MRI features of pediatric multiple sclerosis

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Abstract—*Background:* MRI has revolutionized the diagnostic accuracy of multiple sclerosis (MS) in adults, and is now used extensively to evaluate efficacy of immunomodulatory therapies. Although MRI has also been used to aid in the diagnosis and care of children with MS, the MRI features of MS in children are less well understood. *Methods:* The present review summarizes the available literature on MRI in pediatric MS, outlines the specific features of other disorders affecting the CNS white matter in children, compares the MRI appearance of MS in children to seminal neuroimaging studies in adult-onset MS, and discusses the potential role of advanced MRI technologies in delineating the underlying pathobiology of acquired demyelinating disease in children. *Results:* Although the MRI features of MS in children have similarity to adult-onset MS, children tend to have fewer lesions and a lower propensity for lesions to enhance with gadolinium. The MRI findings in children presenting with a clinical phenotype of acute disseminated encephalomyelitis may be indistinguishable from the first attack of MS. *Conclusions:* MRI criteria specific for pediatric-onset multiple sclerosis (MS) and criteria predictive of MS outcome in children experiencing a first demyelinating event will be challenged by the overlap in MRI features between acute monophasic demyelinating syndromes and MS, particularly in younger children. Emergence of new clinically silent lesions on MRI scans separated by at least 3 months is characteristic of MS. Newer MRI techniques evaluating white matter biochemistry and integrity in the youngest MS patients may provide new insights into the relative contributions of inflammation and neurodegeneration in MS.

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MRI is exquisitely sensitive to the white matter lesions that characterize multiple sclerosis (MS). The pattern and appearance of MRI lesions in MS, and the ability of MRI to detect evolving new lesions, have led to the creation of new diagnostic criteria for MS that incorporate MRI into the diagnostic algorithm.[1] These MRI criteria were based solely on the appearance of MS in adults.

The MRI appearance of MS in children is less well described. Conceptually, there are many possible reasons why the MRI appearance of MS in children may differ from that of adults: 1) the subclinical phase of the MS disease process is inherently brief in young MS patients by virtue of their young age, and thus there may be fewer pre-existing lesions notable on MR images obtained at the time of the first demyelinating event; 2) although the majority of developmental modifications in myelin biochemistry take place during the first 24 months of life, full myelin maturation proceeds in a caudal-rostral pattern until early adulthood,[2] and thus myelin maturity may influence the regional proclivity for MS lesions, particularly in the very young MS patient; 3) immunologic maturity, the capacity for transmigration of immune cells through the blood–brain barrier, and secretion of cytokines may differ between children and adults, leading to differences in the inflammatory nature of lesions in children compared to adults; and 4) children may differ from adults in their innate capacity for myelin repair, leading to fundamental differences in the MRI appearance of lesion evolution.

The purpose of this review is to summarize literature data on the specific MRI features in pediatric MS and related acquired demyelinating diseases. Comparison to the MRI criteria already well established in the adult MS population as well as the predictive value for conversion to clinically definite MS will be provided. Finally, we discuss future avenues of research including quantitative evaluation of MRI lesion pattern and evolution in pediatric MS, and the potential insights to be gained by advanced MR imaging techniques as applied to the pediatric MS population, a subgroup of MS patients uniquely close to the biologic onset of their disease.

MRI appearance of MS in children. The MRI appearance of childhood MS is typically one of multiple white matter lesions,[3-6] as depicted in figure 1A. Recent clinical studies have indicated that over 98% of pediatric-onset patients with MS experience a relapsing-remitting MS (RRMS) course.[7,8] There are no publications detailing the MRI features of the

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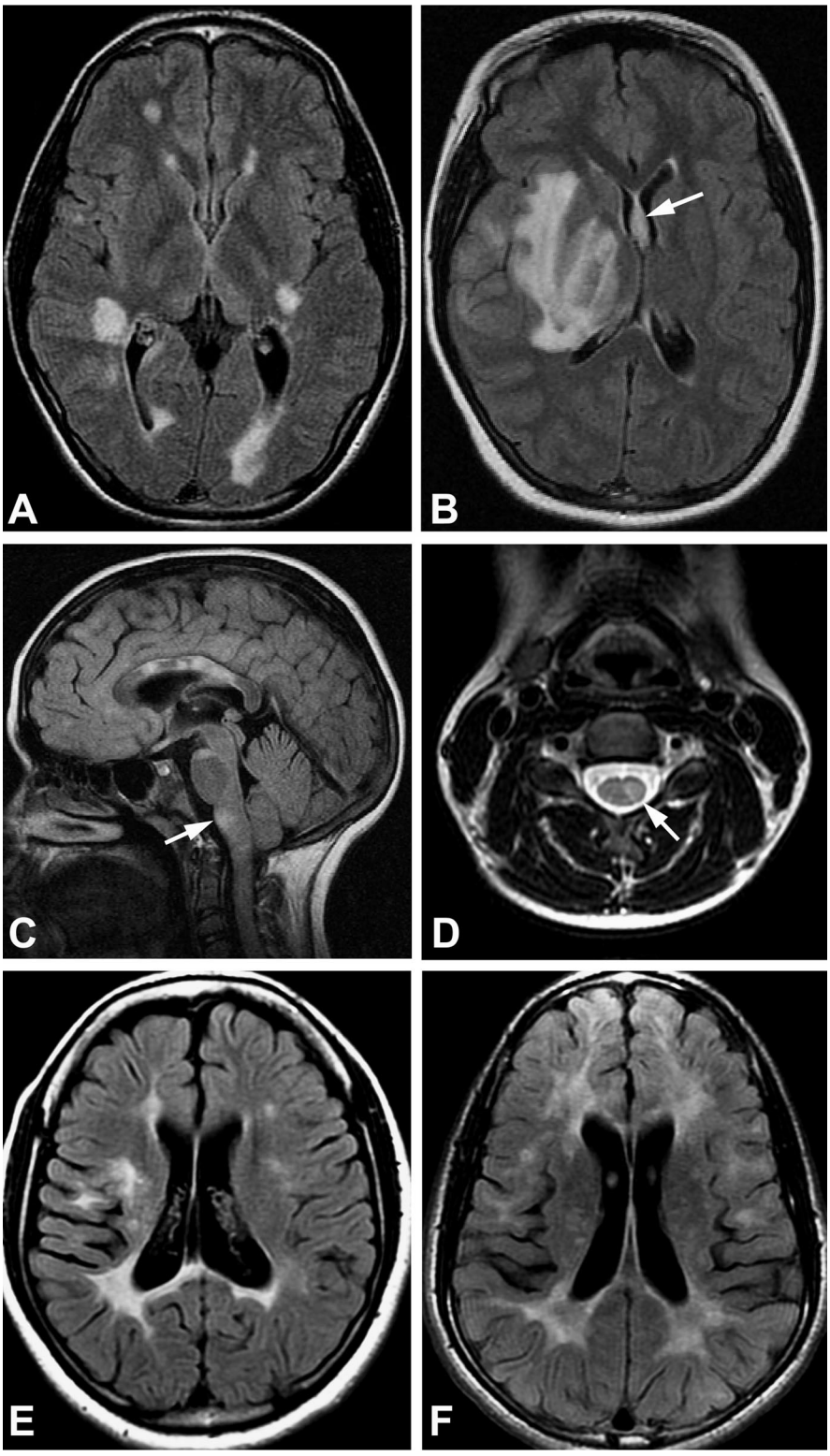

Figure 1. MRI appearance of multiple sclerosis (MS) in children. (A) Axial fluid-attenuated inversion recovery (FLAIR) image of an adolescent patient with MS demonstrating typical ovoid white matter lesions in the periventricular and deep white matter. (B) Axial FLAIR image demonstrating a large lesion involving the deep gray and white matter associated with significant mass effect, consistent with tumefactive demyelination. Note the white matter involvement in the fornix (arrow). The child, an 11-year-old Korean girl, presented with focal seizures and hemiparesis. She had presented with optic neuritis several months prior to the present scan. She has experienced four MS relapses over the last 3 years. (C) Sagittal FLAIR image highlighting multiple lesions within the corpus callosum in a 9-year-old girl with MS. A lesion in the brainstem is also visible. (D) Axial T2 image through the cervical cord demonstrates a hyperintense lesion in the left side of the cord (arrow) at the C4 level. This child, a 15-year-old, presented with hemisensory loss and l'Hermitte symptom. (E, F) Axial FLAIR images of two pediatric-onset patients with MS. The patient represented in E is a 17-year-old adolescent with MS disease duration of 9 years. The patient represented in F is a 14-year-old boy diagnosed with MS for 3 years. He has experienced more than eight clinical relapses and has progressive cognitive impairment. The confluent appearance of the white matter lesions represents coalescence of multiple smaller lesions, as was confirmed on evaluation of their prior MRI studies (not shown).

extremely rare child with primary progressive MS (PPMS), and thus the remainder of the discussion will focus solely on the MRI appearance of pediatric RRMS.

Gadolinium administration is used to demonstrate acute lesions. In adults presenting acutely with their first episode of demyelination, 52% have enhancing lesions.[9] The propensity for lesion enhancement may differ in children relative to adults. In a French pediatric demyelination study gadolinium was administered to 61 of the 116 children imaged at the time of an initial acute demyelinating attack, and was positive in only 13% of the children with monophasic illness and in only 24% of the children ultimately diagnosed with MS.[4] The timing of MR imaging relative to treatment with corticosteroids was not de-

scribed, and thus it is possible that recent corticosteroid exposure may have mitigated the propensity for gadolinium enhancement.

Another feature of acute demyelination in children includes the potential for large demyelinating lesions with marked perilesional edema. The appearance of giant or tumefactive demyelinating plaques has been reported in several children.[5,10] In a study of 20 children with MS, review of MR images found four children with tumefactive lesions.[3] Figure 1B highlights a large tumefactive lesion in a child presenting with hemiparesis and a past history of optic neuritis (ON), and the subsequent dramatic resolution of the lesion following treatment with corticosteroids.

The MRI appearance of MS of very young children may be particularly unique from that of adult-onset MS. The first attack of demyelination in children younger than 10 years may show diffuse, bilateral, white matter lesions with ill-defined borders,[4] as shown in figure 2A. Despite the rather dramatic initial MRI appearance, MRI resolution of initial lesions may occur (figure 2B). Emergence of new lesions over time (figure 2, B and D) accompanied by clinical attacks confirmed the diagnosis of MS.

Application of adult MS MRI criteria to MRI scans of children with MS. Application of adult MS criteria for lesion dissemination in space to MRI scans of a cohort of 20 Canadian children ultimately diagnosed with MS demonstrated that although all children had one or more T2 lesions, only 53% met the McDonald criteria for lesions dissemination in space at the time of their initial demyelinating event.[3] Children in this cohort often failed to demonstrate nine or more lesions, perhaps as a reflection of a shorter subclinical period of lesion accrual in children. Gadolinium was only administered to 9 of the children, 4 (44%) of whom had enhancing lesions. The MRI scans in children failing to meet the McDonald criteria for lesion dissemination in space typically demonstrated low lesion numbers, with lesions in regions not identified by the McDonald criteria. Application of the Paty[11]or Fazekas[12] MRI criteria yielded a higher sensitivity of over 80%, in part due to the reduced stringency of these criteria. Similar findings on the utility of applying adult MS MRI criteria to MRI scans in children have been reported by others.[4,8] Application of the McDonald MRI criteria for lesion dissemination in space in the French study of 116 children under age 16 years yielded a sensitivity of 52% with a specificity of 63%.[4]

Earlier studies demonstrated a high sensitivity (74%) and specificity (86%) for the McDonald MRI criteria in prediction of MS outcome in adults.[13]A more recent study in which the McDonald MRI criteria for lesions dissemination in space were applied to adults experiencing their first demyelinating event found a sensitivity of only 49%, similar to that in both the Canadian[3] and French[4] pediatric cohorts.[9] The utility of the McDonald MRI criteria at the time of a first demyelinating event may be similar in pediatric and adult MS, although further studies are required to validate this.

Correlation of MRI and clinical outcome. In longitudinal studies of adult MS, T2-weighted lesion burden, the volume of T1-weighted hypointense lesions, and the extent of brain atrophy were positively correlated with variable degrees of predictive value, with physical and cognitive disability, and with likelihood of clinical disease progression.[14-18] In adult-onset MS, correlation of white matter lesion load (measured in the T2-weighted and fluid-attenuated inversion recovery [FLAIR] images) at the time of a initial demyelinating event correlates relatively poorly with physical disability.[18] This likely relates to the low pathologic specificity of T2 scans, highly sensitive to increased water content such as is seen in inflammation, edema, demyelination, remyelination, reactive gliosis, and axonal loss.[19] However, when studied longitudinally, the rate of accumulation of T2 lesions in the first 5 years of disease does show a positive correlation with subsequent physical disability (as measured by EDSS scores).[18] Although there is a paucity of such data in children, in the French pediatric demyelination cohort (discussed further below), white matter lesion number did not correlate with early development of physical disability (mean duration of clinical observation was 4.9 ± 3 years).[4]

Volumetric MRI measures of total brain volume, of major white matter tracts, and of specific brain regions demonstrate progressive loss of tissue in patients with MS, even early in the disease course.[15] Progressive global brain atrophy may better correlate with physical[16] and cognitive disability,[14] and thus may be a more sensitive measure of the irreversible destructive processes in MS that are more likely to lead to CNS dysfunction. A study of the absolute width of the third ventricle in four children with MS studied in a non-standardized fashion over 6 to 8 years demonstrated a 50% increase in diameter of the third ventricle in three children, consistent with generalized cerebral atrophy.[5] None of the children had developed significant physical disability, but detailed cognitive evaluations were not performed. Comprehensive measures of brain atrophy, or failure of expected normal pediatric brain growth, are currently underway in a prospective cohort of Canadian children experiencing an initial demyelinating event (funded by the Multiple Sclerosis Scientific Research Foundation).

The role of MRI in monophasic or transiently multiphasic acquired demyelination, and the predictive value of MRI for MS diagnosis in children. MRI is a sensitive tool to detect clinically silent white matter lesions in both children and adults with acute demyelination. In a study of 139 adults presenting with acute demyelination (58 with ON), 80% of patients meeting the MRI criteria for lesions dissemination in space and for lesion evolution in time were diagnosed with clinically definite

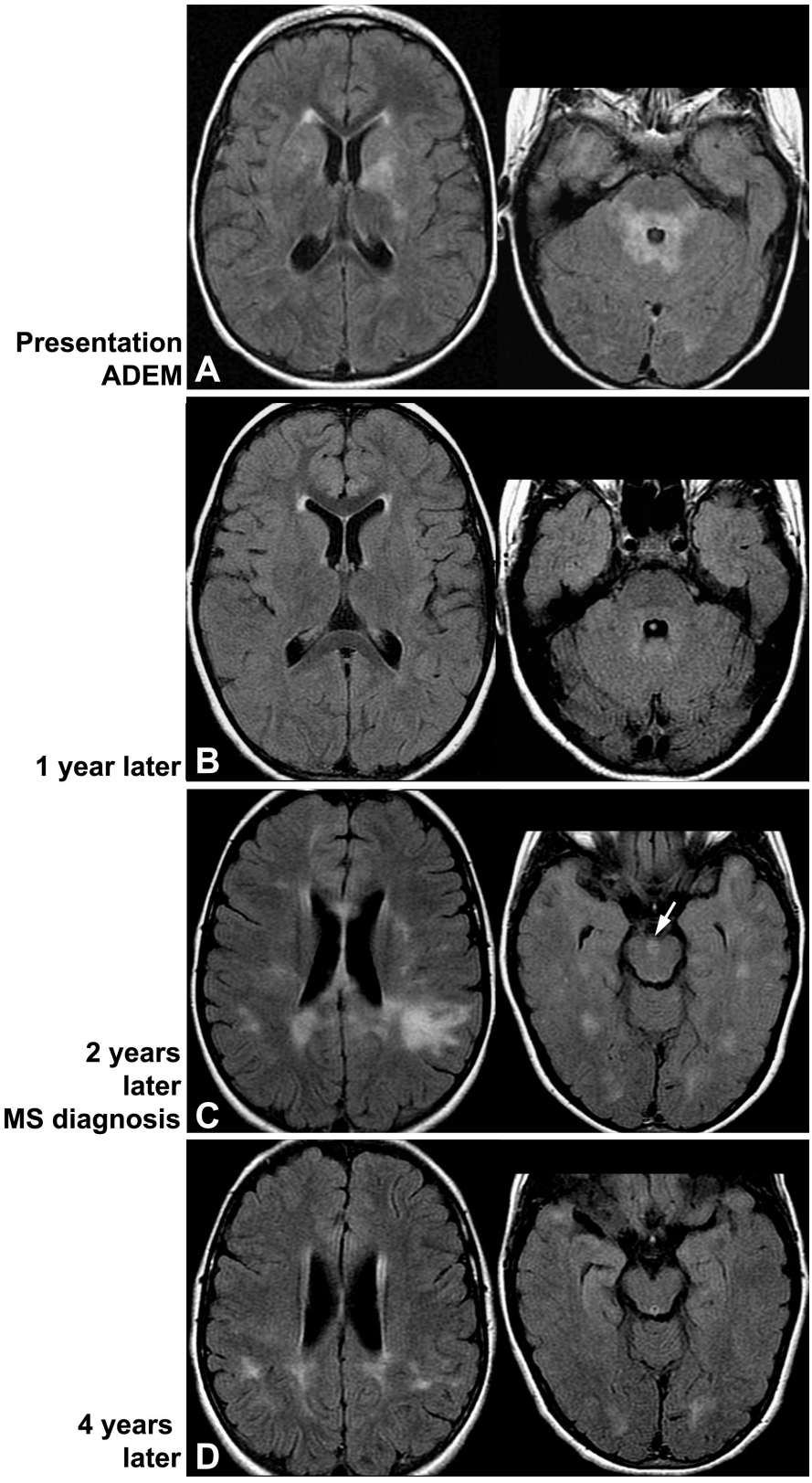

Figure 2. Capacity for dramatic MRI resolution of white matter lesions in children with multiple sclerosis (MS). (A) Axial fluid-attenuated inversion recovery (FLAIR) images of an 8-year-old girl presenting with acute encephalopathy, ataxia, and tremor, diagnosed as acute disseminated encephalomyelitis. Images show ill-defined increased signal in the white matter of the brainstem and cerebellum as well as the deep gray matter. (B) Axial FLAIR images of the same child obtained 1 year later. The patient was clinically well. Near complete resolution of the prior lesions in the brainstem, cerebellum, and deep white matter is noted. No new white matter lesions are present. (C) Axial FLAIR images 2 years after her initial presentation demonstrate new lesions in the brainstem (arrow), periventricular white matter, and splenium of the corpus callosum. The patient presented with new neurologic deficits (without encephalopathy) and was diagnosed with MS. (D) Axial FLAIR images obtained 4 years after her initial presentation (2 years after the MRI shown in C). Although there has been considerable resolution of some of the prior lesions, improvement is not as dramatic as the near-complete MRI lesion resolution noted in B, suggesting that remyelination capacity may diminish either with increasing disease duration or with increasing age. The child has experienced four MS relapses, and the MRI shown in D was obtained with the child on therapy with glatiramer acetate.

MS after a mean of 49 months follow-up.[13] In a series of 14 children with ON, 8 demonstrated white matter lesions in the brain, and 7 of these children were ultimately diagnosed with MS.[20] In a prospective cohort of 36 children with isolated ON (35 of whom had MRI studies), 19 (54%) had one or more T2 lesions on MRI of the brain or spine at presentation.[21] The MRI appearance met the McDonald criteria for lesion dissemination in space in 12 children, 10 of whom (83%) have been diagnosed with MS. Of the 16 children with normal brain MRI, 15 have shown no evidence of clinical disease, and one has been diagnosed with

neuromyelitis optica based on recurrent demyelinating episodes involving the optic nerve and spinal cord. Although the data gained from a cohort study are limited by the number of patients studied, the data suggest that the prognostic value of an abnormal MRI at the time of acute ON in children is similar to that of adults, and even that the McDonald criteria derived for adult MS may have a similar sensitivity in pediatric and adult ON. Further studies of the prognostic role of MRI in pediatric-onset ON are required to confirm the positive predictive role for MRI, and longer duration of follow-up is required to determine whether absence of lesions outside the optic nerves is truly associated with a very low MS risk.

MRI studies of the spine looking for longitudinally extensive lesions and serologic evaluation for the recently reported aquaporin-4 antibody[22] will also be important in predicting the likelihood of further episodes of demyelination of the optic nerves and spinal cord that characterize neuromyelitis optica.[23]

Analysis of the MRI features of 116 children enrolled in the French cohort of acute CNS demyelination found that a subsequent diagnosis of MS was positively correlated with nine or more lesions, with the presence of white matter lesions located perpendicular to the long axis of the corpus callosum, and with the sole presence of well-defined lesions (the latter two features deemed KIDMUS MRI criteria).[4] In contrast, a large lesion load (defined by involvement of greater than 50% of the white matter) or a single large area of demyelination were more often associated with monophasic disease. Lesions of the basal ganglia and thalami were found on the initial MRI of children with monophasic disease and children with recurrent demyelination. Although all 11 children with the two KIDMUS MRI criteria were diagnosed with MS, yielding 100% specificity, it is relevant to note that the MRI scans of the remaining 41 children diagnosed with MS in this cohort did not meet the two KIDMUS MRI criteria, yielding a sensitivity of only 21%. In addition, the authors applied the Barkhof MRI lesion dissemination in space criteria to the MRI scans from the entire cohort. Fifty-one of the 116 children met three of the four Barkhof criteria (thus would have qualified as positive for lesion dissemination in space), but only 27 of these children experienced a second demyelinating attack during the study period. Overall, the presence of three or more Barkhof criteria in this cohort was associated with a positive predictive value of MS diagnosis of 53%. When stratified by age, the positive predictive value of a Barkhof positive MRI at the time of acute demyelination in children younger than 10 years was 27%, compared to 80% in children over age 10 years. This may suggest that the MRI appearance of children under age 10 years differs from that of older children and adolescents. Further studies are required to validate this issue. There are several limitations to this study: 1) the field strength of the MRI scanners employed varied from 0.5 to 1.5 Tesla; 2) MRI protocols were not standardized; 3) gadolinium-enhanced scans were not available from all patients; 4) determination of well-defined lesions was poorly explained; and 5) serial MRI studies were not performed and thus determination of MRI appearance of new lesions over time was not reported.

The presence of hypointense lesions on T1-weighted MRI scans obtained at the time of an initial demyelinating event, so called black holes, could be considered to be indicative of remote demyelination indicative of a chronic demyelinating process. However, of the 116 children in the KIDMUS cohort, T1 hypointense lesions were detected in 72 (62%), 41 of whom had a monophasic disease course. Thus, the presence of black holes on MRI scans obtained at the time of an initial demyelinating event in children may be the reversible hyperacute black holes reported in adults,[24] rather than residual lesions from prior clinically silent demyelinating events. This would be consistent with studies of monthly MRI scans in adult patients with MS in which 66% of black holes disappeared over 6 to 8 months.[24]

Distinguishing MS from acute disseminated encephalomyelitis. Of all the acute inflammatory demyelinating phenotypes, acute disseminated encephalomyelitis (ADEM) is perhaps the most challenging. Clinical features include encephalopathy, polysymptomatic neurologic deficits, fever, and recent viral infection.[25] ADEM is typically considered a monophasic illness, although approximately 10 to 29% of children[4] and 35% of adults[26] presenting with ADEM will ultimately meet criteria for MS. Attempts to delineate MRI features have been hampered by a lack of consensus on the clinical features required for the diagnosis of ADEM, and in particular by the tendency of some clinicians and radiologists to use the term ADEM for any child with acute demyelination (irrespective of clinical phenotype) in whom multiple lesions are visible on MRI.

In general, the MRI findings in ADEM are characterized by large, multifocal, often symmetric, subcortical, white matter lesions; bilateral thalamic or basal ganglia lesions are often prominent. The MRI features are highly variable,[25] and similar features have been reported in children ultimately diagnosed with MS.[25,27] Although it has been suggested that lesions in the thalami and deep gray nuclei are a more characteristic feature of ADEM compared to MS, it is relevant to note the increasing evidence of both cortical and deep gray matter involvement in adult-onset MS.[28] Even in the pivotal article describing the MRI features strongly associated with MS in adults, Paty et al. comment specifically that the MRI features do not distinguish ADEM, and that the diagnosis of ADEM remains subject to clinical judgment.[11]

In a study of 31 children diagnosed with ADEM, 90% had lesions in the supratentorial white matter, 29% had lesions in the corpus callosum, and 61% had gray matter involvement.[25] Gadolinium was administered to 90% of the children, only 8% of whom dem-

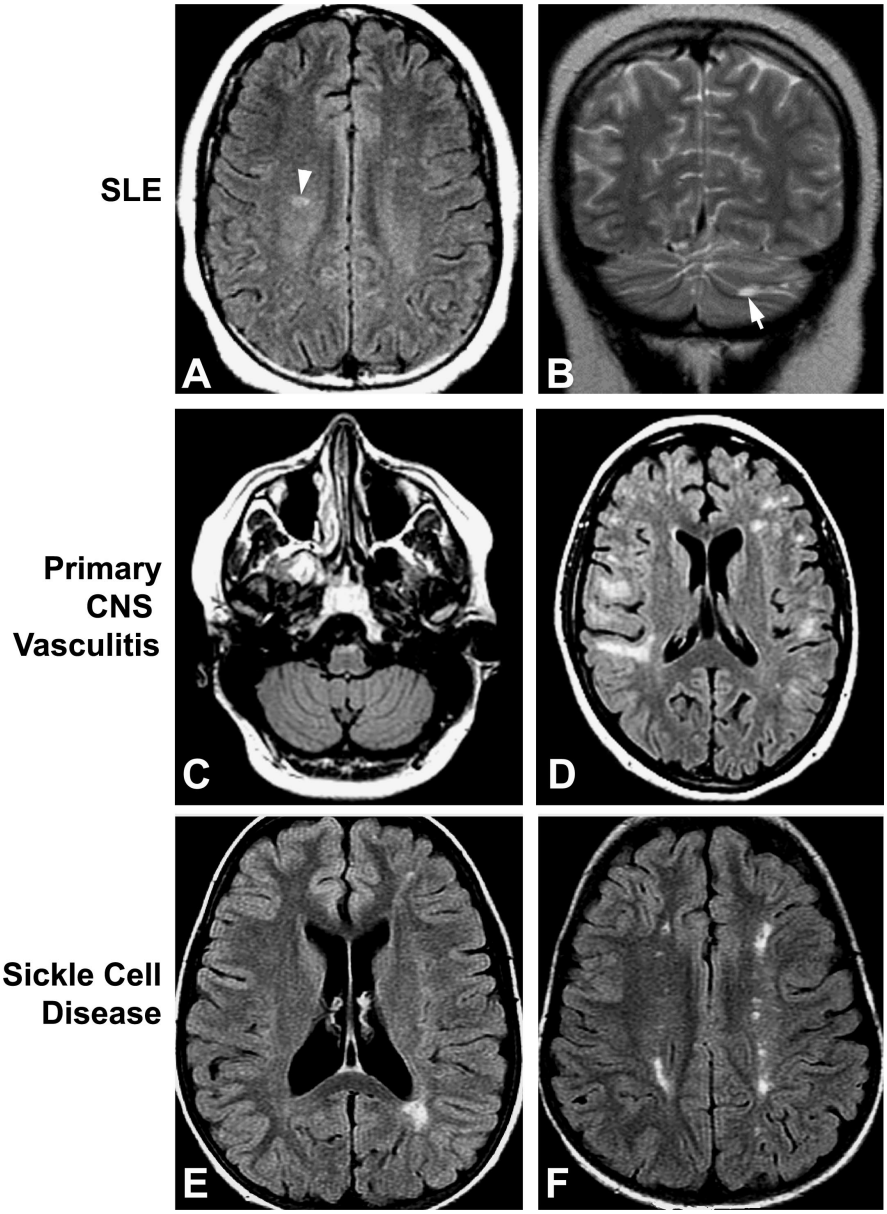

Figure 3. Differential diagnoses of white matter lesions: ischemic etiologies. (A, B) Axial fluid-attenuated inversion recovery (FLAIR) and coronal T2 images of a child with CNS vasculitis associated with systemic lupus erythematosus (SLE). Small punctate white matter lesions are noted in the right centrum semiovale (arrowhead) and in the left cerebellar hemisphere (arrow). There are no periventricular white matter lesions or involvement of the corpus callosum, as would be expected in a child with multiple sclerosis (MS). MR angiography demonstrated vascular beading and narrowing of the A1 segment of the anterior cerebral artery (not shown), findings not present in patients with MS. (C, D) Axial FLAIR images through the brainstem and the cerebral white matter show multiple foci of increased signal. The patient, a 16-year-old girl, presented with headache, optic neuritis, and fatigue. Systemic serum markers for vasculitis were negative. Brain biopsy confirmed primary CNS vasculitis. (E, F) Axial FLAIR images demonstrating periventricular and punctate deep white matter lesions in a patient with sickle cell disease. The MRI appearance is difficult to distinguish from MS, and delineation of the diagnosis requires careful clinical history of features compatible with sickle cell disease. MR angiogram in patients with sickle cell disease frequently demonstrates abnormal vasculature, which would not be present in MS.

onstrated lesion enhancement. This retrospective study did not employ a standardized definition of ADEM, did not include serial MRI studies, and clinical follow-up was not consistent.

Some children with ADEM will experience replication of their initial symptoms and re-emergence of their initial MRI lesions in the first few months following treatment (recurrent ADEM), while others will experience a clinically and radiographically distinct second ADEM episode (multiphasic ADEM).[29] However, serial MRI studies show an absence of new clinically silent lesions separate from the ADEM episodes.[29] The emergence of new, clinically silent lesions on MRI is one of the most powerful predictors of future MS diagnosis in adults who have experienced an acute demyelinating event.[30] Thus, although MRI evidence for lesion dissemination in time requires careful study before a specific time criterion can be applied to the MRI evaluation of demyelination in children, particularly children with an initial ADEM phenotype, the available literature suggests that clinically silent lesion evolution may assist in distinguishing ADEM from MS.

MRI appearances of other disorders affecting CNS white matter in children. The typical MRI appearance of inherited leukodystrophies and metabolic disorders affecting white matter in children are summarized elsewhere.[31] The clinical features of progressive neurologic decline or systemic illness rarely lead to confusion with MS.

CNS vasculopathies, particularly isolated CNS vasculitis, however, may present with acute neurologic deficits, ON, or transverse myelitis, making differentiation from MS difficult. Infectious or postinfectious vasculopathies can also lead to white matter changes, as can primary infections of the CNS such as Lyme disease, West Nile virus, and mycoplasma. Figure 3 highlights the MRI appearance of disorders affecting small vessels in the CNS.

MR angiogram or formal angiography may demonstrate vascular beading and intraluminal narrowing, or may be normal in children subsequently confirmed to have vasculitis on brain biopsy.[32-34]

Advanced MR imaging and MS pathobiology. MRI techniques such as MR spectroscopy (MRS), magnetization transfer (MT), and diffusion tensor (DT) imaging yield more tissue-specific insights into neuro-axonal and white matter integrity than conventional MRI assessment. Such studies have shown that axonal and myelin injury begins much earlier in the MS disease process than was previously believed,[35,36] and provide new tools to examine the relationships among neuro-axonal loss, myelin disruption, and immune-mediated processes.[37,38] Application of these techniques to the MRI obtained at first clinical attack in children ultimately diagnosed with MS will provide insight into whether myelin disruption occurs at this very early time point in the MS disease process. Unlike adult-onset MS, where subclinical disease activity may have been present for many years prior to the first clinical event, the very young age of some pediatric-onset patients allows for a very limited subclinical disease duration.

MR spectroscopy. Early MRS studies demonstrated that children with MS revealed decreased *N*-acetylaspartate (NAA) levels and increased choline peaks within acute MS lesions, consistent with acute neuronal dysfunction and myelin breakdown.[39] NAA was also reduced in neighboring gray matter regions. No difference in the NAA or choline peaks in normal-appearing white matter of children with MS was detected relative to the white matter characteristics of healthy controls.[39] However, the study involved only eight children with MS. Future studies of MRS in children with MS are clearly required.

MT and DTI. Only one study of MTI and DTI, in 13 children with MS and 14 age-matched controls, has been published to date.[40] Measurements taken at the level of the cervical spinal cord revealed a significantly increased mean diffusivity in normal-appearing spinal cord tissue in the MS cohort compared to controls. There was no difference in magnetization transfer ratio (MTR). The median number of cervical cord lesions was 1.6 (range 0 to 6). The authors did not report diffusivity or MTR measures in lesional tissue specifically, but did report that the total lesion load in the cervical spine did not correlate with MT metrics of normal-appearing tissue in this region. The mean diffusivity and MTR characteristics of the normal-appearing brain tissue did not differ between patients with MS and controls. The study is limited by the small sample size, but suggests that neurodegeneration in non-lesional areas may not be an early features of MS in children. Further studies are required to evaluate this important issue.

Summary. There is little doubt that MRI will play a key role in the diagnostic evaluation of MS in children. Emerging immunomodulatory therapies in MS, and increasing evidence that treatment early in the disease positively influences outcome, provide impetus to develop or modify MRI criteria that facilitate accurate and timely diagnosis of MS in children. Longitudinal MRI studies are required to evaluate the rate of lesion accrual, and the progression of brain atrophy, and to determine whether these measures correlate with physical and cognitive outcomes of MS in children. Of key importance are further studies of the role of MRI in distinguishing acute monophasic demyelination from MS. Application of more advanced MRI techniques to measure biochemical characteristics of white and gray matter, application of techniques capable of delineating white matter tract integrity, and measures of atrophy may be of greater value in identifying children with MS, may correlate with long-term outcome, and may provide invaluable insights into the earliest aspects of MS pathogenesis.

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Appendix

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