Multiple Sclerosis and Acute Disseminated Encephalomyelitis: Evidence-Based Neuroimaging

9

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Contents

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Key Points

- There is limited evidence that MRI improves diagnostic accuracy for MS, with several recent reviews providing differing conclusions (limited evidence). However, MRI-based measures have been formally incorporated into widely accepted clinical diagnostic criteria for MS for nearly a decade. Experts perceive that use of MRI in these patients serves multiple clinical purposes beyond diagnosis, including the exclusion of other pathologies (limited evidence).
- There is insufficient evidence to suggest that MRI findings can distinguish MS from ADEM (insufficient evidence).
- Regarding prognostic utility of MRI in MS, observational studies have yielded inconsistent results with regard to correlations between MRI-based measures and cognitive performance or disability in MS patients (limited evidence). However, use of MRI-based measures in recent clinical trials suggest that some imaging-based measures (especially the number of new T2 lesions and number of enhancing lesions) may correlate with both relapse rate and risk of disability progression (moderate to strong evidence).
- There is insufficient evidence to suggest that advanced MRI techniques improve the diagnostic accuracy of MRI for MS (insufficient evidence).
- Studies involving advanced MRI techniques in MS patients have largely contributed to a better understanding of the pathophysiology of the disease. There is early evidence that advanced techniques could be prognostically useful: based on one recent RCT of a new treatment, rate of cerebral atrophy (a semiautomated volumetric MRI-based measure) may correlate with relapse rate (moderate to strong evidence).

Definition and Pathophysiology

Among the demyelinating diseases (characterized by destruction of normal myelin with relative preservation of the axon) affecting the CNS, multiple sclerosis is the most common [1, 2]. While the etiology of multiple sclerosis remains uncertain, the current most widely held view is that MS is an autoimmune process resulting from the interplay of environmental factors in those with a genetic predisposition [3]. The mechanism of injury includes inflammation, focal demyelination, and variable degrees of axonal destruction [4, 5]. At pathologic evaluation, the microscopic appearance will vary based on the activity of disease, with active lesions demonstrating perivascular and parenchymal inflammation with associated macrophage and lymphocyte infiltration, and inactive lesions demonstrating hypocellularity, astrogliosis, and loss of oligodendrocytes [1]. Remyelination may occur with early MS lesions ("shadow plaques"), though histologically, the myelin density in these areas is diminished with sparse or absent remyelination seen in chronic MS plaques [6]. MS lesions are distributed throughout the CNS with a predilection for involvement of the periventricular white matter, corpus callosum, optic nerves, spinal cord, brain stem, and cerebellum [5]. MS exhibits a wide diversity of neurologic signs and symptoms, with the clinical presentation largely based on location of the demyelinating lesion[s].

The clinical presentation of MS is quite heterogeneous, but common clinical manifestations include deficits in sensory or motor pathways, brain stem, and cerebellar structures, as well as autonomic function. Individuals that initially present with an acute focal neurologic disturbance referred to as a clinically isolated syndrome (CIS) are at risk for developing MS [7]. In adult patients with optic neuritis, the 10-year risk of developing MS is 38 % but increases to 56 % when one or more lesions typical for MS are present on MRI. The disease course varies from a single acute monophasic attack to the more common relapsing-remitting or progressive phases [8]. Relapses reflect worsening of neurologic function secondary to a new inflammatory lesion or reactivation of an existing lesion, with a relapse defined by symptom duration of at least 24 h [7]. Progression is defined as continual worsening of clinical signs and symptoms over a minimum of 6–12 months [9]. For standardization of nomenclature, the

various clinical courses have been defined in 1996 by Lublin et al. [10]:

1. Relapsing-remitting MS (RRMS) – relapses with full recovery or with sequelae and residual deficit upon recovery; periods between disease relapses characterized by a lack of disease progression.
2. Secondary progressive MS (SPMS) – initial relapsing-remitting disease course is followed by progression with or without occasional relapses, minor remissions, and plateaus.
3. Primary progressive MS (PPMS) – disease progression from onset with occasional plateaus and temporary minor improvements allowed.
4. Progressive-relapsing MS (PRMS) – progressive disease from onset, with clear acute relapses, with or without full recovery; periods between relapses characterized by continuing progression.

Treatment is aimed at preventing neurologic disability. Acute relapses are typically treated with intravenous or oral corticosteroids with several disease-modifying agents currently approved by the Food and Drug Administration for use in reducing the number of attacks in relapsing-remitting MS including immunomodulating injectable and more recently emerging oral therapies [11–13].

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated disorder of the CNS resulting in perivascular inflammation and demyelination [14]. ADEM usually presents in individuals within weeks following a viral illness, after vaccination, or in some cases may occur spontaneously [2]. Pathologic evaluation demonstrates inflammatory infiltrates consisting of lymphocytes and macrophages along a perivenular distribution, with preservation of the axon [15]. ADEM typically involves white matter of the cerebrum and spinal cord as well as cerebral cortex and deep gray structures. In contrast to multiple sclerosis, ADEM is typically a monophasic, self-limited disease lasting 2–4 weeks, although relapses have been reported [16]. ADEM is more frequently seen in children but can occur at any age. Prodromal symptoms of fever, headache, malaise, and myalgias commonly occur prior to the onset of neurologic signs. Like MS, neurologic signs and symptoms are manifested based on location of the demyelinating lesion, with severity ranging from irritability to depressed consciousness and coma. Neurologic abnormalities include unilateral or bilateral long tracts signs, hemiparesis, ataxia, optic neuritis, cranial nerve palsies, and seizures. Despite the lack of placebo-controlled, double-blinded studies evaluating efficacy of treatment options, steroids are the primary treatment for ADEM with patients typically receiving an intravenous course of therapy for 3–5 days followed by a taper of oral steroids. Treatment options also include IV acyclovir in combination with steroids, IV immunoglobulin with or without steroids, or plasmapheresis in those who fail initial treatment courses [14].

Epidemiology

Multiple sclerosis is the most common nontraumatic neurologic disorder resulting in disability in young and middle-aged people in the developed world, affecting approximately 350,000 people in the United States and 1–2 million people worldwide [7, 11, 12, 17, 18]. Risk factors for developing MS include both genetic and environmental factors. Genetic factors include those that are familial, with first-degree relatives at 10–25 times increased risk of developing MS over the general population; ethnic, with whites having the greatest prevalence and near absence of the disease in Chinese; and sex related, with the disease being more common in women [19]. Environmental risk factors include history of positive Epstein-Barr virus serology, smoking history and geography, with a general trend of increasing latitude conferring increased risk of developing MS [19]. MS has the greatest incidence in Europe, North America, southern Australia, and New Zealand (prevalence rate of 30 or more per 100,000), with the country of origin persisting as a risk factor despite later migration to a region with a lower prevalence [3, 17, 19]. The reported protective effect of vitamin D in the prevention of MS may help explain the link between latitude and development of MS [limited evidence] [20].

Of the various clinical courses of MS, the relapsing-remitting type is the most common, representing approximately 85 % of cases, while progressive forms comprise the remaining 15 % [21]. Females are affected more frequently than males (ranging from 2:1 to 3:1) with a peak age of onset at 30 years [3, 9, 11, 22, 23]. Onset after the age of 55 is rare, with greatest proportion of cases presenting between 20 and 40 years of age. Females tend to have a younger age at disease onset, and the female preponderance over males declines with increasing age at initial diagnosis. Predominantly small, retrospective studies reporting the incidence of MS in the pediatric population estimate that 2.7–5 % of all MS patients have disease onset before the age of 16, while onset before the age of 10 is rare (0.2–0.7 %) [24, 25]. Over time, most cases of relapsing-remitting MS will convert to secondary progressive form, with a median of 19 years disease duration [9, 26]. Time between the first and second neurologic attacks has a mean of 6 years and median of 2 years [21]. The primary risk factor for conversion from the relapsing-remitting to secondary progressive forms is age at the time of disease onset, with more advanced age correlating with a shorter time to progression [27]. Females and those with a longer interval between the first and second neurologic attacks are more likely to experience a later evolution of the progressive phase [26]. Accumulative disability varies between individuals, with overall life expectancy only marginally reduced [21, 28].

ADEM is relatively uncommon with incidence in children less than 15 years of age reported to be 0.64/100,000 persons per year in a Japanese study between 1998 and 2003 [29]. Similar results were obtained in a San Diego County-based population with an incidence of 0.4/100,000 persons per year among individuals <20 years of age, with increased incidence in children aged 0–4 (0.6/100,000) and in children aged 5–9 (0.8/100,000) [30]. In contrast to MS, a slight male preponderance has been described with the mean age at presentation ranging between 5 and 8 years of age [31–34]. Seasonal variation has been reported with increased incidence in winter and spring months [31]. Long-term outcome is excellent with full recovery reported in 57–94 % [16, 35, 36].

Overall Cost to Society

The economic burden to society secondary to multiple sclerosis is substantial and based largely on loss of work capacity in younger individuals who are in the early phases of their careers [37]. The estimated annual combined direct and indirect costs of multiple sclerosis in the United States are $6.8 billion and in the United Kingdom, £1.2 billion [38, 39]. Physical disability impacts the ability to conduct activities of daily living and often necessitates skilled assistance. The need for hospitalization with disease exacerbations and the development and increased utilization of disease-modifying agents are directly related to increased costs of MS in the health-care system. The costs related to MS increase with disease progression. A cross-sectional cost-of-care study in patients with mild, moderate, and severe MS (grouped according to the Expanded Disability Status Score) revealed total 3-month cost estimates ranging from $1,928 to $5,678 in France, $2,772 to $5,701 in Germany, and $5,125 to $14,622 in the United Kingdom, with increased cost associated with greater disability [39]. In the United States, annual expenditures were reported as $7,677 per privately insured enrollee with MS versus $2,394 for all privately insured enrollees [40]. Asche et al. estimated the total mean 12-month all-cause costs were $18,829 for MS patients versus $4,038 for healthy comparisons, including higher rates of hospitalization, radiology services, ER, outpatient visits, and mean cost of $8,839 for use of an MS injectable drug [41].

Goals of Neuroimaging

- MRI is a sensitive paraclinical study (defined as a test that can identify a nonclinically evident lesion in the CNS) for detecting white

matter lesions that in the appropriate clinical context provides supporting evidence for predicting or confirming the diagnosis of multiple sclerosis (limited to moderate evidence). MRI is also useful to diagnose alternative pathology that could mimic a demyelinating disease (limited evidence).
- MRI can potentially help to differentiate ADEM from the first presentation of MS based not only on the initial distribution of lesions but also on follow-up imaging (insufficient evidence).
- MRI is used as a surrogate marker for evaluating disease progression (moderate to strong evidence), predicting cognitive and physical disability (limited evidence), and as an outcome measure in clinical trials.
- Advanced MR imaging techniques, likely the focus of future research, have contributed to our knowledge of the pathophysiology of MS and may correlate with disease relapse (moderate to strong evidence).

Methodology

A comprehensive MEDLINE search was performed using PubMed (National Library of Medicine, Bethesda, Maryland) for original research publications relating to the accuracy of test used to diagnose multiple sclerosis and acute disseminated encephalomyelitis performed between 1966 and December 2010. The search strategy employed different combinations of the following terms: *multiple sclerosis, acute disseminated encephalomyelitis, demyelinating disease, clinical criteria, imaging criteria, MRI, gadolinium enhancement, fMRI, DTI, spectroscopy, perfusion, CSF, oligoclonal bands, and evoked potentials*. Review of the reference lists of relevant papers identified additional articles. This review was limited to human studies and the English language literature. The authors performed initial reviews of the titles and abstracts of the identified articles followed by review of the full text in articles that were relevant.

Discussion of Issues

How Accurate Are the Diagnostic Criteria for Multiple Sclerosis?

Summary

There have been numerous studies investigating the diagnostic utility of MRI (conventional imaging techniques) in MS, most of which have provided limited strength of evidence that MRI improves diagnostic accuracy for this disease (limited evidence). Three reviews (two from expert groups and one systematic) of the available literature in 2003–2004 presented various conclusions (limited to moderate evidence) about the diagnostic accuracy of MRI or partly MRI-based diagnostic criteria, but all acknowledged that the clinical utility of MRI scanning in these patients involves more complex issues than basic measures of sensitivity and specificity (e.g., excluding other diseases, possibly facilitating earlier diagnosis, providing patient reassurance, providing a baseline for monitoring disease progression). MRI-based measures have been formally incorporated into the most widely accepted clinical diagnostic criteria for MS (Table 9.1); therefore, it seems unlikely that future strong or moderate evidence studies of the diagnostic accuracy of MRI will be performed in the future.

Supporting Evidence

No single clinical or diagnostic test is sufficient to establish the diagnosis of multiple sclerosis. Evaluation requires both detailed clinical history and neurologic examination with objective evidence of demyelinating lesions involving the CNS. Because it is not feasible to have histologic confirmation to definitively diagnose patients suspected of having MS, various diagnostic models have evolved over the past several decades. While the criteria have changed over time, certain features among the various iterations have remained constant including (1) the diagnosis of multiple sclerosis can be based solely on clinical evidence of demyelinating lesions involving the CNS and (2) the diagnosis

requires that there is no better alternative explanation of the patient's signs and symptoms [4]. A hallmark of clinically definite MS is that lesions are disseminated in time and space. While this characteristic feature can be ascertained by clinical history and evaluation, patients presenting initially with a clinically isolated syndrome (CIS) have some delay until the second neurologic attack. In one of the longest follow-up studies of patients with optic neuritis, the estimated 15-year risk of developing MS was 40 % (95 % CI 31–52 %) with 60 % of patients diagnosed with MS within 3 years from onset of optic neuritis [42]. A definitive diagnosis of MS is desirable after this first neurologic episode since the institution of early therapy with disease modifying treatment can delay the onset of future attacks [moderate to strong evidence] [43–46].

Criteria established by Poser et al. in 1983 were the reference standard for diagnosing MS for nearly 20 years and were applied not only to clinical practice but also to experimental trials as inclusion criteria (e.g., by which other tests were evaluated). The criteria included categories of (1) clinically definite MS, (2) laboratory-supported definite MS (dependent on CSF analysis for oligoclonal bands/increased IgG), (3) probable MS (supported by clinical or laboratory evidence), and (4) possible MS [47]. Because MRI was relatively new at this time, Poser classified it as a supporting paraclinical study, but no specific imaging criteria were described. Inconsistencies exist among even neurologists in differentiating clinical symptoms caused by one or more separate lesions in the CNS, potentially misclassifying patients with clinically definite MS [48]. While clinical diagnosis of MS remains the gold standard for diagnosis, inherent inconsistencies in clinical evaluation support the use of paraclinical studies to aid in the diagnosis of MS [48, 49].

Multiple studies have suggested that MRI is a valuable paraclinical test to demonstrate anatomic evidence of discrete lesions separated in space at the time of initial clinical presentation (Table 9.2). Paty et al. reported a high sensitivity of MRI in detecting T2 signal abnormalities in patients with clinically definite MS, although a study by Lee et al. demonstrated a relatively low specificity when followed prospectively (57 %) [49, 50]. Fazekas et al. applied retrospective criteria to review patients with an established diagnosis of MS in order to improve specificity (100 %); however, specificity decreased when applied to subsequent prospective studies [51, 52]. Tas et al. demonstrated that contrast enhancement of white matter lesions improves specificity (80 %) in diagnosing multiple sclerosis [52]. Furthermore, because enhancement of an MS lesion may be visible for 2–8 weeks, MRI can establish dissemination in time even at the initial clinical presentation by virtue of identifying both new (enhancing) and old (non-enhancing) lesions on a single study [52, 53].

McDonald et al. updated the Poser criteria in 2001 to include MRI specific imaging-based criteria [43, 54, 55]. The MRI criteria adopted by McDonald were established largely based on data from Barkhof et al. and Tintore et al., which showed improved specificity of MRI, particularly with inclusion of enhancement criteria [52, 54–56]. Dalton et al. validated the use of the McDonald criteria in clinical settings with reasonably good sensitivity (83 %), specificity (83 %), positive predictive value (75 %), and negative predictive value (89 %) for predicting development of clinically definite MS at 1 year with an overall accuracy of 83 % at 3 years [57].

While MRI is a major component in the current diagnostic algorithm for MS, several reviews have been recently published on the utility of MRI in diagnosing suspected MS. In 2003, Frohman et al. presented a review and recommendations undertaken by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology, based upon their review of the literature to date [58]. Based upon this group's review of the literature (in which they found serious concerns about the validity of some study results), they concluded that there was strong evidence that, in patients with CIS, the presence of three or more T2 WM lesions is a sensitive predictor (>80 %) of the development of MS within the next 7–10 years. Other imaging-based features that they

concluded were predictive included two or more enhancing lesions at baseline and new T2 lesions or enhancing lesions three or more months after the CIS episode. Miller et al. in 2004 presented the review and recommendations of the European Magnetic Resonance in MS Group, which they based on the available literature at that time, in which they focus especially on limitations of the McDonald 2001 criteria [59]. They conclude that longer term follow-up studies suggest that the presence of T2 lesions in CIS does not guarantee the development of MS but that MRI can provide a more accurate prediction of the likelihood of MS. Following these two reviews, a systematic review by Whiting et al. concluded that MRI is a relatively poor test for either ruling in or ruling out MS and the disease remains predominantly a clinical diagnosis, suggesting that previous studies have not focused on the more relevant question of what added value MRI has in diagnosing MS compared with history and clinical examination alone [60]. Nevertheless, in 2005, the McDonald criteria were revised specifically to provide clarification of MRI criteria in order to show dissemination in time and for spinal cord lesions [61] (Tables 9.1, 9.3). Though these revised criteria have not been prospectively validated formally, a recent expert panel included a consensus statement that MRI has an important role in the diagnosis of MS and a recommendation for adopting protocols and reporting based on the revised McDonald criteria [62].

Despite the widespread acceptance of the McDonald criteria to diagnose adult MS, its validity in children with possible MS has been called into question. In a retrospective cohort study by Hahn et al., a significant number of children with MS did not meet established McDonald criteria for diagnosis, with dissemination in space criteria only met in 53 % of children at the time of their first neurologic attack and in 67 % of children at the time of their clinical MS defining attack [63]. Potential explanations for reduced sensitivity of the McDonald criteria in children include inherent age-related differences in disease pathology with shorter time for accrual of clinically silent white matter lesions, age-related differences in lesion distribution, or differing reparative mechanisms in children limiting overall lesion burden [64]. While evidence evaluating the McDonald criteria in children with MS is limited, a subsequent consensus report by the International Pediatric MS Study Group in 2007 used the McDonald MRI criteria to define a diagnosis of pediatric MS [65]. In 2009, a retrospective cohort study by Callen et al. proposed pediatric modifications to the McDonald criteria including at least two of the following: (1) total of five or more T2 lesions, (2) two or more periventricular lesions, and (3) one or more brain stem lesions [64]. These criteria yielded improved sensitivity compared to McDonald criteria (85 % vs. 76 %, respectively) and similar specificity (98 % vs. 100 %) but have not been prospectively validated [64].

CSF analysis is another paraclinical test used in the diagnosis of MS. Typical abnormalities include the presence of oligoclonal bands and increased IgG synthesis in the CSF. CSF analysis is also important for excluding other infectious or inflammatory disorders that could mimic MS, or to confirm MS when clinical evaluation and MRI are inconclusive (limited evidence). Jin et al. showed that detection of oligoclonal bands is a prognostic marker (hazard ratio = 5.39, 95 % CI 1.56–18.61) for the development of clinically definite MS in patients initially presenting with optic neuritis (moderate evidence) [66]. However, CSF analysis may be normal in 30 % of patients early in MS [11]. Tintore et al. demonstrated greater specificity (70 %, CI 0.61–0.79 vs. 43 %, CI 0.34–0.52) and accuracy (69 %, CI 0.6–0.78 vs. 52 %, CI 0.43–0.61) for Barkhof's MRI criteria when compared to oligoclonal bands for predicting conversion to clinically definite MS in patients initially presenting with an isolated syndrome (moderate evidence) [67]. Both oligoclonal bands and MRI had similar negative predictive values, 88 % and 87 %, respectively. However, the greatest specificity (77 %, CI 0.69–0.85) and accuracy (73 %, CI 0.65–0.81) were achieved when both MRI criteria and oligoclonal bands were used together, which more closely mirrors common clinical practice.

Evoked potentials are another paraclinical study traditionally used in the diagnosis of MS, with the most common being visual (VEP), brain stem auditory (BAEP), and sensory (SEP). Alterations in conduction pathways due to demyelination cause slowing of electrical activity. The VEP is the most valuable measure and can detect subclinical evidence of optic nerve involvement, particularly at the onset of a clinically isolated optic neuritis [4]. Various studies have demonstrated sensitivity of VEP ranging from 26 % (odds ratio 0.6, CI 0.2–1.6) to 72 % (odds ratio 0.9, CI 0.3–2.2) with specificities of 25 % (odds ratio 0.9, CI 0.3–2.2) to 77 % (odds ratio 2.9, CI 0.8–10.8) [43]. However, data from evidence-based reviews do not substantiate the inclusion of evoked potentials in MS diagnostic criteria (moderate evidence) [43, 68].

Can Clinical and MRI Studies Differentiate ADEM from the First Initial Onset of MS?

Summary

There is insufficient evidence to suggest that MRI findings can distinguish ADEM from MS (insufficient evidence).

Supporting Evidence

Unlike for the diagnosis of MS, there are no established clinical criteria used as a reference standard in the diagnosis of acute disseminated encephalomyelitis. The diagnosis of ADEM is generally presumptive based on excluding disease mimickers by means of clinical history, neurologic evaluation, neuroimaging findings, and CSF analysis, with the differential diagnosis primarily including an acute viral encephalitis or MS [14, 30]. Characteristically, ADEM is a monophasic demyelinating process with clinical findings usually occurring within weeks (mean latency 2 weeks) following an infection or vaccination, or symptoms may occur spontaneously [33, 69]. A clinical relapse in patients with ADEM which is thought to be related to the initial demyelinating event is termed multiphasic disseminated encephalomyelitis (MDEM); however, if the demyelinating events are separated in time and space, a diagnosis of MS is made. In the absence of a clearly definable preceding cause typical for ADEM, differentiation between the onset of MS and ADEM becomes a clinical conundrum with significant implications for long-term prognosis and for instituting immunomodulating therapy [34].

Certain clinical features may help differentiate ADEM from MS. Patients with ADEM commonly present with encephalopathy including headache, vomiting, drowsiness, and meningismus, which are uncommon in MS [33, 69]. Seizures may be seen in 13–35 % of patients with ADEM, whereas seizures are rare in MS [69]. Alteration in consciousness is more common in ADEM (45–75 %) versus MS (13–15 %) [69]. Patients with ADEM are more often polysymptomatic (reported as high as 91 %) versus a more typical monosymptomatic presentation of MS (62 %) [35].

There is significant overlap between the MR imaging findings of ADEM and MS. The most common imaging findings of ADEM are areas of abnormal high T2 signal in the supratentorial white matter, basal ganglia, brain stem, cerebellum, and spinal cord. A longitudinal observational study of 48 children presenting with one or more episodes of demyelination by Dale et al. demonstrated a greater propensity for periventricular distribution with MS compared to ADEM, whereas ADEM had a greater propensity for involvement of the thalamus and basal ganglia (Table 9.4) [35]. A retrospective review by Murthy et al. demonstrated lesion distribution similar to Dale's findings in 18 patients with ADEM [33].

In a cohort study, Mikaeloff et al. defined a brain MRI suggestive of ADEM when lesions were indistinct and also involved the thalamus and/or basal ganglia, while an MRI suggestive of MS showed multiple well-delineated lesions with periventricular and/or subcortical involvement [70]. In this study, MRI criteria suggestive of MS accurately diagnosed 57 % of patients diagnosed with clinically definite MS, while only 11 % of patients with MRI criteria

suggestive of ADEM were ultimately reclassified as having clinically definite MS [70]. A different cohort study by Mikaeloff et al. used MRI findings to predict the likelihood of a second neurologic attack following an initial demyelinating episode, revealing that lesions oriented perpendicular to the long axis of the corpus callosum and/or the presence of well-defined lesions were very specific criteria (100 %), but not as sensitive (21 %) as Barkhof's MS criteria in predicting a second neurologic attack [71]. A retrospective review by Callen et al. reviewed MRI exams at the time of initial presentation in 28 children subsequently diagnosed with MS and 20 children diagnosed with ADEM [72]. Based on Callen's analysis, diagnostic criteria predicting progression to clinically definite MS included any two of the following: (1) two or more periventricular lesions, (2) presence of T1 black holes, and (3) absence of diffuse and bilateral lesion distribution, resulting in 81 % sensitivity, 95 % specificity, 95 % positive predictive value, and 79 % negative predictive value.

Two retrospective observational studies have suggested that lesion size is a poor discriminator between MS versus ADEM with both small (less than 1.0 cm) and large (greater than 2.0 cm) lesions identified in both entities [69, 72]. Overall lesion number also does not differentiate ADEM versus MS, although in ADEM, lesions are often more asymmetric [72]. Both MS and ADEM lesions show contrast enhancement [73]. Case reports have suggested that restricted diffusion in lesions of patients with ADEM was associated with poor clinical outcome based on the presence of cytotoxic edema; however, subsequent reports have not substantiated these findings [74, 75]. Spinal cord lesions in ADEM have been reported as usually larger than in MS, associated with cord swelling, and more commonly present in the thoracic cord, while MS lesions are more common in the cervical cord [69]. Follow-up imaging is helpful to establish complete (37 %) or at least partial (53 %) resolution of initial MRI abnormalities in ADEM, whereas in MS, new lesions can often be expected [35].

According to the longitudinal study by Dale et al., CSF analysis in ADEM typically shows evidence of inflammation with increased protein (60 %) and lymphocytosis (64 %), while intrathecal oligoclonal bands were entirely absent in 47 % of ADEM patients studied [35]. In contrast, CSF analysis in patients with MS showed that 82 % had evidence of intrathecal oligoclonal bands at some point during their course, though in their study, there was not a statistically significant difference in the detection of CSF oligoclonal bands in ADEM versus MS [35]. A summary of significant differentiating features of ADEM versus MS based on this study can be found in Table 9.5.

Do Conventional MRI Sequences Correlate with or Predict Disease Progression and Acquired Disability in Multiple Sclerosis?

Summary

Multiple observational studies have yielded inconsistent results with regard to the correlation between MRI-based measures and cognitive performance or EDSS scores (limited evidence). However, some of the MRI-based measures have been used in recent clinical trials of new treatments for MS, with results suggesting that these imaging-based measures – particularly the number of new T2 lesions and number of enhancing lesions – may correlate with both relapse rates and risk of disability progression (moderate to strong evidence).

Supporting Evidence

The majority of patients presenting initially with a clinically isolated syndrome (CIS) suggestive of multiple sclerosis will go on to develop clinically definite MS. Studies that have supported the use of the McDonald criteria and subsequent revision to predict the development of MS at the time of first clinical onset have been based on the presence of T2-weighted signal abnormalities and T1-weighted enhancing lesions [61]. MRI is an established paraclinical study to diagnose MS and is supported by long-term longitudinal studies revealing that up to 88 % of patients with a CIS and abnormal T2 lesions on MRI at the

time of presentation may develop MS [76, 77]. MRI is also used to predict the natural history of patients with MS and as a measure of clinical disability; however, the association between degree of MRI abnormalities and development of disability is relatively weak [45, 46, 78, 79].

Conventional T2-weighted MRI is highly sensitive for detecting demyelinating lesions disseminated in the CNS at the time of a CIS and also reveals clinically silent lesions between relapses [80]. However, T2 lesions lack specificity, and similar appearing lesions may be caused by inflammation, gliosis, edema, or axonal loss due to other pathologic entities [78, 81]. Despite the lack of specificity, the number and volume of T2 lesions have been used as a surrogate marker for clinical disability. Brex et al. demonstrated that the volume of T2 lesions acquired in the first 5 years following a CIS shows only moderate correlation with long-term disability at 14 years ($r = 0.45$) as measured by the expanded disability status score (EDSS), concluding that the T2 lesion volume alone may not be an adequate marker for instituting therapy with disease-modifying agents [77, 82]. Filippi et al. found a weak correlation between EDSS and the number of new ($r = 0.13$) and enlarging ($r = 0.18$) T2 lesions [83]. Tintore et al. demonstrated a moderate correlation between EDSS at year 5 and the number of T2 lesions at baseline as well as the number of Barkhof criteria fulfilled ($r = 0.40$ and $r = 0.46$, respectively) [84]. Because the EDSS is weighted more heavily toward motor dysfunction, Riahi et al. not unexpectedly demonstrated a slightly greater correlation between EDSS and T2 lesions specifically involving the corticospinal tracts ($r = 0.67$) versus overall T2 volume load ($r = 0.60$) [85]. Minneboo et al. evaluated the significance of T2 lesion location in order to predict EDSS score progression and found that 2 or more infratentorial lesions were the best predictor for disability (hazard ratio, 6.3) [86]. A 20-year follow-up study again demonstrated only moderate correlation between T2 lesion volume at all time points and disability by EDSS (r range = 0.48 to 0.67) [87]. Unlike the moderate correlation demonstrated by the preceding authors, the Optic Neuritis Study Group found no correlation between baseline MRI and disability at 10 years of follow-up in patients with a CIS presenting with optic neuritis [88]. Foong et al. also found no correlation between T2 lesion load and physical disability based on the EDSS, but lesion load did correlate with various neuropsychological and cognitive scores [89].

Gadolinium enhancement reflects blood–brain barrier breakdown and serves as a marker for the active, inflammatory phase of MS lesions. Enhancing lesions can precede new T2 lesions by hours or days [90]. Most enhancing lesions persist for 2–6 weeks, but are rare beyond 6 months [91, 92]. He et al. demonstrated that enhancing lesions are most commonly small with a nodular pattern of enhancement (68 %), while 23 % show ring-like enhancement, and 9 % showed neither of these patterns (arc-like) [91]. The presence of a single enhancing lesion on baseline MRI has been positively correlated with subsequent relapse in the following 6 months; however, most newly enhancing MRI lesions are clinically silent [92, 93]. A small study by Molyneux et al. found no correlation between the presence of newly enhancing lesions and changes in EDSS [94]. A meta-analysis by Kappos et al. in 1999 also concluded that while enhancing lesions on MRI predict subsequent relapses, enhancement is not a strong predictor for developing disability [95].

A number of T2 hyperintense MS lesions (5–20 %) will appear hypointense to normal-appearing gray matter on T1-weighted sequences [96]. In the acute phase, the T1 hypointensity may reflect elements of edema related to inflammation and demyelination, with subsequent normalization of isointense T1 signal as the inflammation resolves and as remyelination may ensue. Chronic T1 "black holes" are thought to reflect more severe injury with greater loss of axonal density than T1 lesions that are not hypointense [97]. Chronic black holes are defined by their persistence for at least 6 months, but in the absence of serial examinations for comparison, a T1 black hole is assumed by the lack of associated contrast enhancement [96, 98]. Various studies have evaluated progressive

whole-brain or central cerebral atrophy associated with an increased volume of T1 black holes, which may contribute to worsening cognitive and physical decline [99]. Paolillo et al. found a significant correlation between T1 hypointense lesion load and supratentorial brain volume ($r = 0.48$), but not with T2 hyperintense lesion load [100]. Bermel et al. found that brain parenchymal fraction was lower in patients with MS and correlated inversely with T1 hypointense lesion volume, but not T2 lesion volume [101]. Conversely, Rudick et al. found no correlation with measurable progressive whole-brain atrophy and clinical manifestations [102].

Despite the sometimes inconsistent findings on these multiple observational studies (predominantly providing limited strength of evidence), multiple investigators have utilized MRI parameters in prospective clinical trials of various medications used in the treatment of MS. Trials involving interferon beta-1b and interferon beta-1a have generally failed to show the expected correlation of MRI measures and treatment effects [103–106]; however, trials of newer treatments have shown more promising results. Using imaging data from an RCT evaluating the efficacy of treatment with glatiramer acetate (GA), Filippi et al. found that the relapse rate was 33 % lower in GA-treated patients compared with placebo patients [107]. MRI findings correlated with clinical findings in this study, with a significant decrease in the number of new T2 lesions, the number of new enhancing lesions, and the percentage of new T2 lesions that evolved into T1 black holes in GA-treated patients compared with placebo patients [107, 108]. Large RCTs involving oral fingolimod as a treatment for MS have provided evidence that MRI parameters correlate with clinical endpoints of disease activity in clinical trial settings. Kappos et al. found that the annualized relapse rate was 0.77 in the placebo group, as compared with 0.35 in the lower dose fingolimod-treated group and 0.36 in the higher dose fingolimod group, and also found a corresponding decrease in the median number of enhancing lesions on MRI in the fingolimod groups compared with the placebo group [109]. In testing the efficacy of fingolimod compared with interferon beta-1a, Cohen et al. in a large RCT found that fingolimod treatment was associated with lower relapse rates, fewer new T2 lesions, and fewer enhancing lesions compared with interferon beta-1a treatment [110]. In a 2-year double-blind RCT, Kappos et al. found that relapse rate, risk of disability progression, number of new T2 lesions, and number of enhancing lesions were all decreased in the fingolimod group compared with the placebo group [111].

Do Advanced Imaging Techniques Offer Clinical Utility over Conventional MRI in Evaluating MS Patients?

Summary

There is insufficient evidence to suggest that advanced MRI techniques improve the accuracy of MRI in diagnosing MS (insufficient evidence). Table 9.6 summarizes areas of research in which advanced MRI techniques may yet prove to be useful. Studies involving advanced techniques have to date largely contributed to a better understanding of the pathophysiology of the disease and have provided direction for future research; Table 9.6 summarizes areas in which early research has suggested potential usefulness beyond pathophysiology. Few of these techniques have been used in recent clinical trials, but one RCT has shown that rate of cerebral atrophy (by semiautomated volumetric MRI-based measurement) correlates with relapse rate (moderate to strong evidence). There is insufficient evidence of the effectiveness of these techniques in improving the clinical care of MS patients (insufficient evidence).

Supporting Evidence

There has been much interest in the use of advanced MRI techniques in the setting of MS, including especially magnetization transfer (MT), diffusion-weighted (DWI) or diffusion tensor imaging (DTI), volumetric measurements, MR spectroscopy (MRS), and perfusion imaging. However, there have not been studies that have evaluated the effect of these techniques on the

accuracy of MRI in diagnosing MS. Rather, most studies have attempted to use advanced MRI techniques to better understand the pathophysiology of the disease, to predict prognosis, or to monitor response to therapy.

Magnetization transfer (MT) imaging is a technique based on the magnetization interaction between bulk water protons and macromolecular protons so that diseased tissues with altered protein-water interactions become more conspicuous with MT technique [112]. Most studies utilizing MT imaging have contributed to an improved understanding of the pathophysiology of MS. Some studies have been more clinically focused, however, with most providing limited evidence given study design issues. In a 5-year study, Pike et al. found that a decline in MT ratio was present not only within T2 lesions in MS patients but also in areas in normal-appearing white matter (NAWM) that later became focal lesions, with the MT ratio abnormalities being detectable up to 18 months before the lesions appeared on T2-weighted images [113]. Cercignani et al. found that MT ratio metrics were lower in NAWM in MS patients compared with NAWM in healthy controls, finding similar MT ratio metric differences in normal-appearing gray matter (NAGM) in MS patients compared with healthy controls. Summers et al. found that MT ratio in NAWM in MS patients predicts cognitive decline over 5 years in relapsing-remitting multiple sclerosis (RRMS) [114]. However, different studies have shown inconsistent results with regard to correlations between MT ratio metrics and disease-related disability [115–118].

Diffusion and DTI techniques have been widely used in research involving MS patients, with Ge et al. providing an inclusive review of interesting findings as of 2005 [119]. Most have been small studies (limited evidence) that have sought to contribute to an improved understanding of the pathophysiology of MS. Multiple investigators have found that plaque-like T2 lesions in MS patients have increased mean diffusivity (MD) compared with NAWM in patients and healthy controls [120–126]. Multiple studies have suggested that NAWM in MS patients shows increased MD and decreased fractional anisotropy (FA) compared with NAWM in healthy controls [124, 125, 127–133]. In two very small observational studies (limited evidence), investigators found some evidence that either diffusivity or ADC changes preceded development of gadolinium-enhancing focal lesions [129, 134]. Multiple studies have shown differences in diffusion-based measures by disease phenotype [123, 135–139]. One of the larger of these focused on GM involvement, finding that GM diffusivity was not different between controls and patients with RRMS, but finding that diffusivity was different between RRMS and SPMS, and between SPMS and PPMS [136]. Recent studies have found correlations between diffusion-based measures and contemporaneous measures of cognitive performance or disability [140, 141]. A prospective observational study of RRMS patients being treated with GA found that there were decreases in MD and entropy in patients at 2 years compared with baseline measures [142].

Although not based on advanced acquisition techniques, *volumetric measurements* have been investigated as a newer post-processing method (i.e., automated or semiautomated) that might be useful in MS patients, given the common clinical finding of global atrophy in these patients. Multiple investigators have found correlations between atrophy measures by MRI and disease disability or disease progression in MS patients [143, 144], with several finding that measures of GM atrophy correlate better than measures of WM volume or lesion load [145–148], and some finding that T1 hypointense lesion volume correlates with clinical disability [149, 150]. A few longitudinal studies have found that various volumetric measures may actually predict future disease progression, but these methods have not been tested prospectively (limited to moderate evidence). Summers et al. found that global atrophy rate over the first year from baseline as well as T1 lesion volume at baseline could predict cognitive decline over 5 years in RRMS patients [114]. Horakova et al. found that percent

brain volume change as early as 6 months could predict clinical progression versus stability in RRMS over 5 years and that GM volume loss in the first 24 months predicted disability progression over 5 years [151]. Lukas et al. suggested that the rate of ventricular enlargement could predict disease progression after medium term follow-up in early MS [99]. In the 2-year double-blind RCT by Kappos et al., the rate of atrophy was found to be lower in those treated with fingolimod compared with the placebo group; the fingolimod-treated group also showed decreased relapse rates and risk of disability progression [111].

MR spectroscopy (MRS) has also been fairly widely used in research settings involving MS patients. Various investigators have sought to find a relationship between decreased NAA or NAA/Cr ratio and T2 lesions or NAWM or disability measures; results have been inconsistent across studies [133, 152–158]. Saindane et al. found that metabolite profiles of high-grade gliomas and tumefactive MS lesions were similar overall, with central NAA/Cr ratio being somewhat lower in high-grade gliomas [159].

MR perfusion imaging techniques have been tried in recent years in MS research. Law et al. found decreased perfusion and prolonged MTT in lesions and NAWM in MS patients compared with controls and found that enhancing lesions showed highly variable CBV [160]. Subsequent studies have found variable-decreased CBF and/or CBV in NAWM, lesions, and GM of patients compared with controls, suggesting that perfusion abnormalities may exist in a continuum beginning in WM and spreading to GM with disease progression [161, 162]. However, these techniques have not been tested prospectively (limited evidence).

Take-Home Tables

Table 9.1 summarizes the combined MRI and clinical criteria established for the 2005 "McDonald Revisions," which is currently the most widely used diagnostic paradigm for MS. Table 9.2 summarizes the sensitivity and specificity of conventional MRI criteria used in diagnosing clinically definite multiple sclerosis. Table 9.3 summarizes the criteria required by MRI to establish dissemination in time of MS lesions, according to the 2005 "McDonald Revisions." Table 9.4 summarizes the common distribution of lesions in ADEM/MDEM versus MS as reported by Dale et al. Table 9.5 summarizes differentiating features between ADEM/MDEM and MS clinical presentations based on data by Dale et al. Table 9.6 summarizes the potential areas of clinical usefulness of advanced MRI techniques.

Imaging Case Studies

Case 1: Typical MRI Findings of Multiple Sclerosis (Fig. 9.1a–e)

History: A 34-year-old female diagnosed with multiple sclerosis 4 years earlier now presenting with worsening gait. Patient has had multiple hospitalizations and treatment with IV steroids, currently managed with monthly natalizumab.

Case 2: Enhancing MS Lesions with Resolution at Follow-Up (Fig. 9.2a–d)

History: A 48-year-old female with 10-year history of relapsing-remitting MS currently managed on interferon beta-1a.

Case 3: Acute Disseminated Encephalomyelitis (Fig. 9.3a–c)

History: A 4-year-old male presented to the Emergency Department with seizure and history of recent fever and leukocytosis.

Case 4: Tumefactive Multiple Sclerosis (Fig. 9.4a–e)

History: A 38-year-old female with 9-year history of relapsing-remitting MS, now with rapidly worsening left hemiparesis and hemianesthesia. Patient was treated with intravenous steroids and plasmapheresis during hospitalization. Due to aggressive nature of patient's MS, she was started on injectable mitoxantrone for therapy.

Table 9.1 2005 McDonald criteria for diagnosing multiple sclerosis

MR imaging criteria	Clinical presentation	Additional data for diagnosis
1. Requires three of the following: (a) At least 1 gadolinium-enhancing lesion or 9 T2 hyperintense lesions if there is no gadolinium-enhancing lesion (b) At least 1 infratentorial lesion (c) At least 1 juxtacortical lesion (d) At least 3 periventricular lesions Note: A spinal cord lesion can be considered equivalent to a brain infratentorial lesion: An enhancing spinal cord lesion is considered to be equivalent to an enhancing brain lesion, and individual spinal cord lesions can contribute together with individual brain lesions to reach the required number of T2 lesions	1. Two or more attacks; objective evidence of ≥2 lesions 2. Two or more attacks; objective evidence of 1 lesion 3. One attack; objective clinical evidence of ≥2 lesions 4. One attack; objective clinical evidence of 1 lesion (monosymptomatic presentation; CIS) 5. Insidious neurologic progression suggestive of MS	1. None 2. Dissemination in space, demonstrated by: (a) MRI *or* (b) ≥2 MRI-detected lesions consistent with MS plus positive CSF *or* (c) Await further clinical attack implicating different site 3. Dissemination in time, demonstrated by: (a) MRI *or* (b) Second clinical attack 4. Dissemination in space, demonstrated by: (a) MRI *or* (b) ≥2 MRI-detected lesions consistent with MS plus positive CSF *and* (c) Dissemination in time, demonstrated by MRI *or* (d) Second clinical attack 5. One year of disease progression (retrospectively or prospectively determined) *and* two of the following: (a) Positive brain MRI (9 T2 lesions or ≥4 T2 lesions with positive VEP) (b) Positive spinal cord MRI (2 focal T2 lesions) (c) Positive CSF

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Table 9.2 Sensitivity and specificity of conventional MR imaging in diagnosing clinically definite multiple sclerosis

Author	No. of patients	Sensitivity (%)	Specificity (%)	Comments	Quality of study
Paty et al. [49]	200	94	57	Prospective, lesions classified as hyperintense on T2WI and at least 3 mm in size; strongly suggestive of MS defined by total # of 4 white matter lesions or 3 lesions, one of which is periventricular	Limited evidence
Fazekas et al. [51]	91	88	100	Retrospective review; defined by 3 lesions with at least two of following criteria: (1) infratentorial lesion, (2) periventricular lesion, or (3) a lesion >6 mm	Limited evidence
Tas et al. [52]	57	59	80	Prospective at 1st presentation; criteria defined as at least 1 enhancing and 1 non-enhancing lesion	Moderate evidence
Barkhof et al. [55]	74	82	78	Criteria defined by three of the four following findings: (1) 1 gadolinium-enhancing lesion or 9 T2 hyperintense lesions, if there is no gadolinium-enhancing lesion, (2) at least 1 infratentorial lesion, (3) at least 1 juxtacortical lesion, and (4) at least 3 periventricular lesions	Limited evidence

Table 9.3 Establishing dissemination in time

2005 MRI criteria requires the following
1. Detection of gadolinium enhancement at least 3 months after the onset of the initial clinical event, if not at the site corresponding to the initial event
2. Detection of a *new* T2 lesion if it appears at any time compared with a reference scan done at least 30 days after the onset of the initial clinical event

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Table 9.4 Distribution of lesions in ADEM/MDEM versus MS

	ADEM/MDEM (%)	MS (%)
Periventricular WM	44	92
Deep and subcortical WM	91	92
Brainstem	50	56
Thalamus	41	25
Basal ganglia	28	8
Spinal cord	28	25

Data from [35]

Table 9.5 Differentiating features between ADEM/MDEM and MS clinical presentations

Finding	ADEM/MDEM (%)	MS (%)
Prodromal illness	74	38
Polysymptomatic presentation	91	38
Encephalopathy	69	15
Seizure	17	0
Serum pleocytosis	64	22
Periventricular WM lesions on MRI	44	92

Data from [35]

Table 9.6 Potential clinical usefulness of advanced MRI techniques

MRI Technique	Potential clinical usefulness	Strength of evidence
MT	Predicting cognitive decline	Limited
DWI/DTI	Distinguishing phenotypes, correlating with cognitive decline/disability	Limited
Volumetrics	Predicting disease progression/cognitive decline, correlating with treatment response	Limited to moderate
MRS	Correlating with disability	Limited
Perfusion	Correlating with or predicting disease progression	Limited

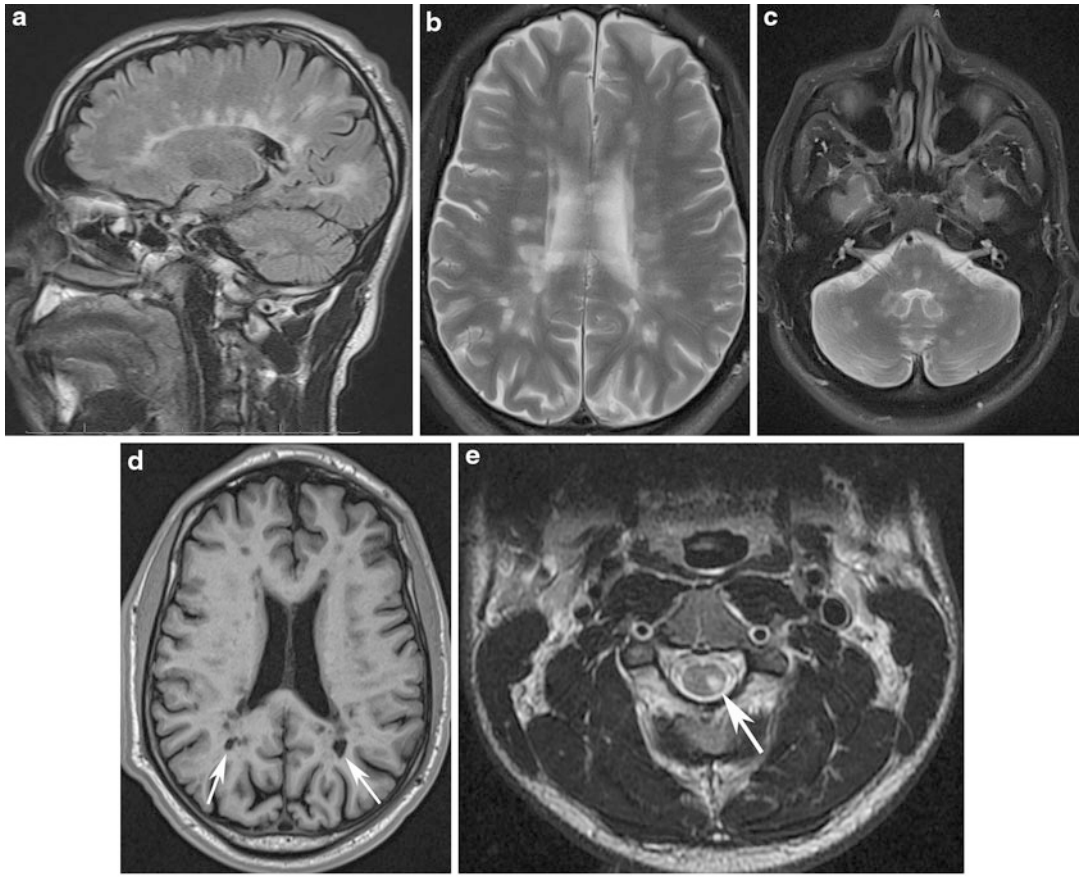

Fig. 9.1 (**a**–**e**) Paramidline sagittal FLAIR (**a**) shows numerous abnormal hyperintense lesions in the pericallosal white matter, many of which have an ovoid configuration radiating away from the ventricular margin. Axial T2 sequences demonstrate numerous round and ovoid hyperintense lesions in the supratentorial (**b**) and infratentorial (**c**) white matter with involvement of the corpus callosum, pons, and cerebellar white matter. Axial T1 FLAIR (**d**) shows multiple "T1 black holes" (*arrows*). Axial T2 of the cervical spine (**e**) reveals a hyperintense lesion in the left dorsolateral aspect of the cord (*arrow*)

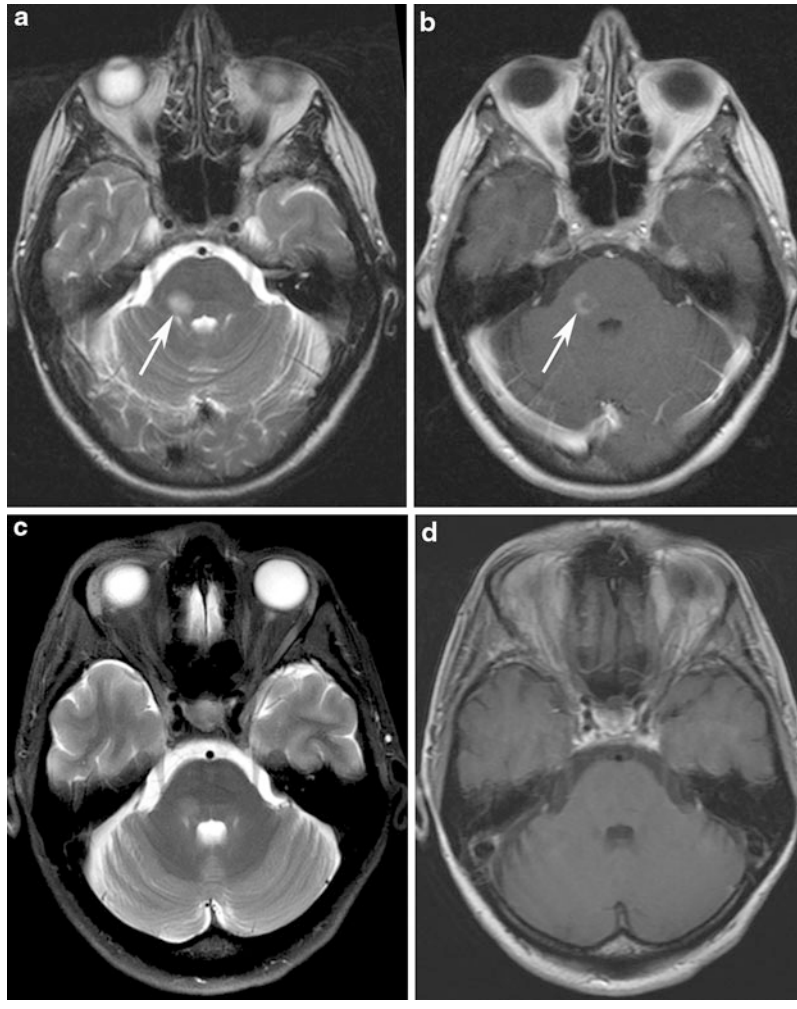

Fig. 9.2 (**a**–**d**) Axial T2 at the level of the brainstem (**a**) demonstrates globular hyperintense signal in the posterior right pons (*arrow*). Accompanying postcontrast T1 (**b**) shows corresponding incomplete ring enhancement (*arrow*). Follow-up MRI 4 weeks later shows residual, but improved T2 hyperintensity (**c**) and complete resolution of enhancement (**d**)

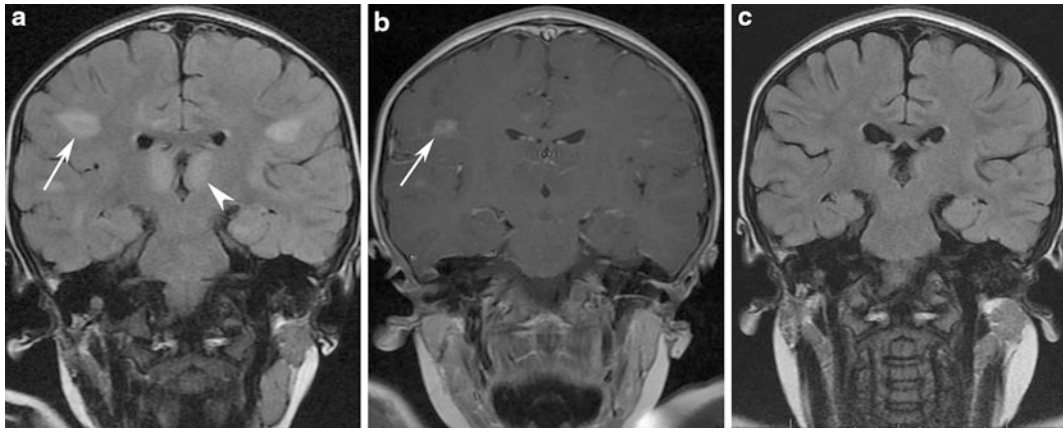

Fig. 9.3 (**a**–**c**) Coronal FLAIR (**a**) demonstrates multiple hyperintense lesions within the subcortical white matter (*arrow*) and involving the thalamus bilaterally (*arrowhead*). Postcontrast coronal T1 (**b**) shows enhancement of some of these lesions, with the largest irregular focus of enhancement in the right parietal white matter (*arrow*). Coronal FLAIR (**c**) obtained 5 weeks later after course of intravenous and oral steroids shows resolution of previous regions of hyperintense signal abnormality with no residual neurologic sequelae

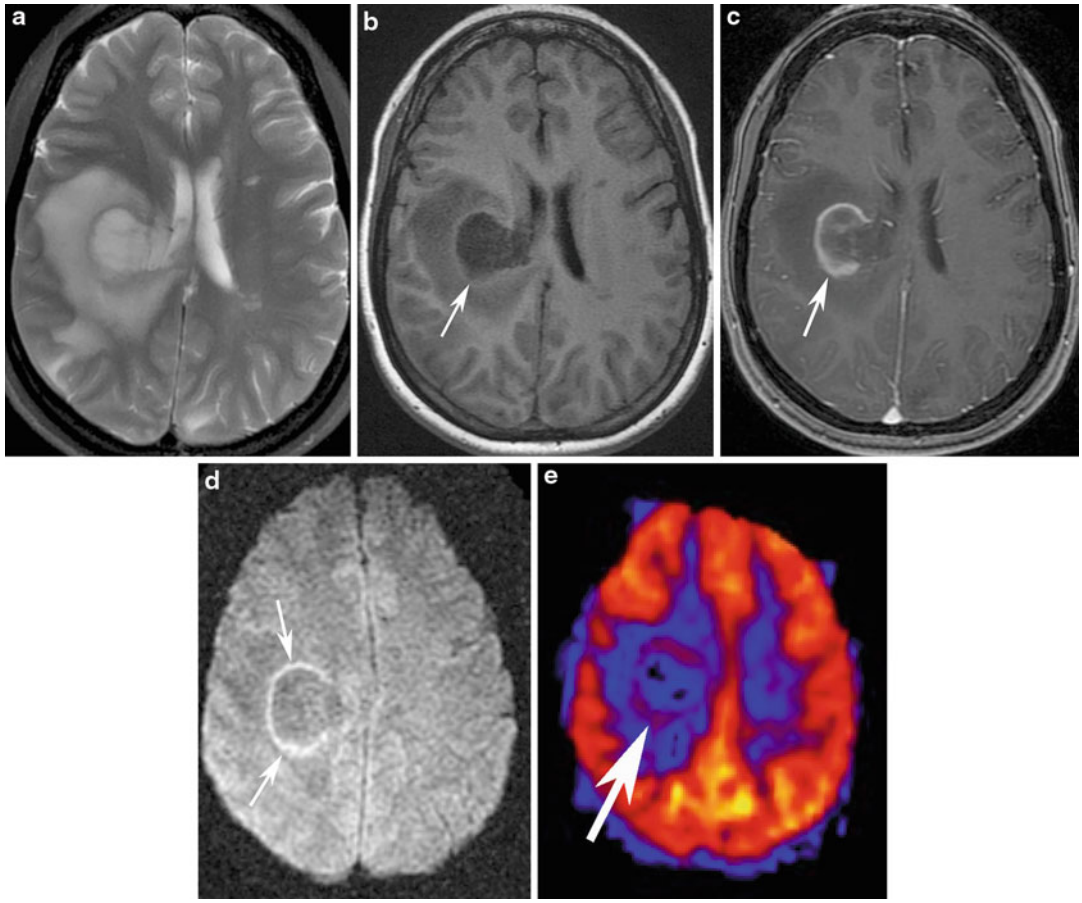

Fig. 9.4 (**a**–**e**) Axial T2 (**a**) demonstrates large mass-like hyperintense lesion in the posterior right frontal white matter abutting the ventricular margin. Axial T1 FLAIR (**b**) at the same level shows marked central hypointensity (*arrow*). Postcontrast T1 (**c**) shows incomplete ring enhancement (*arrow*) with open portion of ring facing the ventricle. Diffusion-weighted sequence (**d**) shows restricted diffusion along the leading edge of demyelination (*arrows*). Pulsed arterial spin-labeled MR perfusion (**e**) also reveals increased blood flow corresponding to the leading edge of demyelination (*arrow*)

Suggested Imaging Protocols

The following MRI brain and spinal cord protocols are recommended (some are modified from published guidelines by an international consensus group sponsored by the Consortium of Multiple Sclerosis Centers (CMSC) in 2001) [163] (insufficient to limited evidence):

Brain

- Axial sections should follow the subcallosal line (joins the undersurface of the rostrum and splenium of the corpus callosum).
- Axial FSE PD/T2 and axial FLAIR – both are recommended when acquiring a diagnostic scan for CIS and also for MS follow-up.

- Axial gadolinium-enhanced T1 is recommended for a diagnostic scan for CIS.
- Axial pregadolinium T1 is optional, but nonetheless considered useful for comparison with non-contrasted images.
- Sagittal FLAIR is recommended for diagnostic scan for CIS, but optional for MS follow-up.
- The CMSC gave no specific guidelines for acquiring diffusion-weighted imaging, but a subsequent review by Lovblad et al. included DWI as an optional sequence and helpful to differentiate other diagnoses [155].

Spine

- Pre- and postgadolinium-enhanced sagittal T1 sequences are recommended.
- Precontrast sagittal FSE PD/T2 sequence is recommended.
- Precontrast axial FSE PD/T2 is recommended (through suspicious lesions).
- Postcontrast axial T1 is recommended (through suspicious lesions).
- 3D T1 is optional.

General Imaging Principles

- Standard dose of 0.1 mmol/kg is injected over 30 s, and image acquisition should begin a minimum of 5 min after start of injection.
- In MS, MRI of the brain and spinal cord should be performed on at least a 1 T magnet, if possible.

Future Research

- Though desirable from an evidence-based perspective, Level 1 or Level 2 studies of the diagnostic accuracy of MRI (conventional) are not likely to be performed in the future – since MRI-based measures have been formally incorporated into clinical diagnostic criteria for MS since 2001.
- There is a paucity of literature on the effect of advanced MRI techniques on the diagnostic accuracy of MRI in MS.
- Though some advanced techniques have been used in recent clinical trials, there is a need for more prospective evidence that these advanced MRI measures correlate with or predict clinical outcomes such as relapse or progression of disability.

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