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*Review*

# Saudi Consensus Recommendations on the Management of Multiple Sclerosis: Diagnosis and Radiology/Imaging

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**Abstract:** Multiple sclerosis (MS) is an inflammatory neurological illness common in young adults. The prevalence and incidence of MS are regionally and globally increasing. Recent data from Saudi Arabia (SA) estimate the prevalence to be 40.40 cases per 100,000 population, and 61.95 cases per 100,000 population for Saudi nationals. With the increasing availability of treatment options, new challenges for treatment selection and approaches have emerged. There is a clear need for national guidelines to standardize practice, guide the personalization of decisions, and contain increasing costs. A multidisciplinary expert panel was formed to develop evidence-based Saudi consensus recommendations on the diagnosis and clinical care of MS, to aid healthcare practitioners in advising

patients on treatment decisions. The recommendations were agreed upon after a thorough review, an evaluation of existing international guidelines, and the latest emerging evidence.

**Keywords:** multiple sclerosis; prevalence; incidence; consensus; radiology; imaging; Saudi Arabia

## 1. Introduction

In 2016, around 2,221,188 people around the world had Multiple Sclerosis (MS), and this translated to a prevalence of 30.1 cases per 100,000 population [1]. A recent nationwide, multicenter MS registry study in Saudi Arabia reported the overall prevalence of MS to be 40.40/100,000 population [2]. Among Saudi nationals, prevalence was found to be much higher (61.95/100,000). MS affects the central nervous system (CNS), and is characterized by the invasion of autoimmune cells (B and T lymphocytes, monocytes, and natural killer cells). B lymphocytes migrate to the perivascular space where they drive an ectopic inflammation in lymphoid tissue. This inflammation gives rise to oligoclonal bands [3]. Recent data suggest that migrating B cells contribute to MS pathogenesis through T-cell activation and direct tissue injury [4,5].

Depending on disease activity (frequency of relapses and findings on imaging) and disease progression, individuals with MS generally follow one of two main forms: relapsing-remitting MS (clinically isolated syndrome [CIS] and relapsing-remitting MS [RRMS]) and progressive MS (secondary progressive MS [SPMS] and primary progressive MS [PPMS]), with each classified as either active or not active [6]. Ten to twenty years after onset, most RRMS patients progress to SPMS [7].

Although MS typically occurs in young adults, an estimated 2–5% of patients at 18 years of age or younger could develop pediatric-onset MS [8,9]. Moreover, MS can first appear later in late adulthood after 50 years old, where it is considered late-onset MS [10–12]. MS shows sex bias with a female predominance (around 3:1), with the disease arising commonly in women of reproductive age [13]. Several environmental factors and genetic alleles impact MS development [2].

The diagnosis of MS can be challenging and currently there is no one physical exam or laboratory finding that solely supports MS diagnosis [14]. Conditions that mimic the clinical features of MS, especially other forms of idiopathic inflammatory demyelinating disorders, like Neuromyelitis Optica Spectrum Disorder (NMOSD) and acute disseminated encephalomyelitis (ADEM), may complicate the diagnosis of early stages of MS [15]. In addition, MS management is further complicated by the continuously growing number of available treatment options. The drugs have varied costs, effectiveness, and safety profiles [16]. Moreover, each drug differs in its route of administration and mechanism of action [16]. Therefore, high-quality evidence-based clinical practice guidelines are needed to support clinicians and provide them with clear evidence-based recommendations on the management of health conditions, which help in reducing the gap between clinical practice and research. Such consensus recommendations can facilitate clinical decision-making and help optimize patient care, health outcomes, and the delivery of resources while minimizing cost.

The Ministry of Health (MOH) of the Kingdom of Saudi Arabia (KSA) has established a working group formed by an all-encompassing committee of neurologists, clinical pharmacists, neuroradiologists, and nurses with experience in the care of MS, and tasked the group to develop the Saudi Consensus Recommendations on Diagnosis and Management of Multiple Sclerosis and Related Disorders: Diagnosis and Radiology/Imaging. The overall aim of these evidence-based recommendations is to support all healthcare professionals who encounter patients with MS and related disorders in their diagnosis and management.

This article summarizes the methodology used to build the recommendations, the clinical diagnosis of MS in adults, and recommendations for diagnosis, classification, and

imaging practices useful throughout initial evaluation, follow-up, and the monitoring of treatment of patients.

## 2. Methods

An expert working group, including specialist MS neurologists, neuroradiologists, clinical pharmacists, and MS nurses (a total of 44 participating experts), representing all regions of Saudi Arabia, met on 5 October 2019. The workshop was directed by an expert in a specific area. Workshop facilitators identified all related internationally published recommendations for the clinical diagnosis and care of MS and guidelines and consensus statements/recommendations that satisfied the criteria for use in the generation of the updated consensus recommendation document were adopted. Other peer-reviewed studies with new data have also been identified and evaluated.

The nominal group technique was utilized to reach unanimous decisions on identified items [17]. Consensus was defined as the approval of ≥75% of voters. The validity of the recommendations was not agreed on. The final document was then drafted to include all of the recommendations agreed upon and shared with the MOH experts and committee for additional review for a 30-day feedback phase. Recommendations received were later considered for additional agreement by work group leaders in four virtual meetings held between June and July 2020, and appropriate revisions were made.

## 3. Diagnosis of MS

### *3.1. The 2017 McDonald Diagnostic Criteria*

#### 3.1.1. Overview of the 2017 McDonald Criteria

The diagnosis criteria for MS are based on evidence from clinical and paraclinical studies. The "McDonald criteria" for MS diagnosis have evolved over the past two decades to maximize precise and early diagnosis, and to reduce the risk of misdiagnosis, most recently in 2017 [18–20].

The 2017 McDonald criteria are based on two key principles that must be fulfilled for the diagnosis of clinically definite MS to uncover evidence that demonstrates CNS (brain and spinal cord) lesions: "dissemination in time" (DIT) and "dissemination in space" (DIS) (Box 1).

**Box 1.** Criteria for determining the presence of dissemination in time (DIT) and dissemination in space (DIS) in the 2017 McDonald criteria for the diagnosis of MS[13]. [a] For individuals >50 years old or with vascular risk factors, clinicians should expect more periventricular lesions.

**DIS:** One or more hyperintense T2 lesions suggestive of MS in two or more regions of the CNS: periventricular [a], cortical, or juxtacortical brain regions, infratentorial brain regions, or the spinal cord. The lesions could be symptomatic or asymptomatic.
**DIT**: Simultaneous presence of gadolinium-enhancing and non-enhancing lesions at any time, or by a new hyperintense T2 or gadolinium-enhancing lesion on follow-up MRI, while comparing to a baseline scan, regardless of the time it was taken. Lesions could be symptomatic or asymptomatic.

If objective clinical proof for one attack suggestive of demyelination related to MS is confirmed, with no further satisfaction of criteria of MS diagnosis, this is classified as CIS [21]. The 2017 McDonald criteria define CIS as a monophasic clinical episode with symptoms and objective findings of focal or multifocal inflammatory demyelinating events in the CNS that appear in an acute or sub-acute time frame [21]. These inflammatory flares happen without fever or any underlying infectious process and last at least 24 h with or without recovery [21]. Thus, a patient presenting with a monofocal or multifocal pathology will be considered to have had a CIS and will be subsequently diagnosed with MS after fulfilling the DIS and DIT, and ruling out other diagnoses [21]. Some examples of typical presentations are partial myelopathy, focal brainstem or cerebellar syndrome, unilateral optic neuritis, or focal supratentorial syndrome [21]. On the other hand, atypical presentations like complete ophthalmoplegia, meningismus, headache, isolated fatigue, bilateral optic neuritis, or alteration of consciousness could be suggestive of MS [21].

In addition to the documentation of evidence of CNS demyelination suggestive of MS, the lack of alternative explanations for symptoms is a necessary criterion that should be fulfilled [21]. It is vital to consider the differential diagnosis of MS, with vigilance to signs of red flags [18]. For patients who have an atypical clinical presentation or magnetic resonance imaging (MRI) findings, additional assessments in addition to the requirements of the McDonald criteria are needed to establish an MS diagnosis [21].

The fulfillment of the 2017 McDonald criteria in the absence of an alternative diagnosis allows for diagnosing MS [21]. In people with a typical CIS presentation, with the fulfillment of criteria for DIS and absence of a substitutional diagnosis, documentation of cerebrospinal fluid (CSF)-specific oligoclonal bands (OCBs) with the lack of other CSF findings atypical of MS allows for MS diagnosis [21]. It is vital to consider that although the presence of CSF-specific oligoclonal bands may not fulfill the "dissemination in time" requirement, it can replace the latter in terms of diagnostic criteria [21].

#### 3.1.2. The Use of the McDonald Criteria

Misdiagnosis of MS remains a problem in routine clinical practice [18–21], and the following are important caveats to the application of the McDonald criteria:

MRI findings alone are insufficient for MS diagnosis. It is vital to integrate clinical, imaging, and serological findings to make a reliable MS diagnosis.

McDonald criteria should be used only in patients with a typical CIS presentation as they have a greater likelihood of developing MS.

Care must be taken to rule out alternative diagnoses and presentations suggestive of an MS-related demyelinating episode or relapse, including optic neuritis, brainstem syndromes (for example, trigeminal neuralgia), cerebellar syndromes, and transverse myelitis [18].

Revisions made to the McDonald criteria in international consensus recommendations, such as MAGNIMS, may also aid in the diagnosis of MS. In 2016, these recommendations consisted of several revisions put forward by neurologists and neuroradiologists gathered in a workshop to recognize and discuss MS diagnostic areas requiring revision and clarification. For instance, it was recommended that there should be at least three lesions on MRI of the periventricular region for the establishment of the "dissemination in space" criteria. There were also other suggestions, such as the adoption of MS dissemination in time and space MRI criteria for patients being assessed for radiologically isolated syndromes [22]. Subsequently, the 2021 MAGNIMS revision took into consideration more recent scientific advances and provided novel suggestions, including recommended modifications to the protocols of MRI acquisition [23]. Clinicians may refer to these recommendations to assist in decision-making related to diagnostic procedures.

### *3.2. Conditions That May Mimic the Presentation of MS*

The most common reason for incorrect diagnosis of MS is the misinterpretation of inaccurate clinical signs, radiological results, or laboratory tests [18,19], which are briefly summarized in Tables 1–3.

#### Neuromyelitis Optica Spectrum Disorders (NMOSD)

Neuromyelitis Optica Spectrum Disorders (NMOSD) are differentiated from MS in terms of diagnosis when certain features are fulfilled. This should include a clinical presentation of any neurological manifestation or a CNS lesion not corresponding with a neurological manifestation with positive Aquaporin 4 (AQP4)-IgG, or NMOSD symptoms with MRI criteria of the International Panel for NMO Diagnosis (IPND) [24]. To the latter diagnostic criteria, additional features include the absence of AQP4-IgG and anti-myelin oligodendrocyte glycoprotein (MOG) antibodies in serum and CSF, neutrophilic or eosinophilic pleocytosis with an absence of oligoclonal bands in the CSF, and ensuring that testing of antibodies is carried out during attack presentations and when the patient is not on immunotherapy [24]. Furthermore, asymptomatic AQP4-IgG does not establish

NMOSD diagnosis and double positivity for AQP4-IgG and anti-MOG is present in a very rare percentage of patients (0.7%) [24]. NMOSD symptoms are caused by pathophysiology involving antibodies attacking aquaporin-4 channels, causing episodes of optic neuritis, myelitis, and brainstem syndromes. However, patients with NMOSD symptoms, negative AQP-4 IgG, and positive MOG-antibodies are diagnosed with Myelin oligodendrocyte glycoprotein (MOG) antibody-associated encephalitis [25]. Clinically, these patients may present at a younger age compared to NMOSD and are less commonly diagnosed with other coexisting autoimmune diseases [25]. On brain MRI, they present more often with acute disseminated encephalomyelitis (ADEM)-like lesions, deep grey matter, pons, and thalamus involvement, while NMOSD patients are more frequently found to have medulla and thalamus lesions. Both NMOSD and MOG show thoracic lesions on spinal cord MRI; however, lumbar lesions are more frequently seen in MOG and cervical lesions are usually detected in NMOSD. In regards to optic neuritis, NMOSD displays prominent RNFL thinning on optical coherence tomography, while MOG shows severe optic swelling at onset [25]. Radiologically, both show orbital involvement, but NMOSD displays chiasmatic lesions and MOG patients are often found to have canalicular and intracranial lesions [25].

**Table 1.** Clinical red flags and possible diagnoses.

| Clinical Red Flags | Possible Diagnoses |
|---|---|
| Age < 16 years | Possible genetic leukoencephalopathies, other demyelinating disorders (for example, post-viral encephalitis or ADEM) |
| Age > 50 years | Vascular etiology |
| Positive family history | Inherited genetic disorders |
| Systemic signs such as fever, weight loss, night sweats, oral ulcers, genital ulcers, pain in the joints, dry eyes and mouth, skin rash | Systemic autoimmune conditions such as SLE, Behçet disease, Sjogren's syndrome, and others. Infections, for example, TB, brucellosis, and others |
| Vague neurological symptoms, not localizable and not consistent with a neuroanatomical site | Malingering or somatoform disorder with depression or anxiety |
| Hyperacute presentation | Vascular etiology |
| Atypical symptoms at presentation such as hearing loss, tinnitus, impaired consciousness, cognitive decline, aphasia, seizures, extrapyramidal manifestations | Susac's syndrome, infections, neurodegenerative or neurometabolic disorders |
| Rapidly progressive and fulminant disease course | Non-MS inflammatory CNS conditions |
| Lack of response to a high dose of corticosteroids | Noninflammatory etiology |
| Simultaneous bilateral optic neuritis, severe optic neuritis with incomplete recovery | NMOSD, MOG-related diseases |
| Progressive optic neuropathy, painless | LHON, sarcoid, neoplasm |
| Complete transverse myelitis | NMOSD, ADEM, idiopathic TM |
| Patients irresponsive to MS treatment or experiencing deterioration | NMOSD |
| Progressive spastic paraparesis | Familial spastic paraparesis, HTLV-1, HIV, vitamin B12 deficiency, CSM, PLS, and dAVF |

ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; CSM, cervical spondylotic myelopathy; dAVF, dural arteriovenous fistula; HIV, human immunodeficiency virus; HTLV, human T-cell leukemia virus; LHON, Leber hereditary optic neuropathy; MOG, myelin oligodendrocyte glycoprotein; NMOSD, neuromyelitis optica spectrum disorder; PLS, primary lateral sclerosis; SLE, systemic lupus erythematosus; TB, tuberculosis; TM, transverse myelitis.

**Table 2.** Radiological red flags and possible diagnoses.

| Radiological Red Flags | Possible Diagnoses |
|---|---|
| Small lesions less than 3 mm, lack of ovoid lesions, peripheral, subcortical lesions | Small vessel disease, nonspecific white matter abnormalities, migraine |
| Lack of spinal cord, posterior fossa, and corpus callosum lesions | Nonspecific white matter lesions |
| Symmetrical or semi-symmetrical lesions | Inherited disorders, for example, leukodystrophies, CADASIL |
| Large corpus callosum lesions | Susac's syndrome NMOSD, lymphoma, tumors |
| Stable lesions in consecutive MRIs | Nonspecific white matter lesions |
| Absence of contrast-enhancing lesions in all MRIs | Migraine, nonspecific white matter lesions, majority of genetic disorders |
| Persistent Gad-enhancing lesions in subsequent MRIs | Vascular anomalies |
| Continuous contrast enhancement over months | Neurosarcoidosis, infections |
| Large mass effect | Tumors, infections, granuloma forming disorders |
| Longitudinally extensive spinal cord lesions | NMOSD; MOG-myelopathies; neurosarcoidosis; vascular anomalies, tumors, neuroBehçet disease/autoimmune/paraneoplastic |
| Large brainstem lesions affecting diencephalic structures and basal ganglia | NeuroBehçet syndrome |
| Meningeal enhancement | Neurosarcoidosis, metastasis, infections |
| Several punctate enhancing brain lesions | CNS vasculitis, neurosarcoidosis, CNS lymphoma, CLIPPERS |

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts; CLIPPERS, chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids; CNS, central nervous system; MOG, myelin oligodendrocyte glycoprotein; NMOSD, neuromyelitis optica spectrum disorder.

**Table 3.** Laboratory red flags and possible diagnoses.

| Laboratory Red Flags | Possible Diagnoses |
|---|---|
| CSF: negative oligoclonal bands, normal IgG index identical bands in CSF and serum | Conditions other than MS such as NMOSDs, migraine, small vessel disease, genetic disorders Systemic condition (inflammatory or infectious in the CNS), Guillain-Barré syndrome, and ADEM |
| CSF white blood cell count >50 | Neuroinfections or other non-MS inflammatory diseases such as ADEM, NMOSDs, neurosarcoidosis, neuroBehçet disease |
| CSF protein >60 mg/dL | Neuroinflammatory conditions other than MS, infections |
| CSF/serum glucose ratio <0.4–0.5 | Infections, leptomeningeal metastatic infiltrate, neurosarcoidosis |
| High titer of autoimmune antibodies, for example, ANA, anti-SSA, anti-SSB, anti-dsDNA | Rheumatological diseases, comorbid NMOSDs |

ADEM, acute disseminated encephalomyelitis; CNS, central nervous system; CSM, cervical spondylotic myelopathy; dAVF, dural arteriovenous fistula; HIV, human immunodeficiency virus; HTLV, human T-cell leukemia virus; MOG, myelin oligodendrocyte glycoprotein; NMOSD, neuromyelitis optica spectrum disorder; PLS, primary lateral sclerosis.

### *3.3. Classification of MS*

#### 3.3.1. Criteria for Classifying MS

Accurate categorization of the clinical course of MS is critical. In 2013, the International Advisory Committee on Clinical Trials in MS developed a revised version of the 1996 definitions of the clinical subtypes of MS, considering the two primary forms of the disease: relapsing forms of MS (CIS and RRMS) and progressive forms of MS (SPMS and PPMS) [6]. Every form is further classified as either active or inactive [6]. Disease activity is decided on by a clinical relapse and/or MRI activity (new or enlarging contrast-enhancing lesions assessed at least every year) [6].

### Radiologically Isolated Syndrome (RIS)

Radiologically isolated syndrome (RIS) applies to patients who present with asymptomatic brain lesions compatible with the radiological description of MS lesions [18]. A recent retrospective analysis of 451 patients with RIS reported that 51.2% developed a clinical event during a 10-year follow-up period [18]. Significant predictors of a first clinical event were young age, MRI with infratentorial brain and spinal cord lesions, positive CSF (two or more CSF-specific OCBs or IgG index >0.7), and follow-up MRI showing gadolinium-enhancing lesions [26]. The indication for the initial MRI (for example, headache) was not predictive of future disease activity [26].

Currently, RIS is not included in the proposed classification of MS (see above) and is not considered a distinct MS phenotype because of the lack of clinical evidence of prior demyelinating events (a current criterion for MS diagnosis), and MRI findings alone may be nonspecific [6]. Nonetheless, clinicians should exercise extreme caution in classifying this group of patients as asymptomatic patients with RIS [17]. RIS patients with no clinical signs or presentations suggestive of MS must be both clinically and radiologically followed up and monitored [6,26].

### Clinically Isolated Syndrome (CIS)

CIS represents the initial neurologic attack caused by inflammation or demyelination in the CNS [6]. If subsequent clinical activity fulfills current MS diagnostic criteria, the diagnosis of CIS is updated to a diagnosis of RRMS [6].

### Relapsing-Remitting Multiple Sclerosis (RRMS)

RRMS may be characterized as inactive, active/highly active, or aggressive. Inactive RRMS is defined as patients with MS who have not had any clinical attack (relapses) within the previous 2 years and no evidence of new active MRI lesion activity on recent imaging [18]; active/highly active RRMS is described by the presence of relapses and/or MRI activity in the past 12 months [18]. Aggressive RRMS has one or more of the following characteristics, irrespective of prior treatment history [18]:

- Expanded Disability Status Scale (EDSS) score $\geq$4 within 5 years of the start of illness
- $\geq$2 relapses within the past year with incomplete resolution
- >2 MRI scans showing new or growing T2 lesions or gadolinium-enhancing lesions after management
- Lack of response to therapy for up to 1 year with one or more DMTs

### Progressive MS

The hallmark of progressive MS is the gradual accumulation of disability [6]. Since PPMS and SPMS have many imaging, clinical, and pathological features in common, they are now considered to be involved in the spectrum of progressive disease. Progressive disease has four possible subclassifications considering the level of disability [6]:

- Active with progression (patient has experienced a clinical relapse or MRI activity [6], as previously described in the "Criteria for classifying MS" section, and is also progressing)
- Active but without progression (for example, the individual has had an episode within a previously determined timeframe; that is, 1 year, 2 years)
- Not active but with progression (for example, decrease in walking speed)
- Not active and without progression (stable disease)

### Secondary Progressive Multiple Sclerosis (SPMS)

SPMS is characterized by a primary relapsing-remitting disease course, then progressive worsening with or without superimposed relapses and plateaus [6]. However, there are no established consensus criteria to determine when RRMS transforms to SPMS; therefore, the diagnosis of SPMS is retrospectively made [6]. Some experts do not consider the diagnosis of SPMS to occur with an EDSS score of <4.0 [18].

Primary Progressive Multiple Sclerosis (PPMS)

PPMS is characterized by an insidious progression of neurological symptoms over 1 year (retrospectively or prospectively determined) with no other explanation, independent of clinical relapse. Moreover, patients should have evidence of a minimum of two hyperintense T2 lesions in the spinal cord or at least one hyperintense T2 lesion in one or more of the periventricular, cortical, juxtacortical or infratentorial areas, or the presence of CSF-specific OCB [21] (Box 2).

**Box 2.** Key points on the diagnosis of MS. MS: Multiple Sclerosis; CIS: Clinically Isolated Syndrome; SPMS: Secondary progressive MS; PPMS: Primary progressive MS.

| |
|---|
| Currently, no one symptom, clinical presentation, or diagnostic test allows for an MS diagnosis. We recommend the use of the 2017 McDonald criteria for the diagnosis of MS, based on dissemination of disease activity in time and space. |
| Important caveats to the use of McDonald criteria include the following: (1) MRI results alone are insufficient to diagnose MS; (2) criteria should be only utilized for patients with a typical CIS, and vigilance must be taken to rule out other possible diagnoses and syndromes that are typical for an MS-related demyelinating event. |
| Consider classification of clinical subtypes of MS in accordance with the 2013 criteria. Two major subsets of the disease are considered: relapsing remitting MS (CIS and RRMS) and primary progressive MS (SPMS and PPMS), with each classified as "active" or "not active". |

### *3.4. Radiology and Imaging*

The most recently revised 2017 McDonald criteria to identify potential MS lesions with DIT and DIS will likely facilitate the diagnosis of MS, as described above. MRI scans are important for diagnosis and regular follow-up to monitor treatment response and disease progression. Interpretation of MRI scans should be performed by experienced radiologists who are familiar with the patient's clinical and laboratory data, and who are able to detect evidence supporting or refuting a diagnosis of MS.

#### 3.4.1. Brain MRI Recommendations

The recommendations for patients with a CIS and/or suspected MS include a baseline gadolinium brain MRI to establish DIT [18]. Performing cervical cord and brain MRIs at the same time could be valuable in the diagnosis of myelitis in CIS patients and in reducing the need for subsequent MRI appointments [18]. If the patient has myelitis with insufficient features on brain MRI or is above the age of 40 with nonspecific MRI changes, a spinal cord MRI is recommended [18]. Finally, patients with severe optic neuritis and poor recovery require orbital MRI imaging [18].

MRI Follow-Up

Based on the current McDonald Criteria [14], patients with suspected MS and/or CIS should have follow-up MRIs to look for DIT evidence, which includes new T2 lesions or gadolinium-enhancing lesions. Monitoring is recommended at 6–12 months for high-risk CIS, where the patient has two or more ovoid lesions on initial MRI. For low-risk CIS patients with normal brain MRI, less than two lesions on MRI, or undetermined clinical syndromes with suggestive MRI lesions (like RIS), follow-up is recommended at 12–24 months [14].

Brain MRI is recommended at presentation for patients with an MS diagnosis if no previous imaging is obtainable, postpartum to determine a new baseline, and before changing or escalating DMT treatment along with close supervision on side-effects, relapses, and current modalities [27,28].

Moreover, patients on DMT should have imaging done every 1–2 years to evaluate any subclinical disease activity (i.e., gadolinium-enhancing lesions or new T2 lesions). For clinically stable patients with 2 to 3 years of unvaried management, less frequent MRI scans are required [29].

Using gadolinium-based contrast agents is not necessary, but may be useful for discovering mild disease activity because new T2 MS lesions could be missed if there is a preexisting large T2 lesion burden obscuring new T2 lesion activity. Gadolinium-based contrast is also recommended in case there is a need for reassessment or unexpected clinical deterioration [29].

For pregnant patients, MRI imaging may be cautiously used in pregnancy only if the benefits outweigh the risks in terms of diagnostic performance and medical outcome [29].

Due to the minimal distribution of gadolinium-based contrast into the breast milk and subsequently to the infant's gut, studies recommend continuing breastfeeding after receiving such an agent [29].

#### 3.4.2. Spinal Cord MRI Recommendations

Consider spinal MRI when:

- Spinal cord-specific symptoms (myelitis, progressive myelopathy)
- Recurrent myelitis
- Older age of start of symptoms
- Inability to establish DIT

Typical MRI findings in the spinal cord in MS are short, less than three vertebral segments, peripheral white matter, and constitute less than 50% of the cross-sectional area. Conversely, other inflammatory CNS diseases, such as NMO/MOG, display longitudinally extensive lesions, with at least three vertebral segments and 50% of the cross-sectional area affected, and more grey matter involvement is detected [30]. Moreover, in addition to the extensive involvement of grey matter on MRI, NMOSD often displays the characteristic "H-shaped" cord lesion [31]. In MOG, "pencil-thin" linear enhancement of the ependymal canal may be spotted [32].

##### MRI Protocols

Brain: 3D T1-weighted, 3D T2-FLAIR, 3D T2-weighted, post-single-dose gadolinium-enhanced T1-weighted sequences, and a diffusion-weighted imaging (DWI) sequence [29].

Spinal cord: Sagittal T1-weighted and proton attenuation, short-tau inversion recovery (STIR) or phase-sensitive inversion recovery, axial T2- or T2-weighted imaging through suspicious lesions, and, in some cases, post-contrast gadolinium-enhanced T1-weighted imaging [29]. Thoracic and conus imaging is proposed if symptoms spread to this region to exclude a different diagnosis [29].

Whenever available, using 3T scanners may offer the advantage of a higher rate of lesion detection and efficiency in regard to acquisition time when compared to scanners of lower magnetic field strength [23].

##### Gadolinium-Based Contrast Agents (GBCAs)

In CIS, the utilization of gadolinium-based contrast agents (GBCAs) is invaluable as it allows for an earlier diagnosis by demonstrating lesions' DIT (GBCA-enhancing lesion) and DIS. Early diagnosis allows for early management, which may impede disease progression and enhance long-term projection [29]. However, the detection of T2 lesions with relapsing–remitting MS predicts a worse diagnosis.

For patients with established MS, GBCA is beneficial for evaluating highly active disease, rapid decline, unexpected or unexplained worsening, or possible alternative diagnoses [29].

GBCA is an option for long-term monitoring of patients with MS for detection of mild disease activity, which may cause changes in therapy. The use of GBCA could be useful during the first 2 years of management, but is not necessary in the absence of a large T2 lesion burden because new T2 MS lesions could be detected on high-quality MRI utilizing a standardized protocol [29].

Selecting a GBCA could be complicated due to the need for balancing risks vs. benefits for an individual patient, the patient population, and the health care system in general [18].

Concerns over the safety of GBCA have been raised in recent years [18]. GBCA, which is valuable for the assessment of patients with MS, is not without risk. Nephrogenic systemic sclerosis as a complication of GBCA has been described in patients with preexisting renal dysfunction, requiring assessment of renal function prior to receiving these agents. More recently, gadolinium retention has been detected in patients with MS who have undergone gadolinium-enhanced MRI of the brain [18]. This evidence has prompted the U.S. Food and Drug Administration (US FDA) to issue a drug safety alert and request manufacturers to update the medication guide for patients to inform them of this issue [18].

The long-term consequences of gadolinium retention in the CNS remain unknown. Additionally, there is variability in the CNS retention of GBCAC based on its chemical structure. GBCA can be categorized as linear or macrocyclic, with linear agents retained at higher concentrations and for longer periods than macrocyclic agents. In all cases, written informed consent should be obtained when GBCA is used to describe the possible complications of nephrogenic systemic fibrosis and gadolinium retention. In addition, radiology departments should be encouraged to use GBCA, which has shorter retention times [18].

Recommendations for Communication

MRI requisition:

When making an MRI requisition, the clinician must request a standardized MRI brain and/or spinal cord protocol with questions on diagnosis, monitoring for management decision addressed, relevant medical history, and examination findings addressed. Updates on current DMT status and JCV status (if on natalizumab) should be included. Finally, dates of previous examinations, as well as locations, should be provided if applicable.

### *3.5. Other Tests/Investigations*

Optical Coherence Tomography (OCT)

Optical coherence tomography (OCT) is a non-invasive, efficient, and easy-to-use technique that utilizes near-infrared light to form retina images. Retinal nerve fiber layer and ganglion cell layer thickness loss correspond with clinical and paraclinical parameters like visual function, disability, and MRI findings [33]. OCT parameters could be used to evaluate disability prognosis and visual function in MS [18]. Reductions in the ganglion cell layer thickness in the retina of MS patients lacking previous optic neuritis may reflect subclinical structural injury, and OCT might help in identifying patients with optic neuritis who have a higher likelihood to develop MS [33]. In addition, OCT could possibly help in the differentiation between MS subtypes and could contribute to the evaluation of visual function, clinical disability, and MRI parameters during long-term monitoring [33] (Box 3).

**Box 3.** Key points on radiology/imaging for MS. MS: Multiple Sclerosis; MRI: Magnetic resonance imaging; CIS: clinically isolated syndrome; DMTs: disease-modifying treatments; OCT: optical coherence tomography.

- MRI is central to the diagnosis of MS following the 2017 McDonald diagnostic criteria.
- Interpretation of MRI scans should be performed by trained radiologists who are capable of fully interpreting them and are aware of the patient's clinical and laboratory information.
- A baseline brain MRI with gadolinium is proposed for a patient with CIS/suspected MS, to establish DIT. Consider a spinal cord or orbital MRI, depending on the presentation.
- Follow-up MRI is recommended at 6–12 months/12–24 months for those with high/low risk of progression.
- For established MS, perform MRI if no recent scan is available, postpartum, escalating DMT, and every 1–2 years while on DMT.
- MRI can be cautiously used in pregnancy when the benefits outweigh the risks in terms of diagnostic performance and medical outcome.
- The administration of Gadolinium-based contrast with MRI should be avoided in pregnancy unless crucial for the improvement of maternal and fetal outcomes.
- Breastfeeding should not be interrupted after gadolinium administration.
- Minimize the use of gadolinium where possible (although this is essential for CIS), due to potential safety concerns (use a contrast agent with a lower retention time, and discuss risks and benefits with the patient).
- OCT is a non-invasive, quick, and easy-to-use technique that uses near-infrared light to produce images of the retina. It may also contribute to the evaluation of visual function over time as MS progresses.

## 4. Conclusions

With the rising prevalence of Multiple Sclerosis (MS) in Saudi Arabia and emerging novel therapy selections, it is important to establish guidelines and recommendations to standardize and clarify decision-making options for clinicians in regard to the diagnosis of MS patients. Moreover, evidence-based radiology-related recommendations are of crucial value in the management of MS, knowing that the diagnosis of this disease significantly relies on imaging, and particularly magnetic resonance imaging.

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