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Clinical Observations

Diffusion Tensor Imaging as a Biomarker to Differentiate Acute Disseminated Encephalomyelitis From Multiple Sclerosis at First Demyelination

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ABSTRACT

BACKGROUND: There are no clinical features or biomarkers that can reliably differentiate acute disseminated encephalomyelitis from multiple sclerosis at the first demyelination attack. Consequently, a final diagnosis is sometimes delayed by months and years of follow-up. Early treatment for multiple sclerosis is recommended to reduce long-term disability. Therefore, we intend to explore neuroimaging biomarkers that can reliably distinguish between the two diagnoses. **METHODS:** We reviewed prospectively collected clinical, standard MRI and diffusion tensor imaging data from 12 pediatric patients who presented with acute demyelination with and without encephalopathy. Patients were followed for an average of 6.5 years to determine the accuracy of final diagnosis. Final diagnosis was determined using 2013 International Pediatric MS Study Group criteria. Control subjects consisted of four age-matched healthy individuals for each patient. **RESULTS:** The study population consisted of six patients with central nervous system demyelination with encephalopathy with a presumed diagnosis of acute disseminated encephalomyelitis and six without encephalopathy with a presumed diagnosis of multiple sclerosis or clinically isolated syndrome at high risk for multiple sclerosis. During follow-up, two patients with initial diagnosis of acute disseminated encephalomyelitis were later diagnosed with multiple sclerosis. Diffusion tensor imaging region of interest analysis of baseline scans showed differences between final diagnosis of multiple sclerosis and acute disseminated encephalomyelitis patients, whereby low fractional anisotropy and high radial diffusivity occurred in multiple sclerosis patients compared with acute disseminated encephalomyelitis patients and the age-matched controls. **CONCLUSIONS:** Fractional anisotropy and radial diffusivity measures may have the potential to serve as biomarkers for distinguishing acute disseminated encephalomyelitis from multiple sclerosis at the onset.

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Statistical analysis was conducted by Amber Salter, PhD; Washington University School of Medicine, Saint Louis, MO.

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Introduction

Both acute disseminated encephalomyelitis (ADEM) and multiple sclerosis (MS) are immune-mediated disorders of the central nervous system. MS is a progressive debilitating disease, whereas ADEM is generally considered a monophasic condition where 6% to 30% may relapse.[1] At the time of initial presentation, there are no clinical features or clinical biomarkers that can reliably differentiate ADEM from MS as ADEM and MS share overlapping clinical features, laboratory findings, and magnetic resonance imaging (MRI) abnormalities.[1,2] A final diagnosis is based on the presence of clinical relapses and MRI changes, and it is often delayed by months and sometimes years of follow-up, causing anxiety and delay in appropriate treatment in some patients.[3-5] Axonal injury is present in ADEM, but the predominant pattern is perivascular demyelination, cortical microglial activation with limited axonal loss.[6] Conversely, in MS, axonal loss often occurs early in the course of disease and is most prominent within the first year of disease onset.[7] Diffusion tensor imaging (DTI) is a noninvasive, quantitative MRI technique that measures water diffusion within tissues. Normally, water diffusion within tissue becomes increasingly restricted (or anisotropic) in the brain during development as fiber bundles develop and myelinate.[8] Axial diffusivities (ADs) and radial diffusivities (RDs) derived from DTI measurements have been shown to differentially detect axon and myelin abnormalities in several mouse models relevant to MS.[9] One previous study has demonstrated lower fractional anisotropy (FA), lower AD and higher RD in children with MS compared with monophonic demyelination, including ADEM patients.[10] However, these limited studies were performed retrospectively with a short follow-up duration. Therefore, we performed a prospective study with a longer duration of clinical follow-up to explore differences in DTI measurements at onset between children with final diagnosis of ADEM and MS.

Method

Twelve children presenting with acute demyelination were prospectively enrolled. Figure 1 summarizes the study design. In addition to standard anatomic sequences, the MR protocol included a 25-direction multiple b-value DTI protocol performed at 3 Tesla. Patients included 12 with acute demyelination: six with demyelination and encephalopathy with presumed diagnosis of ADEM (multifocal presentation, brain MRI findings of diffuse, poorly demarcated, larger than 1- to 2-cm lesions involving predominantly the cerebral white matter); and six without encephalopathy with a presumed diagnosis of MS or clinically isolated syndrome with high risk for MS (optic neuritis, transverse myelitis, hemispheric or brainstem symptoms with brain MRI findings consistent with revised McDonald criteria for space) after first demyelination. Scans were obtained within six months of first demyelination attack. DTI scans were processed off-line using an in-house program to obtain directional diffusivity maps consisting of FA, RD, AD, and mean diffusivity (MD). The images were registered to age-matched atlas space. Regions of interest (ROIs) were selected by a neurologist and medical physicist team, and were drawn based on hyperintensity abnormality on T2 weighted fluid-attenuated inversion recovery (FLAIR) MRI of subject using ImageJ.[7,11] The selection criteria were as follows: the lesion must appear in at least five continuous slices and ROIs selected only once in the highest hyperintensity slice. It is known that DTI measurements are age-dependent, thus four age-matched controls were imaged for each subject, and ROIs were selected at corresponding locations based on the matched patient case (Fig 2). Mean and standard deviations (SDs) were used to summarize DTI measures (FA, RD, AD, MD) for each group. Mixed models using restricted maximum likelihood estimation were used to test for differences in DTI measures between patients with final diagnosis of ADEM, MS, and controls. Specifically, we conducted pairwise comparisons of DTI measures between ADEM and MS, ADEM and control, and MS and control. To account for multiple comparisons in the *post hoc* analysis, a Tukey-Kramer adjustment was used to calculate an adjusted *P* value.

Results

Baseline patient characteristics are summarized in Table 1. At the last follow-up (mean follow-up duration of 6.5 years) using the 2013 International Pediatric MS Study Group criteria, eight patients were determined to have a final diagnosis of MS. Two children with presumed initial diagnosis of ADEM were ultimately diagnosed with MS after having clinical relapses and new lesions fulfilling 2013 International Pediatric MS Study Group criteria for MS. These two children aged 15 and 17 at the initial onset presented with encephalopathy, large bilateral white matter lesions (in the cerebral hemispheres) and ultimately diagnosed with MS after nine and 33 months from initial presentation, respectively (Table 2).

DTI ROI analysis from baseline scans revealed differences between final diagnosis of MS and ADEM patients (Table 3). Significant differences were observed for MS versus controls for all unadjusted and adjusted FA, RD, AD, and MD maps ($P < 0.05$). Significant differences were also observed for ADEM versus MS for unadjusted FA map ($P = 0.025$) and RD map ($P = 0.049$) with lower FA and higher RD in MS patients compared with ADEM patients. However, after post

TABLE 1.
Patient Characteristics

	Final Definitive Diagnosis	
	MS (n = 8) *	ADEM (n = 4)
Age at first presentation Mean (SD)	15.6 (1.6)	9.5 (4.2)
Sex (n, %)		
Female	8 (100%)	2 (50%)
Male	0 (0%)	2 (50%)
Clinical follow-up, years Mean (SD)	5.4 (2.9)	8.3 (3.1)
Number of lesions at baseline Median [IQR]	21 [18, 62]	17 [4, 42]

Abbreviations:
ADEM = Acute disseminated encephalomyelitis
IQR = Interquartile range
MS = Multiple sclerosis
SD = Standard deviation
* Two children with presumed initial diagnosis of ADEM were ultimately diagnosed with MS after having clinical relapses and new lesions fulfilling 2013 IPMSSG criteria for MS.