PART I: MAKING THE DIAGNOSIS

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1. Making the diagnosis

The diagnosis of MS has moved from primarily history and exam based (Schumacher *et al.*, 1965) to include paraclinical evidence (Poser *et al.*, 1983) to the newest modifications of the McDonald criteria in which a diagnosis of MS can be made in the setting of a clinically isolated syndrome (CIS); a single characteristic clinical event along with specific findings on a single MRI scan. Although the approach has changed, the underlying principle of establishing evidence of multiple episodes (dissemination in time) affecting multiple areas of the central nervous system (dissemination in space) is still the basis for diagnosis. MRI plays a critical role in the newest diagnostic criteria, and has undoubtedly contributed to the earlier initiation of disease modifying treatment in people with MS, a shift that has been associated with better long-term outcomes.

A. Dissemination in Space (DIS): As first described by Barkhof (Barkhof *et al.*, 1997) and subsequently modified by Tintore (Tintore *et al.*, 2000), the criteria for DIS were an important component of the original McDonald criteria first published in 2001 (McDonald *et al.*, 2001). The fulfillment of DIS at the time of a typical CIS presentation (optic neuritis, transverse myelitis, brainstem syndrome) increases the risk of developing a second MS attack and all of the first generation MS disease modifying agents (DMAs) have been shown to delay the onset of a second attack in this setting (Jacobs *et al.*, 2000, Kappos *et al.*, 2006, Comi *et al.*, 2009). The McDonald criteria have undergone several further modifications since the initial publication. The newest version of the McDonald criteria (Polman *et al.*, 2011) has been modified so that DIS can be demonstrated with as few as two white matter lesions (see Table 2), representing a significant change from the minimum previously required (see Table 1).

Table 1: Old MRI Criteria for Dissemination in Space

At least 3 out of 4 of the following:
1. One gadolinium enhancing lesion or nine T2 hyperintense lesions if no gadolinium enhancing lesion is present.
2. At least one infratentorial lesion
3. At least one juxtacortical lesion
4. At least 3 periventricular lesions

From Tintore (Tintore *et al.*, 2000).

Table 2: New MRI Criteria for Dissemination in Space

≥ 1 T2 Lesion in at least 2 of the 4 areas of the CNS:
Periventricular
Juxtacortical
Intratentorial
Spinal cord*

Based on Swanton et al. 2006, 2007 (Swanton *et al.*, 2006, Swanton *et al.*, 2007).
*If a subject has a brainstem or spinal cord syndrome, the symptomatic lesions are excluded from the criteria and do not contribute to the lesion count.

A recent expert commentary assessed the advances and limitations of the McDonald criteria, highlighting the need for further validation utilizing real world clinical settings and longitudinal outcomes (Selchen *et al.*, 2012, Deangelis and Miller, 2014). Also important to note is that the presence of oligoclonal bands in the spinal fluid along with the presence of 2 or more T2 lesions fulfilled the requirement for DIS.

The MAGNIMS group recently published a consensus statement and has proposed further modifications to the McDonald 2010 criteria (Filippi *et al.*, 2016), including the requirement of 3 periventricular lesions and the addition of the optic nerve to make 5 CNS regions. Other proposed changes were to combine cortical/juxtacortical lesions to encompass all cortical lesion types, to recommend imaging of the entire spinal cord to fulfill dissemination in space, and to utilize the same criteria for DIS in RRMS for the diagnosis of primary progressive MS.

B. Dissemination in Time (DIT): The establishment of dissemination in time as initially described by McDonald was complicated, and the requirement of a new Gd+ lesion on a follow up scan meant that a total of three separate MRIs might be required in order to definitively establish DIT. The 2005 revision simplified this by allowing *either* a new Gd+ *or* T2 lesion and the 2010 revision further simplified this allowing for a single scan to demonstrate DIT as described in Table 3.

Table 3: MRI Criteria for Dissemination in Time: 2010 McDonald Revisions (Polman *et al.*, 2011)

Two ways to demonstrate dissemination in time (DIT):
1. A new T2 and/or gadolinium-enhancing lesion(s) on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline scan.
2. Simultaneous presence of asymptomatic gadolinium-enhancing and non-enhancing lesions at any time.

Based on Montalban et al 2010 (Montalban *et al.*, 2010).

C. Primary Progressive MS

Table 4: Criteria for Diagnosis of PPMS: Progression from disease onset (Polman *et al.*, 2011)

1. One year of disease progression (retrospective or prospective)
2. Plus 2 of the 3 following criteria:
a. Evidence of DIS in the brain based on ≥ T2 lesions in at least one characteristic area (periventricular, juxtacortical, infratentorial)
b. Evidence of DIS in the spinal cord based on ≥ 2 T2 lesions in the cord
c. Positive CSF: 2 or more oligoclonal bands, elevated IgG index

*If a subject has a brainstem or spinal cord syndrome, all symptomatic lesions are excluded from the criteria

The new MAGNIMS consensus calls for the elimination of the requirement that symptomatic lesions are excluded, thus symptomatic lesions can be used to fulfill DIS requirements (Filippi *et al.*, 2016).

D. The Radiologically Isolated Syndrome (RIS), or "pre-MS": An abnormal scan – even one that fulfills dissemination in space by McDonald criteria – is not sufficient to make the diagnosis of MS in the absence of a clinical event or exam abnormality. This syndrome, termed "radiologically isolated syndrome" (RIS) (Okuda *et al.*, 2009) or preclinical MS (Lebrun *et al.*, 2008), is now increasingly recognized as routine MRI studies become more common. Serial studies of individuals with RIS suggest that at least a third will develop a clinical attack and the majority will show evidence of radiological progression in a relatively short time (Lebrun *et al.*, 2008, Okuda *et al.*, 2009). The presence of spinal cord lesions (Okuda *et al.*, 2011), abnormalities on visual evoked potential testing (Lebrun *et al.*, 2009), pregnancy (Lebrun *et al.*, 2012), age <37 years, and male sex (Okuda et al., 2014) are associated with an increased risk for transition to CIS. One report found that clinical events occurred in 34% of RIS subjects followed for 5 years (Okuda *et al.*, 2014) and there may be an increased risk of developing PPMS (Kantarci et al., 2016). Current practice is to monitor these individuals closely and begin treatment only if there is clinical activity (Sellner *et al.*, 2010) with the possible exception of patients with cord lesions. There is evidence of cognitive impairment in some of these individuals similar to that seen in RRMS (Lebrun *et al.*, 2010) and cortical lesions have been detected (Giorgio *et al.*, 2011). Advanced techniques can be used to better predict the clinical evolution of RIS to CIS (De Stefano *et al.*, 2011, Sbardella *et al.*, 2011).

2. Defining the disease course and type

A 2014 consensus paper revisited the nomenclature of MS disease phenotypes, last developed in 1996, that included 4 cardinal types:

a. Relapsing remitting MS (RRMS)
b. Secondary progressive MS (SPMS)
c. Progressive relapsing MS (PRMS)
d. Primary progressive MS (PPMS)

The new proposed scheme utilizes both clinical and imaging findings to characterize disease phenotypes and includes radiologically isolated syndrome, clinically isolated syndrome, and utilizing disease modifiers (Lublin *et al.*, 2014). Each subtype of MS can be further classified as "active" or "not active" based on evidence of new inflammatory activity on MRI. In addition, progressive disease (PP, SP) can be further characterized with regards to "with" or "without progression". This scheme eliminates the PRMS type.

3. Ordering confirmatory tests and ruling out mimics

In order to establish the diagnosis of MS it is important to document dissemination in time and space and to assess for MS mimics. Table 5 lists commonly used tests and the rationale for their use in confirming a diagnosis of MS and ruling out its mimics.

Table 5: Tests for suspected multiple sclerosis

Test	Rationale	Notes
MRI - **Brain** - **Spinal Cord**	-Identify lesions c/w demyelination -Rule out mimics -Establish dissemination in space and time -Obtain baseline burden of disease	-Do with and without contrast (check GFR prior) -Spinal cord lesions can be clinically silent -Request MS protocol with sagittal FLAIR and thin, non-gapped slices
Evoked Potential - **Visual** - **Brainstem** - **SSEP**	-Establish dissemination in space -Provide evidence of demyelination	-VEPs highest yield
Lumbar Puncture	-Rule out infectious causes -Provide diagnostic support -Prognostication (RIS)	-Standard MS panel: IgG synthesis rate and index, oligoclonal bands (OCBs)*, myelin basic protein (MPB), cell counts, protein, glucose -Must provide blood sample at the time of fluid collection
Laboratory studies	-Rule out mimics -Stratification for DMT choices	-B12, TSH, sedimentation rate, ANA panel, HIV, Lyme titers, ACE level, anticardiolipin Abs, NMO Ab, SSa/SSb -Vitamin D levels, JC virus antibody status, VZV antibody status
Ocular coherence tomography (OCT)	-Establish baseline -Monitor disease progression -Prognostication?	-May not be a sensitive measure for PPMS (Balk *et al.*, 2014)

*Of cerebral spinal fluid measures, OCBs are most specific for MS. Recent studies suggest possible detection of OCBs through tear fluid, which would certainly be easier than a spinal tap (Salvisberg *et al.*, 2014).

4. Monitoring disease activity

Clinical and radiographic monitoring for breakthrough disease is recommended, especially in the early stages of relapsing disease. MRI at the time of diagnosis to establish a baseline and to monitor disease activity and treatment response is common in clinical practice (Tornatore *et al.*, 2012). Evidence of new inflammatory disease activity on MRI is one factor in defining breakthrough disease and may justify a switch to a different or more potent disease modifying therapy (Tornatore *et al.*, 2012). Ultimately, treatment success may be defined as an absence of both clinical and radiographic disease activity, commonly referred to as "no evidence of disease activity" (Fox and Rhoades, 2012, Havrdova *et al.*, 2013, Bevan and Cree, 2014).

5. Managing progressive disease

Primary progressive disease is more difficult to diagnose, and a careful evaluation for treatable mimics is important (Miller and Leary, 2007, Comi, 2013). It is also difficult to identify the transition from relapsing remitting to secondary progressive MS (Miller, 2004, Sand *et al.*, 2014). Treatment options for progressive disease are limited (Ontaneda et al., 2015). Some practitioners use chemotherapeutic agents in this setting, but long term benefits are uncertain (Stankiewicz *et al.*, 2013). There are on-going clinical trials of newer agents for progressive disease and future approaches such as remyelination are under development (Rommer and Stuve, 2013, Mei et al., 2014, Kremer et al. 2015). At the time of submission, there are no FDA approved therapies for PPMS, but the first such approval for ocrelizumab (Montalban et al., 2017) is expected in March 2017. Several other promising treatments are currently under study (Ontaneda et al., 2015).

6. Facilitating a better quality of life

Multiple sclerosis impacts all aspects of life for those affected, and recognition of the "hidden symptoms" is an important aspect of patient care. Cognitive impairment, fatigue, depression and pain are very common in MS and impact quality of life (Jonsson *et al.*, 1996, Grossman *et al.*, 2010, Kinsinger *et al.*, 2010, Miller *et al.*, 2010, Amato *et al.*, 2013, Magrinelli *et al.*, 2013, Rubin, 2013, Minden *et al.*, 2014).

Spasticity, sexual dysfunction and bladder issues are also important areas that should be addressed (Berger, 2013, Calabro *et al.*, 2013, Sand and Sand, 2013, Tapia *et al.*, 2013, Svensson *et al.*, 2014). Because MS affects younger individuals, general health issues should also address concerns regarding reproduction in addition to usual health maintenance activities (Marrie and Hanwell, 2013, Oreja-Guevara *et al.*, 2014). Focus on neurological issues and disability often leads to neglect of general health maintenance in this population that now has an almost normal life expectancy (Shabas and Weinreb, 2000).

Finally, exercise and stress reduction techniques have been shown to improve measures of disease activity as well as quality of life and should be discussed with all patients (Grossman *et al.*, 2010, Mohr *et al.*, 2012, Latimer-Cheung *et al.*, 2013, Padgett and Kasser, 2013, Simpson *et al.*, 2014, Giesser 2015).

7. The MS team

It takes a dedicated team, working together with open lines of communication, to manage the many concerns of persons with multiple sclerosis. Important members of the health care team include physical, occupational, and speech therapists, mental health professionals, urologists, and community support groups (Jonsson *et al.*, 1996, Stein *et al.*, 2003, Khan *et al.*, 2007, Khan *et al.*, 2008, Pelletier *et al.*, 2009). Together with the patient and their family, the neurologist can help facilitate a patient centered care paradigm to maximize outcomes and patient satisfaction (Holland *et al.*, 2011).

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