Very early MS — insights from MRI

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Abstract
Magnetic resonance imaging (MRI) is likely to play an increasing role in efforts to understand the earliest changes in multiple sclerosis (MS) and narrowing the gap to new insights provided by the recent pathology literature showing early meningeal and cortical inflammatory disease and cortical gray matter demyelination. Much of the insight into early MS already comes from MRI as it evaluates patients at the time of a clinically isolated syndrome (CIS). Series show transition of tissue from normal to abnormal, and now often reveal gray matter more so than white matter pathology, deep gray more than cortical gray, and quantitative MRI changes preceding atrophy in early MS. But the CIS population is heterogeneous, likely including patients with many years’ duration, as well as relatively recent onset disease. Efforts to evaluate earlier disease, possibly sub-populations of CIS, patients at risk for MS with strict criteria for a radiologically isolated syndrome, and tumefactive MS, combined with advanced MRI technology, may bring us closer to in vivo insight into truly early or earliest MS.

Keywords
Clinically isolated syndrome, multiple sclerosis, magnetic resonance imaging, atrophy, gray matter

Introduction
Much of today’s magnetic resonance imaging (MRI) focus is concerned with improved early diagnostic criteria, the development of quantitative MRI (qMRI) metrics for monitoring therapy and efforts related to predicting pace and the prognosis of disease. But new excitement and energy is likely to be devoted to imaging’s increasing role in understanding the early pathogenesis of multiple sclerosis (MS), and possibilities for new, more sensitive measures of the earliest pathology affecting both structure and function. Questions of concern relate to identification of the earliest pathology, including early inflammatory, meningeal and cortical gray matter pathology observed by microscopy; transition from normal to abnormal in both the focal and/or diffuse pathology; and where these changes preferentially occur, and why? The optimist’s hope is that the gap between the microscopic pathology and in vivo MRI will continue to narrow, and we might more realistically come to “view” the entity of very early MS, earliest MS or the original events of MS.

The importance of defining, measuring and monitoring the earliest changes and therapeutic interventions is underscored by recognition of early pathology, including within the gray matter, and the potentially related clinical consequences. At a time when physical disability is mild at most in patients presenting with a CIS and a positive MRI, cognitive impairment can be measured in more than a quarter of the patients, as can abnormal cortical recruitment during cognitive tasks by functional MRI, and this impairment increases to more than half the population in only five years as physical disability also increases.

Miller et al. provide a recent comprehensive review of CIS from a clinical and imaging perspective. From that background and as a point of departure, the discussion that follows will more narrowly focus on what we know (or don’t) for the very earliest disease defined by MRI. It should be disclosed that the title of this topical review, Very early MS — insights from MRI, might benefit from a question mark at the title’s end to emphasize the obvious: that insights are for the most part in their infancy, yet the goal, to have a more seamless transition from elements of the

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early pathology to imaging the pathology either directly or its consequences, is a bit closer these days.

**Early and very early MS — operational definitions based on the CIS**

The defining criteria for early MS is constantly evolving. Diagnosis of MS based on the classical definitions emphasizing dissemination in time and space changed as the McDonald criteria permitted far earlier diagnoses, including closer to the time of the CIS, in part based on MRI for documentation of dissemination in time. The most recent modifications can set diagnosis to even earlier time points based on simplified, validated criteria, for example, two of four Barkoff-derived MRI anatomic criteria, where as few as two T2 hyperintense (T2) lesions, and co-existing enhancing and non-enhancing status, may be sufficient for satisfying dissemination in time.

We know from long-term (multi-decade) follow-up series that the vast majority (~83%), but not all patients presenting with a characteristic CIS and supporting laboratory studies, with an initially positive MRI (here noted as CISMRI+), will develop clinically definite MS. The short-term (18-month) conversion fraction is similar, about 80% when combined clinical activity (relapse) and MRI activity are utilized. While there are sometimes subtle differences in the selection criteria for the early MS populations, the nomenclature generally includes recognition of the subgroup of CIS patients destined to develop MS, designated here as CISMRI+, based on follow-up, which after McDonald revisions might be designated additionally as conversion by purely clinical and/or MRI criteria. With improvements in MRI, and criteria for accurate and earlier identification, yesterday’s CISMRI+ is very different from today and tomorrow’s CISMRI+.

**The focal lesion and refined definitions**

Despite enormous advances in and contributions of conventional and qMRI, much of what we know about identifying early MS at the time of a CIS remains based on the focal T2 lesion. Beyond their role in diagnosis, population analyses show that T2 lesions are important (albeit imperfect) predictors of subsequent disease activity, time to MS diagnosis, irreversible injury and disability.

Focal T2 white matter lesions harboring a central vein appear to be more characteristic of MS. These are well depicted on high-resolution heavily T2*-weighted imaging at ultra-high MR field strength (e.g. 7T). Focal T2 lesions in the cortical gray matter have been found in about one-third of adult patients after a CIS and may strengthen early diagnostic accuracy.

We learn about early MS through prospective and post-hoc CIS series. But it should be recognized that this population is highly heterogeneous. Factors including the true (currently undeterminable) interval from disease initiation to first presentation, pace and severity of disease, mono versus multiphasic presentations, and possibly differential anatomic (regional) vulnerability to pathology have all been considered contributors to this group’s heterogeneity. A wide range in MRI characteristics is observed for both the focal pathology and the pathology of the normal-appearing brain tissue (NABT) (see below). Yet in the vast majority of “CIS” series, these patients are analyzed as a single group, primarily because of a lack of a better classification system, and practically to ensure adequate statistical power for analyses. Baseline T2 lesion counts in the phase III CISMRI+ trials vary from the minimum of two lesions required for entry to 30–40 or more, and over two orders of magnitude in volume, from about 0.1 to 10 cc or more. Obviously the pathology of many “CIS” or CISMRI+ study populations overlap considerably with what we typically observe for established relapsing and even secondary progressive MS.

Beyond the baseline lesion load, all CIS series show annual subclinical T2 lesion increments. If we take a giant leap of faith and extrapolate back in time, many, if not most of these “early” MS cases have been incubating in a pre-clinical state, potentially for years at the time we analyze them as “early” MS based on their CIS. There is some support for this view from the frequent reports of prior neurologic events, in retrospect, recalled by CIS patients at the time of their first clinical event. This extrapolation may also be misguided, as abrupt lesion development from none to an initial many is also a possibility, but this remains to be discovered and, of course, we do not know how long a pre-MRI discoverable pathology, such as the microscopic inflammatory meningeal nests, cortical pathology and demyelination, linger before the focal or diffuse pathology of the NABT are readily detected by even the best MRI technique.

If T2 lesions accumulate with some regularity, it might be possible to identify patients within a given CIS group as potentially in earlier stages of their disease. However, as the rate of accumulation of new lesions is highly variable, simply evaluating patients with low lesion numbers as earlier MS cannot be a reasonable approach. Low T2 load CISMRI+ subgroups are expected to be enriched for early disease, but also include, to an unpredictable degree, patients with low activity, longer duration and more “benign” disease. Higher T2 lesion sub-groups will be generally enriched for more long-duration pre-clinical disease, but will also include an indeterminate fraction of very high activity, short duration, relatively early-disease patients. Lesser disease aggressiveness in minimal (T2 lesion) MS is suggested by long-term follow-up series that relate risk for MS to baseline T2 lesion number or volume. Our “minimal” (lesion load) MS series, identified at the time of the CISMRI+ from the low T2 lesion quartile of the Controlled High-Risk Subjects Avonex Multiple Sclerosis Prevention...
Study (CHAMPS) trial, with two to eight focal T2 lesions, shows clinical and MRI progression in disease, but on average a lower rate of lesion progression, relapse and possibly disability, supporting the concept of mixed early but also less aggressive disease. Nevertheless, on average the lower T2 lesion patients provide an opportunity for investigating relatively early transitions from normal to abnormal tissue, in both focal and diffuse microscopic pathology, and potentially move the point of observation for early disease closer to the time of disease initiation, as these cases are less encumbered by confounding advanced pathology.

**MRI in NABT in early MS**

One need not do an exhaustive literature search for strong indications that the NABT is less abnormal (lower magnitude and a more restricted anatomic distribution) in CIS compared to relapsing and secondary progressive MS. Additionally, the NABT is most often already abnormal at the time of the CIS, based on comparisons with healthy control populations, by most qMRI measures, in the vast majority of (but not all) published studies.

Many important details of the earliest pathology by MRI and/or magnetic resonance spectroscopy are unknown or remain controversial. For example, elevated myo-inositol, a putative glial marker, was initially considered from some series to be finding in CIS, similar to established MS. But in more recent, higher field (3T) series, abnormally elevated myo-inositol is not detected in CIS at a time when reduced N-acetylaspartate (a neuronal marker) is readily detected.

Another potential pathology transition is early development of elevated subcortical iron, which is shown in recent studies to be absent in CIS, compared to relapsing MS. Several studies suggest abnormal qMRI metrics including reduced fractional anisotropy in CIS, prior to the time atrophy can be detected in corpus callosum, gray or white matter fractions. In one recent study that highlights both the extent and heterogeneity of the early pathology in CIS, the magnetization transfer ratio of gray matter was found to be abnormal in about half of the patients.

**Atrophy**

Brain atrophy is now most often localized to the gray matter fraction, more so than white matter and from loss of subcortical even more so than cortical gray matter. This pattern may continue into early relapsing stages of disease. Gray matter atrophy or its detection is more likely in CISMS compared to CIS and CIS+MRI. When detected, early cortical gray matter atrophy does not appear to be uniformly distributed across the anatomy. Progressive brain atrophy can be detected in CIS+MRI patients over relatively short, one-year intervals. While there is still some controversy regarding the details of the earliest change in white versus gray matter, both regions show continual volume loss from the time of CIS. In a four-year longitudinal series, Fisher et al. found a three-fold increase and steady rate of atrophy for white matter in CIS, relapsing and secondary progressive MS. Interestingly, while the rate of gray matter atrophy was about 3.4 fold greater than normal in the CIS group, atrophy accelerated in more advanced disease to an astounding pace of 14-fold normal in secondary progressive MS.

**Tumefactive MS**

Tumefactive MS, defined as large, atypical, cerebral demyelinating lesions, may be another population offering MRI insight into early MS, frequently as first clinical presentations, and especially as these often provide direct pathology correlation. In the large series by Lucchinetti et al., 70% developed MS over a median duration of 3.9 years. The index tumefactive lesion is typically not isolated, as it is accompanied by either additional non-enhancing T2 or enhancing lesions, and in a sizeable fraction (possibly as great as one-third), additional spinal cord lesions. Based on MRI around the time of presentation, about half of this enriched for MS group satisfy the 2007 Barkhof criteria for dissemination in space. Of those patients with additional T2 lesions, about half had fewer than 11 lesions. From subsequent work, we now know that biopsy tracks through the cerebral cortex that reach these tumefactive white matter lesions will include cortical gray matter plugs containing evidence for cortical demyelinating lesions that are inflammatory and associated with meningeal inflammation. Just how representative the cortical tissue in tumefactive (early) MS is for other early MS groups, including non-tumefactive CIS presentations, is not yet known. Quantitative and other advanced MRI studies outside the tumefactive lesion may be logistically difficult, but potentially highly informative.

**The radiologically isolated syndrome**

Patients identified as having radiologically isolated syndrome (RIS) provide another potential early MS group, as they can be followed for new T2 lesions and clinical events, including those consistent with a CIS. The recent literature shows an impressively high frequency of new T2 lesions and conversion to MS, if strict entry criteria are utilized, with conversion fractions by clinical attack in 33% percent in one series over one to five years. There has been speculation that RIS patients may be enriched for more benign or less clinical attack-inciting pathology. In one study, tissue damage assessed by magnetization transfer ratio was milder in the more clinically relevant areas. It should be noted that the RIS population in many current series is not a very low T2 burden group, bringing up the
possibility that a fraction, as in CIS, may be a long duration from earliest disease. Nevertheless, longitudinal series of RIS cohorts provide an opportunity for evaluating pre-clinical changes — very early MS in select cases — prior to overt disease expression.

**Pediatric MS**

Another population potentially relevant to MRI in early MS is pediatric MS. Pediatric MS in theory has the potential to provide insight into early stages of disease, if only because the pre-clinical disease stages are more likely to be of shorter duration than for early adult-onset disease. Like adult-onset disease, most pediatric cases present with multiple, non-enhancing lesions, suggesting the initial stages may have been similarly unapparent for an indeterminate duration prior to discovery. However, this hope for insight has not as yet been fulfilled. While there do appear to be differential imaging characteristics for pediatric MS, including a greater number of posterior fossa lesions, larger T2 lesions, more enhancing lesions and greater subsequent activity compared to adults, the vast majority of imaging findings substantially overlap those typical of adult MS.\(^\text{28}\)

**Conclusions**

Returning to a main point of this discussion, little is known about MRI in early MS, if we define early MS as the currently unidentified subgroup of CIS patients with truly short durations from disease onset to CIS. Yet an MRI insight is unfolding as the literature shows important transitions from normal to abnormal tissue, including early gray pathology more so than white matter, deep gray possibly earlier than cortical gray, and changes in the normal-appearing white matter in some areas (e.g. corpus callosum) preceding volume loss. Pre-CIS disease, based on the RIS, and tumefactive presentations, present opportunity to better define early MS and get closer to earliest MS.

Relevant to early MS, the recent pathology literature sets a new challenge for MRI, to provide in vivo insight into the transitions accompanying meningeal and cortical inflammation. It remains to be determined if current qMRI techniques and the abnormality detected by these will provide the required insight. Studies combining technically advanced MRI, including very high field imaging,\(^\text{29}\) qMRI and cellular (MRI) imaging with specifically targeted subgroups including CIS are likely to advance our understanding of the early pathogenesis, narrowing the gap between the early pathology of microscopic inflammation and demyelination, and imaging.

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