater long-term disability.[7,29]

T1 lesion volume may be better suited to the prediction of disability scales other than the EDSS. Di Filippo et al[29] found that while baseline T1 lesion volume was not associated with EDSS, it did correlate with Multiple Sclerosis Functional Composite at 6 years. Another study found that both T1 lesion number and volume were predictive of future cognitive dysfunction.[4]

Baseline measures of whole-brain volume have not been consistently demonstrated to differentiate subjects with CIS from healthy controls, with a number of studies finding no significant difference at baseline.[22,31,45,46,49,52-54] These findings are in contrast to that of Sbardella et al[55]; however, subjects with CIS included in their study had a high lesion load (mean T2 lesion number 15.5). To date, no study has demonstrated any significant difference in global measures of WM or GM volumes in patients with CIS compared to healthy controls.

In a cross-sectional study, Henry et al[52] reported volume reduction in a number of deep GM structures of subjects with CIS, compared with controls, including the thalamus and caudate nucleus. Although deep GM volumes were not correlated with EDSS, cerebellar volume was associated with baseline tests of cerebellar function.[52] In another study, reduced thalamic volume in subjects

with CIS was not retained after correction for multiple comparisons.[56] Numerous other authors have since failed to demonstrate any convincing GM volume reduction in subjects with CIS.[16,31,47,50,57] A recent study of 212 subjects did find that increased T2LV was associated with reduced volume of a number of deep GM structures; however, the study lacked healthy controls.[45,52]

A fundamental flaw in regional volumetric analysis is inaccurate segmentation of deep GM structures.[58] Greater lesion burden leads to more problems in tissue misclassification.[59] More accurate estimation of atrophy is possible when volume change is measured directly from serially acquired MR imaging scans by using registration-based methods.[58]

Structural Image Evaluation by using Normalization of Atrophy is a robust, well-validated tool that uses registration-based methods to estimate percentage brain volume change between 2 time points.[40,41] Although it does not allow estimation of regional volumes, Structural Image Evaluation by using Normalization of Atrophy is highly reproducible.[60] Estimates of percentage brain volume change range from −0.35% to −0.73% per year in subjects with CIS.[29,51,60,61] Subjects who convert to CDMS have been demonstrated to have greater percentage brain volume change than those who do not.[29,61] Kalincik et al,[22] in contrast, found that percentage brain volume change was not significantly different in subjects with CIS who converted. However, in their study all subjects with CIS had abnormal T2WI.[22]

The corpus callosum is a structure of interest in demyelinating illnesses. In a longitudinal study of 24 subjects with CIS, Audoin et al[62] found that the midsagittal corpus callosal area was significantly reduced at 12 months, when compared with healthy controls. Callosal area also correlated with progression in EDSS. More recently, in a larger cohort of 220 subjects with CIS, change in callosal area in the first 6 months after presentation was predictive of conversion to CDMS by 2 years.[22]

Diffusion Tensor Imaging

DTI allows assessment of the structural integrity of tissues, with water diffusivity being affected by various CNS tissue barriers, including microtubules and cell membranes. Descriptive parameters include fractional anisotropy, reflective of the fraction of anisotropy along 1 direction, and mean diffusivity or apparent diffusion coefficient, which is the average diffusion per voxel, regardless of direction. In WM, fiber organization is reflected by the anisotropy, with the quantity of anisotropy being augmented by the integrity of surrounding myelin.[63]

Although histogram analysis of mean diffusivity has been shown to differentiate subjects with CIS from healthy controls,[64] region-of-interest approaches have not.[65]

Using tractography, Pagani et al[66] found that subjects with CIS with pyramidal symptoms had increased mean diffusivity in the pyramidal tract, compared with both patients without symptoms, and control subjects. On the other hand, another study found that patients with CIS had increased mean diffusivity in all WM tracts.[67] Neither study found a difference in baseline fractional anisotropy in subjects with CIS.[66,67] In contrast, another study using tract-based spatial statistics demonstrated widespread reduced fractional anisotropy in the WM of subjects with CIS.[56] Tract-based spatial statistics is a recently developed technique that allows analysis of microstructural fiber damage,[68] and may be more sensitive to detect subtle anisotropy changes. However, while baseline fractional anisotropy was correlated with GM atrophy at 1 year in the same cohort, there was no association with disability.[56,69]

Magnetization Transfer Imaging

Magnetization transfer imaging measures the transfer of magnetization from hydrogen nuclei of water with restricted motion (bound pool), to hydrogen nuclei of freely moving water (free pool). This allows imaging of the bound pool, which includes protons in macromolecules, including myelin. The magnetization transfer ratio thus represents pathologic changes to macromolecules.[70]

Results of studies by using magnetization transfer imaging have been mixed. Iannucci et al[49] found that the magnetization transfer ratio of patients with CIS differed significantly from healthy controls; however, all patients had ≥4 lesions. In a large multicenter study, magnetization transfer ratio differentiated patients from controls in only 1 of 3 study centers.[46] Therefore, magnetization transfer ratio abnormalities are likely associated with increased lesion number at presentation.[53,71]

Magnetization transfer ratio has been shown to be predictive of conversion to CDMS[49] and future cognitive decline.[72] However, some studies have found conflicting results.[46,73] Another magnetization transfer imaging technique, magnetization transfer ratio texture analysis, has not been demonstrated to have prognostic utility in patients with CIS.[3]

MR Imaging Spectroscopy

NAA is a metabolite considered to be exclusive to neurons. Wattjes et al[74] identified a significant reduction in tNAA (summed NAA and its moeity, N-acetyl-aspartyl-glutamate) in the normal-appearing WM of subjects with CIS compared with healthy controls. Subsequent studies have had conflicting results.[32,75] Other studies found that only those patients with clinical progression demonstrated reduced NAA at presentation.[55,76]

Myo-inositol (mIns or Ins) is a metabolite primarily concentrated in glial cells. As with NAA, studies of this metabolite have demonstrated mixed results. In 1 study, when subjects with CIS were compared with controls, baseline mIns of normal-appearing WM discriminated only those who went on to covert to CDMS.[76] On the other hand, another study of a larger cohort found that mIns concentration was higher across the entire CIS group.[75]

Metabolite concentrations have a temporal evolution after CIS presentation. Audoin et al[62] performed serial MR spectroscopy, with metabolite concentrations measured in the corpus callosum. They demonstrated baseline reduced NAA and increased choline (Cho, associated with myelin), both of which normalized by 6 months. In another study, the rate of increase in mIns concentration in normal-appearing WM over the first year was predictive of poor executive function at 7.2 years.[4]

Although metabolite concentrations may be associated with long-term cognitive change, no single metabolite has demonstrated a correlation with disability, either at baseline or follow-up.[4,75] However, a model combining metabolite concentrations

with other MR imaging variables was shown to demonstrate superior utility in predicting disability at 1 year compared with any variable alone.[55]

Functional MR Imaging

Functional cortical changes are present from the earliest stages of CIS. Compared with healthy controls, subjects with CIS demonstrate increased cortical activation in both cerebral hemispheres,[77,78] with the extent of activation being related to motor task difficulty.[79] Patterns of activation are associated with short-term disease evolution, with converters demonstrating recruitment of a more extensive sensorineural network at baseline.[80] In a study assessing cognitive changes in CIS, more widespread activation on fMRI was associated with improved cognition scores, both at baseline and 1-year follow-up.[81]

Using a novel fMRI technique called dynamic causal modeling, Rocca et al[82] found that subjects with CIS had increased interconnectivity between the left and right sensorimotor cortex. However, subjects were not followed longitudinally.

A recent study measured the amplitude of low frequency alteration in resting-state fMRI. Compared with healthy controls, subjects with CIS demonstrated decreased amplitude of low frequency alteration in numerous cerebral regions.[83] In contrast, subjects with MS have previously been shown to have areas of increased cerebral amplitude of low frequency alteration.[84] The authors hypothesized that amplitude of low frequency alteration may evolve as time passes from the initial presentation.[83]

MR Imaging Perfusion

Varga et al[85] quantified cerebral blood flow with MR perfusion in a mixed cohort of subjects with CIS and MS. Compared with healthy controls, they found hypoperfusion in the periventricular normal-appearing WM of subjects with CIS. However, none of the perfusion parameters were associated with disability measures in either subgroup.

Brain Iron Quantification

T2 hypointensity, attributable to iron deposition, is a frequent finding in subjects with MS.[86] In subjects with CIS, T2 hypointensity has been identified in the left caudate nucleus.[87] Khalil et al[88] used R2* relaxometry to quantify brain iron deposition in a cohort of subjects with CIS and MS. Compared with subjects with MS, patients with CIS had significantly reduced R2* values in a number of deep GM regions. While R2* values correlated with regional brain volumes, there was no association with disability.[88] In another study, patients with CIS had significantly reduced R2* values in the basal ganglia and thalamus.[89] However, this study was limited, as age was not considered in the methodology, despite control subjects being 3 years older than those with CIS.

Hagemeier et al[47] used an SWI phase approach to obtain mean phase of the abnormal phase tissue, a metric for quantification of iron levels. Compared with healthy controls, subjects with CIS had significantly increased abnormal phase and abnormal phase volume in a number of deep GM regions. However, iron deposition was noted in the absence of any significant volume change.

In addition to R2* relaxometry, Langkammer et al[90] performed quantitative susceptibility mapping on 26 subjects with CIS. Quantitative susceptibility mapping detects magnetic charge variations attributable not only to iron, but also but also to myelin. Although R2* relaxometry did not differentiate between subjects with CIS and controls, quantitative susceptibility mapping revealed abnormality in the caudate, putamen, and basal ganglia in subjects with CIS. In apparent contrast, a recently published study by Quinn et al[91] showed that subjects with CIS had increased R2* compared with age-matched healthy controls in a number of regions, including the medial thalamus and right putamen. Furthermore, thalamic R2* relaxometry indices were positively correlated with EDSS ($r = 0.47$, $P = .028$). Apparently conflicting results by these 2 recently published studies may be attributable to differences in image processing techniques. Langkammer et al[90] calculated the mean R2* of segmented cerebral structures, while Quinn et al[91] used voxelwise analysis.

MR Imaging in Clinical Trials

MR imaging features have been included as outcome measures in a number of therapeutic trials. Treatments tested included: plasma exchange,[92] intramuscular interferon β-1a,[93] and interferon β-1b.[94,95] Patients with CIS with abnormal baseline T2-weighted MR imaging are ideal candidates to include in therapeutic trials because of increased risk of conversion to MS.[96]

Emerging MR Imaging Technologies

Multicomponent driven equilibrium single pulse observation of T1 and T2 is a newly developed MR imaging technique used to quantify myelin tissue content in vivo.[97] Kitzler et al[98] examined the utility of multicomponent driven equilibrium single pulse observation for measurement of myelin water fraction across a range of MS subtypes. In subjects with CIS, the total volume of voxels demonstrating deficient myelin water fraction was statistically significant compared with healthy controls. To date, there are no longitudinal studies on subjects with CIS using this technique.

CONCLUSIONS

In subjects presenting with CIS, the primary concern of clinicians and patients is the probability of conversion to CDMS. MR imaging plays a key role in the initial assessment of subjects with CIS.

A number of MR imaging markers have demonstrated prognostic potential. Abnormal T2WI is associated with increased risk of conversion. The number and volume of T2 and Gd-enhancing lesions may be predictive of disability. Changes in corpus callosal area and whole-brain volume over the first year from diagnosis of CIS have also shown prognostic utility; however, studies are limited.

Although new and emerging technologies have not demonstrated any convincing prognostic potential at this stage, they do give insight into the mechanisms underlying the pathology of CIS. While regional atrophy is not present at patient presentation, changes in DTI and MR spectroscopy parameters demonstrate that there is functional change occurring in normal-appearing brain tissue. Widespread increased motor cortical activation visualized on fMRI suggests that neuroplasticity is already a factor at initial presentation. Furthermore, subjects with CIS demonstrate brain iron deposition, a feature that is characteristic of MS.

There are a number of limitations within the published liter-

ature, and thus, of this review. In general, cohort sizes are small, with heterogeneous subject selection criteria. Many studies are cross-sectional, or have limited length of follow-up. Further studies of robust design and long-term follow-up are needed to investigate the utility of MR imaging techniques in the prediction of disease and disability in subjects with CIS.

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