

Acute Disseminated Encephalomyelitis: An MRI/MRS Longitudinal Study

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A clinical and radiologic diagnosis of acute disseminated encephalomyelitis was made in two children: a 6-month-old female who presented with focal seizures and thalamic and cerebral white matter lesions, and a 4.5-year-old male who presented with tremor and dystonia and had bilateral basal ganglia lesions, without evidence of active brain infection. Serial clinical and laboratory evaluations were supplemented by neuroimaging including routine magnetic resonance imaging and ¹H magnetic resonance spectroscopy. They were treated symptomatically, without using steroids or intravenous immunoglobulin, and both children recovered. Single voxel ¹H magnetic resonance spectroscopy data were acquired from the involved areas and from normal-appearing white matter. Abnormalities in *N*-acetyl-aspartate, choline, and lactate peaks were evident during the symptomatic phase, and persistence of low *N*-acetyl-aspartate was observed during recovery. These spectroscopic findings are consistent with neuropathologic findings of neuronal dysfunction, cellular membrane turnover, cellular infiltration, and metabolic stress in the acute phase, and with neuronal loss in the chronic phase. © 2004 by Elsevier Inc. All rights reserved.

Gabis LV, Panasci DJ, Andriola MR, Huang W. Acute disseminated encephalomyelitis: An MRI/MRS longitudinal study. *Pediatr Neurol* 2004;30:324-329.

Introduction

Acute disseminated encephalomyelitis has been characterized as a demyelinating disorder involving mainly the white matter and occurring after an infection or vaccination. It presents with focal neurologic signs and encephalopathy and is differentiated from multiple sclerosis by its

monophasic course [1]. Mortality can be as high as 10-20%, but in most, complete recovery occurs. Pathologically, there are multifocal widespread demyelinating lesions with perivascular mononuclear cell infiltration [2]. Characteristic neuroimaging findings have been reported and are one criterion for diagnosis [3]. On computed tomography the lesions are observed as areas of decreased attenuation with contrast enhancement in the subacute phase of the disease [1]. At present, magnetic resonance imaging is the modality of choice for evaluation of children suspected of having acute disseminated encephalomyelitis. Lesions are usually bilateral, asymmetric, and most commonly in the frontal and parietal lobes. Corpus callosal involvement similar to that observed in multiple sclerosis has been described. Basal ganglia and thalamic involvement is less frequent and typically symmetric [4,5]. Lesions in the acute phase of the illness typically enhance after administration of gadolinium. Most lesions will either resolve or improve over time although progression to necrosis and gliosis can occur. Interestingly, there is no clear correlation between the severity of the magnetic resonance imaging findings and the symptoms [6].

Diffusion-weighted magnetic resonance imaging is a sensitive technique for detecting cellular ischemia. There is restriction of motion of water molecules within ischemic neurons. In one case report, diffusion-weighted magnetic resonance imaging in a child with acute disseminated encephalomyelitis revealed diffusion abnormalities in lesions observed on T₂-weighted sequences with rapid normalization over time [7].

Immunomodulatory treatments, such as steroids, plasmapheresis, or intravenous immunoglobulins are reported as beneficial in multiple case reports [8-11], with concomitant partial resolution of magnetic resonance imaging–documented lesions [3]. To date, there is no controlled and blinded study to validate these data [12].

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Received August 13, 2003; accepted November 13, 2003.

^1H magnetic resonance spectroscopy has become a valuable *in vivo* technique for obtaining biochemical information in patients with neurologic disorders because of its ability to monitor noninvasively metabolic processes in the brain on a regional basis. With both long and short echo time (TE), ^1H magnetic resonance spectroscopy concurrently measures *N*-acetyl-aspartate (NAA), total creatine, choline-containing compounds, and lactate. NAA has been considered as the marker of neuronal integrity, whereas the levels of choline and lactate are indicative of cell membrane turnover and anaerobic glycolysis [13]. A recent case study of acute disseminated encephalomyelitis with ^1H magnetic resonance spectroscopy reported reduced NAA but normal levels of other metabolites in the brain lesions [14]. Magnetic resonance spectroscopy has been used for longitudinal follow-up of lesions in relapsing-remitting multiple sclerosis, as well as evaluation of normal-appearing white matter, and of treatment effects. NAA reduction in normal-appearing white matter has been found to inversely correlate with disability and biochemical abnormalities in lesions correlated with treatment response [15,16]. Because of the higher sensitivity of magnetic resonance spectroscopy changes compared with magnetic resonance imaging appearance in patients with multiple sclerosis, it has been suggested that magnetic resonance spectroscopy be used as a secondary outcome measure in treatment trials [17].

In this study, we report the clinical and imaging findings in two children with acute disseminated encephalomyelitis. Magnetic resonance imaging (including routine sequences and diffusion-weighted magnetic resonance imaging) and ^1H magnetic resonance spectroscopy both in the acute and subacute phases of the disease were employed to detect possible structural and neurochemical abnormalities. Both children recovered without immunomodulatory treatment.

Patients and Methods

Patient History

Case report 1: A 6-month-old female presented with new onset focal seizures involving the right upper extremity, irritability, and low-grade fever preceded 2 weeks earlier by otitis and rash. Electroencephalogram on admission indicated an epileptogenic focus originating from the left temporoparietal area. Seizures resolved with antiepileptic treatment, but mild hemiparesis of right upper extremity persisted. Initial laboratory tests, including cerebrospinal fluid, were normal. Subsequent cerebrospinal fluid after 4 days indicated 40 cells (100% monocytes) and protein 58 mEq/dL (normal 15-45 mEq/dL). Blood count, electrolytes, and liver enzymes were in the normal range. *Mycoplasma*, Epstein-Barr virus, antibodies to nuclear antigens, and viral titers were all negative. Cerebrospinal fluid, urine and blood bacterial cultures, and herpes polymerase chain reaction were negative as well. Evaluation for a disorder of coagulopathy (factor V Leiden, antibodies to nuclear antigens, anticardiolipin antibodies) and a metabolic disorder (ammonia, lactate, organic acids, amino acids) were negative. After the first 4 days she began to improve clinically, and she slowly began to regain use of her right upper extremity. Acyclovir was discontinued after 4 days. Immunomodulatory treatment was not administered because of a delay in herpes polymerase

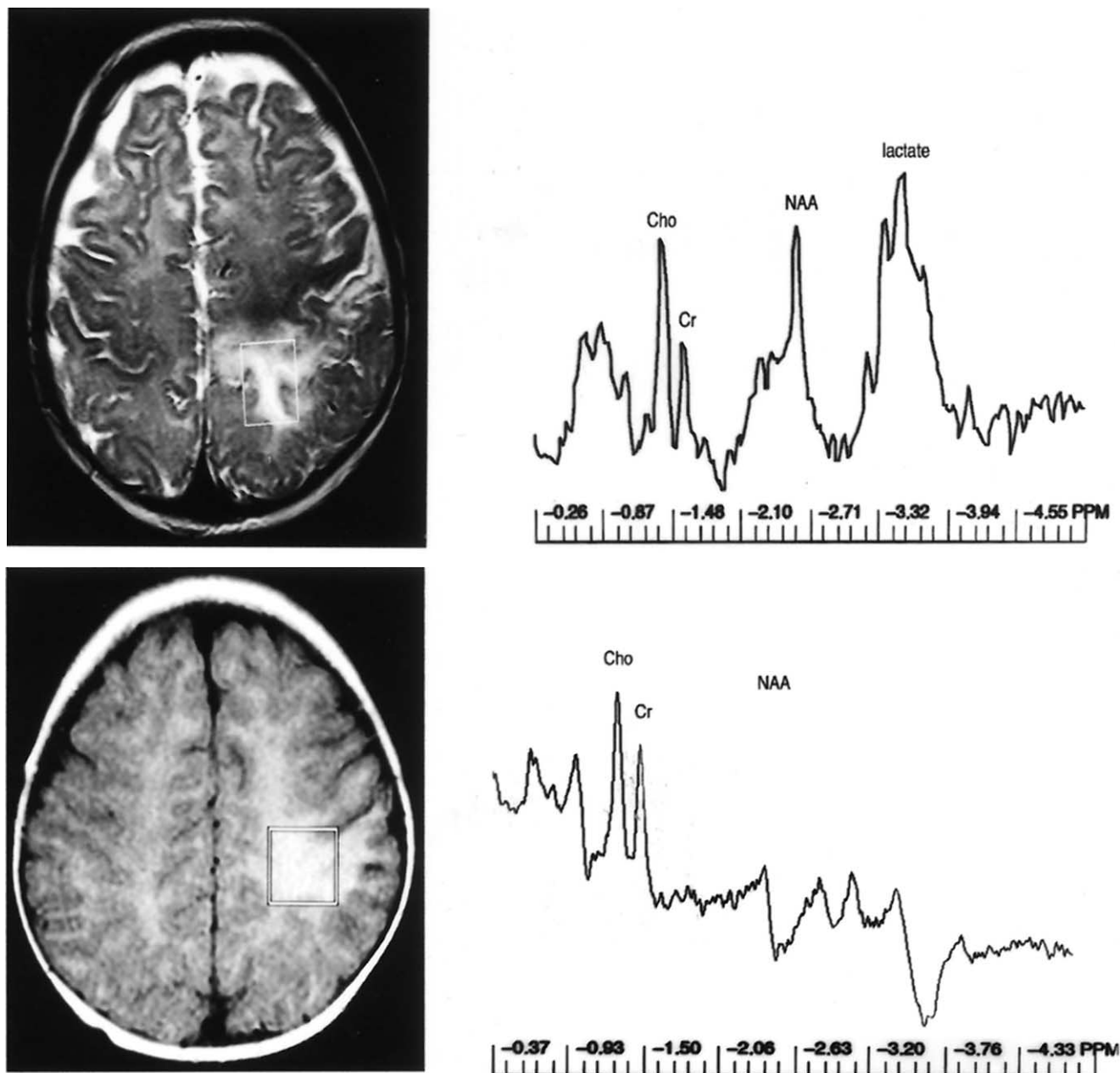
chain reaction results and subsequent recovery. After 1 month she had full passive and active motion of upper and lower extremities, but at 6 months follow-up she manifested left preference, which suggested a residual right hemiparesis. She continued to attain age-appropriate developmental milestones.

Case report 2: A clinical and radiologic diagnosis of acute disseminated encephalomyelitis was made in a 4.5-year-old child who had abrupt onset of abnormal movements, preceded by an upper respiratory infection. Head computed tomography was reported as revealing bilateral basal ganglia lesions. After 9 days he was transferred to our hospital owing to decreased activity and feeding, and frequent tremors of arms. Examination revealed dystonia, dysarthria, and choreoathetosis. Laboratory results including blood count, electrolytes, liver function tests, cerebrospinal fluid cell count and protein, lactate in blood and cerebrospinal fluid, serum amino acids, ceruloplasmin, carnitine and acyl carnitines, and urine organic acids were all within normal limits. Serologic titers for Epstein-Barr virus, *Mycoplasma*, Lyme disease, antibodies to nuclear antigens, and antistreptolysin-O test were negative. Echocardiogram performed before his transfer was normal. After his transfer, he began to improve clinically and the immunomodulatory treatment was deferred. Over the next month the patient continued to improve, with minimal residual speech and balance difficulties. He received only supportive treatment and physical therapy. At 6 months follow-up, his language and physical examination were normal for his age.

Brain Magnetic Resonance Imaging and ^1H Magnetic Resonance Spectroscopy

The two patients underwent brain magnetic resonance imaging/magnetic resonance spectroscopy scanning sessions after hospital admission and as follow-up. Magnetic resonance imaging was performed for clinical purposes, and the addition of magnetic resonance spectroscopy was approved by the State University of New York Stony Brook Institutional Review Board. Brain magnetic resonance imaging and ^1H magnetic resonance spectroscopy examinations were performed using a 1.5-T GE Signa whole-body scanner. Patients were sedated during the procedure. The routine magnetic resonance imaging protocol at our institution includes T_1 - and T_2 -weighted, as well as fluid-attenuated inversion-recovery images obtained in axial, sagittal, and coronal planes. Contrast agent was not injected. Multislice diffusion-weighted magnetic resonance imaging was obtained in Case #1 with $b = 1000 \text{ s/mm}^2$. T_2 -weighted axial images were used as scout images for single-voxel ^1H magnetic resonance spectroscopy data acquisition from regions of T_2 magnetic resonance imaging signal hyperintensity, and from regions of normal-appearing white matter. A stimulated echo acquisition mode (STEAM) sequence was employed to collect proton spectra with TE = 40 ms, mixing time (TM) = 14 ms, repetition time (TR) = 2 s, and 128 scan averages. The magnetic resonance spectroscopy voxel location, size, and acquisition parameters were kept the same for each patient during follow-up studies by using anatomic landmarks and measured size. Because of the large size of lesions in both cases, voxels positioned in the lesion areas incorporated mainly abnormal tissue.

The raw spectral data were processed using 3-Hz line broadening, Fourier transformation, and phase and baseline corrections. Resonance peaks of NAA, creatine, choline, and lactate were identified and fitted using a nonlinear-least-squares fitting procedure with a Levenberg-Marquardt algorithm. The peak area ratios of metabolites to creatine were calculated and used as measures of metabolite levels. Correction for underlying macromolecular signal was made using base corrections with polynomial functions. Peak position of lactate (1.33 ppm) and lipids (1.45 ppm) could overlap, and the existence of lactate was judged on the basis of the characteristic doublet peak.



Figures 1 (Top) and 2 (Bottom). Patient 1: Axial T_2 -weighted images (TE 40 ms) demonstrating focal region of abnormally increased signal in the parietal white matter. Voxel localization and magnetic resonance spectroscopy spectra in acute (Fig 1) and in chronic phases (Fig 2).

Results

Case 1

Initial magnetic resonance imaging obtained 2 days after the onset of symptoms demonstrated multiple bilateral hyperintense lesions in the peripheral white matter of the left frontal and parietal lobes, right frontal lobe, and the left thalamus, without appreciable mass effect (Fig 1). The lesions were characteristic in that they were discrete, nonhemorrhagic, asymmetrical, and initially correlated with clinical symptoms and signs. Diffusion-weighted

magnetic resonance imaging demonstrated restricted diffusion in the left frontal lesion only. This phenomenon was observed as increased signal on the diffusion-weighted magnetic resonance imaging trace images with corresponding decreased signal on the apparent diffusion coefficient (ADC) maps.

Magnetic resonance spectroscopy obtained at this time revealed mildly decreased NAA in the left basal ganglia and elevated choline and lactate in both the left parietal area where a lesion was visualized on magnetic resonance imaging, as well as in right normal-appearing white matter (Fig 1).

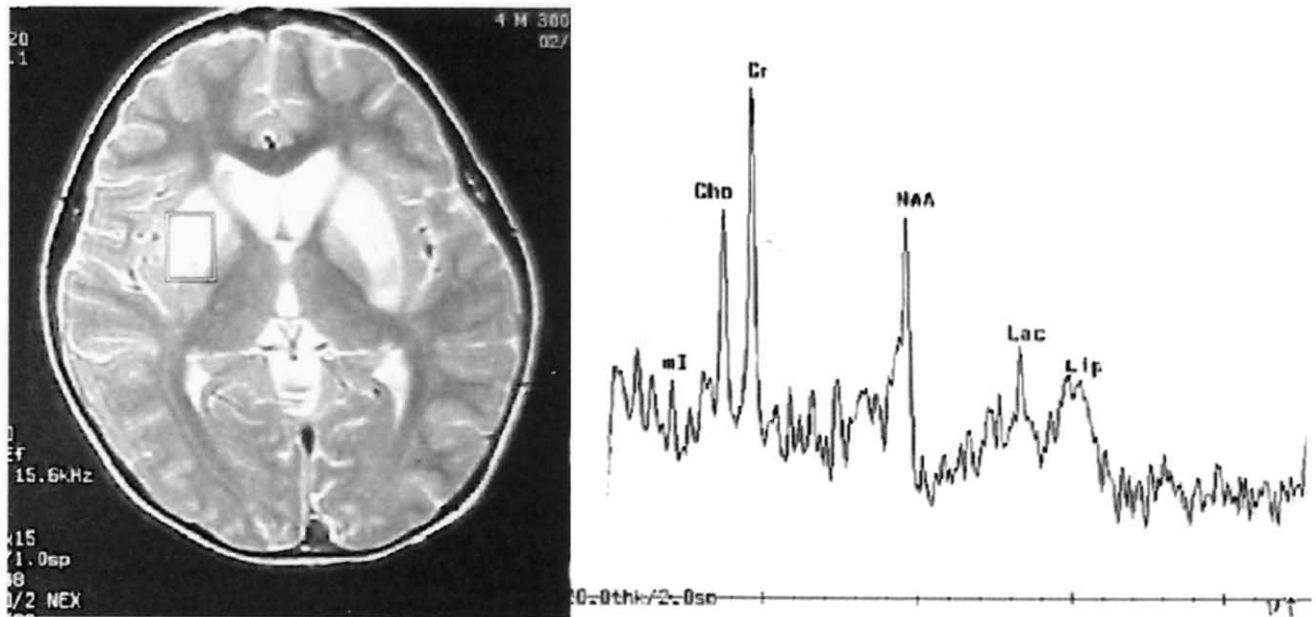


Figure 3. Patient 2: Axial T_2 -weighted image (TE 40 ms) demonstrates abnormally increased signal in the caudate and putamen with mild compression of the adjacent frontal horns of the lateral ventricles. Voxel localization and magnetic resonance spectroscopy spectra in the acute phase are illustrated.

Follow-up magnetic resonance imaging obtained 1 month later revealed interval increase in size of the left parietal lesion, which had become contiguous with the left frontal lesion. The right frontal and left thalamic lesions had decreased in size. No new lesions had developed. Diffusion-weighted magnetic resonance imaging indicated decreased signal in the left parietal area.

Magnetic resonance spectroscopy obtained at this time indicated normalization of choline and lactate. However, there was an interval decrease in NAA in the left parietal lesion, whereas NAA in the left basal ganglia remained low (Fig 2).

A final magnetic resonance imaging obtained 8 weeks after the initial study demonstrated complete resolution of the right frontal lesion. The left thalamic and parietal lesions were unchanged. The left frontal lesion evolved into an area of volume loss and cortical necrosis. No new lesion developed (Fig 3).

Magnetic resonance spectroscopy documented additional decrease in NAA in the left parietal lesion and small NAA recovery in the left basal ganglia area (Table 1).

Case 2

Initial magnetic resonance imaging obtained 9 days after the onset of symptoms demonstrated bilateral, symmetric, abnormally increased signal on fluid-attenuated inversion-recovery and T_2 -weighted images in the caudate and putamen with relative sparing of the globus pallidus. There was mass effect as evidenced by compression of the adjacent frontal horns of the lateral ventricles. The white matter and cortical gray matter of the cerebral and cerebellar hemispheres were normal (Fig 3).

Repeat magnetic resonance imaging obtained 4 weeks later revealed persistent hyperintensity in the caudate and putamen although it was less pronounced and without associated mass effect. No new lesions developed between the two studies. Clinically, the patient displayed improvement with minimal residual speech (stutter) and balance difficulties.

Figure 3 presents proton spectra acquired from the right basal ganglia region in the initial phase. Both initial and follow-up spectra indicated that when compared with spectra from the same region of age-matched healthy control subjects, NAA peak was decreased, whereas choline and lactate peaks were elevated. However, the follow-up magnetic resonance spectroscopy indicated a slight increase in NAA peak and a slight decrease in lactate peak. The choline peak remained elevated. The subcortical normal-appearing white matter spectra in both studies of this child (not shown here) revealed normal NAA peak, but elevated choline peak.

The metabolite ratios from different brain regions obtained in the magnetic resonance spectroscopy studies of both patients are listed in Table 1. Corresponding literature metabolite ratios from age-matched healthy control subjects are also listed for comparison. These values are mean values from the cited studies after correction for the differences in pulse sequence type and parameters [18,19].

Discussion

The young age, antecedent infection, monophasic course, and the multifocal neurologic and radiologic findings in these two patients are compatible with the diagno-

Table 1. Regional brain metabolite ratios in AM children with acute disseminated encephalomyelitis and age-matched healthy control subjects

MRS Voxel	Study	NAA/Cr	Cho/Cr	Lac/Cr
ADEM Case 1				
Left parietal WM (lesion)	Initial	3.20	2.50	29.4
Left BG (lesion)	Initial	1.23	0.90	0.00
Right frontal WM	Initial	2.15	1.13	13.3
Left parietal WM (lesion)	1 month	1.17	1.00	0.00
Left BG (lesion)	1 month	1.27	0.90	0.00
Right frontal WM	1 month	3.02	0.80	0.00
Left parietal WM (lesion)	2 months	0.41	1.22	0.50
Left BG (lesion)	2 months	1.44	0.90	0.00
Right frontal WM	2 months	2.10	0.80	0.00
Age-matched controls				
BG	1.80	0.82	0.00	
WM		2.14	0.90	0.00
ADEM Case 2				
BG	Initial	0.71	0.76	0.51
WM	Initial	1.62	0.91	0.00
BG	Follow-up	0.83	0.88	0.21
WM	Follow-up	1.38	1.10	0.00
Age-matched controls				
BG		2.33	0.65	0.00
WM		1.45	0.80	0.00
Abbreviations				
BG = Basal ganglia	MRS = Magnetic resonance spectroscopy			
Cr = Creatine	NAA = <i>N</i> -acetyl-aspartate			
Cho = Choline	WM = White matter			
Lac = Lactate				

sis with acute disseminated encephalomyelitis. Case 1 had typical magnetic resonance imaging findings of asymmetric cerebral white matter and deep gray (thalamic) lesions. Case 2 was unusual in that lesions were limited to the basal ganglia without cerebral white matter involvement. This uncommon distribution of acute disseminated encephalomyelitis lesions has been previously described [4,5].

Immunomodulatory treatment was deferred and both patients recovered. The sequence of the appearance of the lesions on magnetic resonance imaging pictures correlated with the clinical evolution; however, clinical recovery preceded the magnetic resonance imaging improvement. The addition of diffusion-weighted magnetic resonance imaging sequence in the first patient predicted the severity of one lesion, which evolved similar to the appearance of a stroke.

In the children described, as compared with the corresponding metabolite ratios from similar brain regions of age-matched normal healthy children reported in several prior magnetic resonance spectroscopy studies [15,16], NAA was decreased in neuroradiologically involved areas, whereas choline and lactate were elevated in areas in which lesions were visualized, as well as in normal-appearing white matter. The lactate elevation likely reflects an early inflammatory process. The reduction in NAA suggests neuronal dysfunction in the involved areas of the disease that is at least partially reversible, as indicated by increase in NAA/creatinine values during the

phase of clinical recovery. The NAA value at long-term follow-up suggests neuronal loss. The choline elevation, which is likely the result of increased membrane turnover during demyelination or macrophages infiltration, seems to be more global rather than regional specific. In Case 2, the increase of NAA and the decrease of lactate in involved areas after 1 month coincided with reduced areas of enhancing lesions documented in magnetic resonance imaging and with clinical improvement. Although NAA was still lower than normal in involved areas, there were apparently sufficient surviving neurons to support recovery of normal function. Metabolic analysis using magnetic resonance spectroscopy may provide valuable information from lesions and from normal-appearing areas in acute disseminated encephalomyelitis, aiding in diagnosis with anatomic structure from magnetic resonance imaging. Magnetic resonance spectroscopy might be useful in longitudinal neuroimaging studies for monitoring disease activity and further assessing the need for, and result of, interventions, such as immunomodulatory or neuroprotective agents.

Despite significant neurologic and radiologic abnormalities during the acute and subacute phase, those two patients with acute disseminated encephalomyelitis regained function and continue to improve. It is unknown if treatment would have hastened or optimized the outcome. This uncertainty emphasizes the need for multicenter randomized controlled trials, using magnetic resonance spectroscopy as an additional follow-up measure, and

evaluating indications for immunomodulatory treatments in acute disseminated encephalomyelitis.

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