Parainflammatory Leukoencephalomyelitis: Clinical and Magnetic Resonance Imaging Findings

Warren A. Marks, MD; John B. Bodensteiner, MD; Gary B. Bobele, MD; Mohsen Hamza, MD; Don A. Wilson, MD

Abstract _

Parainflammatory leukoencephalomyelitis is a broad term used to include the spectrum of disorders that affect the central nervous system following infection, immunization, or other noxious stimuli. There is a wide range of clinical and pathologic severity, ranging from acute cerebellar ataxia to acute hemorrhagic leukoencephalopathy. With the improved survival of these patients, magnetic resonance imaging provides a window to the pathologic process, which can aid in the long-term management of these patients. Although lesions of the brainstem and spinal cord correlate well to clinical symptoms, multiple cortical lesions may be present without specific localizing signs. The distribution of magnetic resonance lesions is different from that commonly seen in multiple sclerosis. In some cases, prolonged immunosuppression may be required to prevent recrudescence of the inflammatory response. (*J Child Neurol* 1988;3:205–213).

Encephalomyelitides following apparently mild illnesses have long been recognized, particularly in children. The degree of clinical severity varies widely, as does the spectrum of pathology underlying the clinical disease. Magnetic resonance (MR) imaging, electrophysiology, and examination of the spinal fluid all provide insights to the nature of the underlying disease process and its potential relationship to other acquired demyelinating diseases.

Methods

Twelve patients clinically diagnosed as having a postinfectious or postimmunization encephalomyelitis have been seen by the pediatric neurology service at Oklahoma Children's Memorial Hospital since 1986. All patients underwent MR imaging as part of their evaluation. The clinical course, neuroimaging, spinal fluid, and electrophysiologic data from these patients are reviewed. MR scans were performed using either a Philips or General Electric scanner operating at a field strength of 1.5 tesla. Alternatively, a mobile Philips scanner operating at 0.5 tesla was used.

Case Presentations

Case #3

Two weeks after a nonspecific upper respiratory illness, this 8-year-old white boy developed the acute onset of a severe, persistent, occipital headache associated with progressive lethargy and marked ataxia. There was mild cerebrospinal fluid (CSF) pleocytosis and increased protein concentration (Table 1). Computerized tomography (CT) suggested hypodensity of the cerebellar white matter (Figure 1A). After 48 hours of illness without apparent improvement, MR revealed prominent high-intensity signal abnormalities on T2 sequences in both cerebellar hemispheres, and mild communicating hydrocephalus (Figure 1B). His symptoms resolved completely over the next week without steroid administration. Follow-up MR on the sixth day revealed improvement of the cerebellar signal abnormalities (Figure 1C). Repeat CSF analysis confirmed improvement. He has remained well since that time. He had had varicella four years previously. Elevated titers to Epstein-Barr virus (EBV) were found.

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From the Departments of Neurology, Pediatric Neurology Division, (Drs Marks, Bodensteiner, Bobele, Hamza) and Radiology (Dr Wilson), University of Oklahoma Health Sciences Center, Oklahoma City, OK.

Address correspondence to Dr Warren A. Marks, Fort Worth Child Neurology Associates, 709 West Leuda, Fort Worth, TX 76104.

TABLE 1	
Cerebrospinal Fluid Profiles	

Pt	WBC	Protein	**Glucose	MBP	IgG Index	Synthesis Rate	OCB
1	3	11	97				_
2	256 121	147 51	56 (83) 67 (114)	 1.9	0.8	22	 ND
3	$\frac{46}{8}$	47 10	87 (130)				
4	42 4	57 26	70 (129) 52				
5	20 10 15	212 20 27	51 (72) 55 52 (108)	3.9 2.4			 ND ND
6	140 21 18 21 15 1	51 10 50 57 47 24	50 (93) 44 (85) 46 43 (80) 55 (100) 57				
7	2	20	51 (72)				
8	2 0	12 11	72 (110) 61 (107)	5.4 —	*		ND —
9	44	41	44 (91)	23.7		~	—
11	8	36	59 (93)		—	_	
12	0 4	19 19	37 52	12.5 6.8	2.6 0.3	123 2.9	ND ND

CSF was not available from patient 10. * Patient 8 had a CSF IgG < 1.5 mg/dL. ** Blood glucose in (). MBP = myelin basic protein (normal 0-8 ng/mL); OCB = oligoclonal bands; ND = none detected. Normal IgG index < 0.8; IgG synthesis rate < 3.3.

Case #8

One week after a 24-hour macular rash unassociated with fever or other systemic signs, this 6-year-old white boy developed a right-sided headache with dizziness, nausea, diplopia, and progressive gait difficulty. Examination was remarkable for the following: inability to adduct the right eye; left hemiparesis involving primarily the face and arm, with increased reflexes and an extensor plantar response on that side; dysarthria; and right-sided ataxia of the arm and leg. Hypodense areas were seen on CT in the left cerebellar hemisphere and pons. MR imaging revealed high-signal abnormalities in the left cerebellar hemisphere and right pontine area, as well as the left temporal lobe, on T2weighted images (Figure 2A). He progressed to decorticate posturing with an apneustic respiratory pattern. Treatment with dexamethasone (Decadron) followed by prolonged administration of methylprednisolone sodium succinate (Solu-Medrol) (4 mg/kg/day) resulted in rapid improvement of his respiratory status. Repeat MR imaging six weeks after presentation revealed cystic necrosis of the central pontine area, with some improvement of the cerebellar lesion and complete resolution of the temporal lobe lesion (Figure 2B). No oligoclonal bands were detected in the spinal fluid; myelin basic protein was 5.4 ng/dL (Table 1). Three months later, he remains quadriparetic, with the left side more severely affected, and has severe bulbar palsy.

Case #11

A 10-month-old, previously healthy, American Indian girl was transferred to our hospital 15 hours after the acute onset of quadriplegia. On admission, she was alert and easily consolable, with a low-grade fever. Cranial nerves were intact. There was a flaccid paralysis of the upper extremities, with increased tone of the legs. Rectal tone was decreased, and the bladder was distended, with 200 mL of urine obtained by catheterization. Appreciation of pain was diminished below T4. The cervical spine was tender to palpation. Metrizamide myelography by lumbar approach demonstrated diffuse enlargement of the cervical cord. High-intensity signal

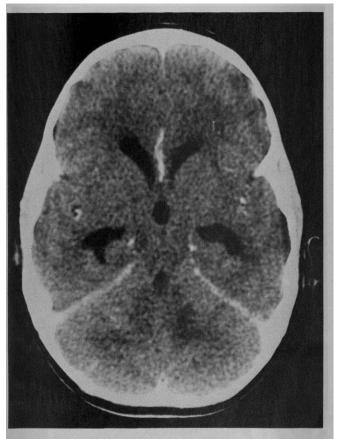


Figure 1A

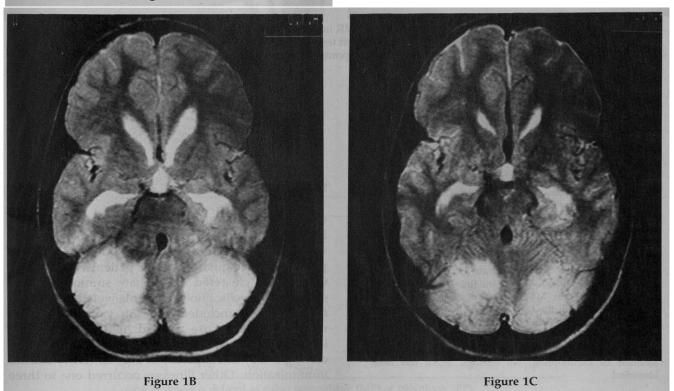
abnormalities were present on T2-weighted MR images from the cervicomedullary junction to midthoracic region (Figure 3). There was mild CSF lymphocytosis (Table 1). Treatment was initiated with dexamethasone, and changed to prednisone for a one-month tapering course. Two weeks after completion of steroids, she was able to ambulate, although moderate spasticity of the lower extremities remains. All cultures remained sterile. IgG antibody titers against EBV were 1:128 and 1:256 on admission and follow-up at four weeks. No IgM antibody was detected.

Case #12

A 4-year-old white girl presented with three days of progressive ataxia of the left side. There was no history of identifiable illness during the preceding month. Examination revealed prominent ataxia of the left side, involving the upper and lower extremity. There was weakness of the left lower extremity and both upper extremities, with hyperreflexia on the left, and bilateral Babinski signs. Sensation was intact. She was irritable, but appropriate. Sphincter tone and control were normal. Cranial CT before and following contrast administration was normal. CSF revealed only mild hypoglycorrhachia (Table 1). MR imaging demonstrated

FIGURE 1

Patient #3: Axial CT on day 1 demonstrating hypodense region in left cerebellum (A). MR imaging demonstrating the cerebellar lesion, with high intensity signal on T2-weighted sequences from day 3 (B), with improvement noted by day 8 (C).



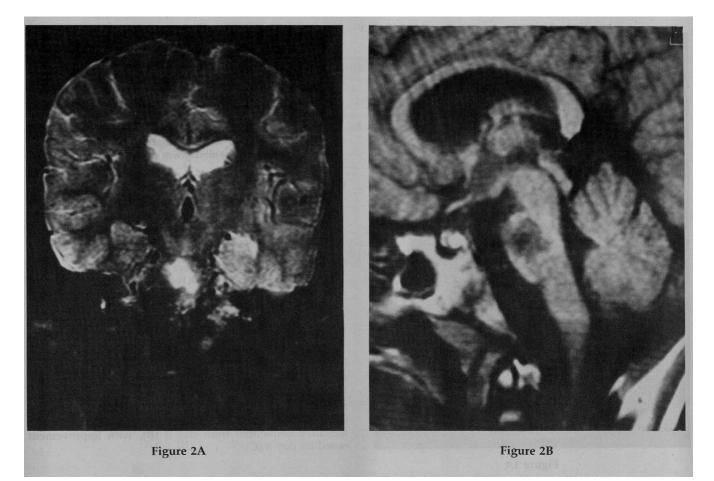


FIGURE 2

Patient #8: T2-weighted coronal plane MR image from day 3 demonstrating high signal intensity abnormalities in the pons and left temporal lobe (**A**). Sagittal T1-weighted image at six weeks showed progression of the pontine lesion to an area of low signal intensity representing cystic degeneration (**B**).

multiple high-signal areas on T2 sequences involving the cerebrum and upper cervical spinal cord; there were no detectable abnormalities of the brainstem or cerebellum (Figure 4). Distal latency and conduction velocity of the right median nerve were normal. A four-week course of prednisone resulted in improvement, with moderate spasticity and some ataxia of the left side persistent at six weeks. One month later, she developed moderate lethargy followed by worsening of the left-sided ataxia and the new onset of rightsided ataxia. Repeat MR imaging demonstrated several additional lesions in the cerebral white matter, in addition to the persistence of previously noted lesions. Repeat CSF studies are outlined in Table 1. There was clinical improvement after the reinstitution of steroids, this time with the addition of azathioprine. No etiologic agent has been identified.

Data

Clinical and Laboratory Studies

Patient demographics are shown in Table 2. There were seven boys and five girls; all but one were prepubertal. Three quarters of our patients were white. Cases were clustered during late summer (7) and spring (3). Specific etiologic agents were identified in five cases and included EBV (3), varicella (1), and mycoplasma (1). Case #7 had mild ataxia without identifiable lesions of MR imaging ten days after receiving a diphtheria-pertussis-tetanus (DPT) booster immunization. Other illnesses occurred one to three

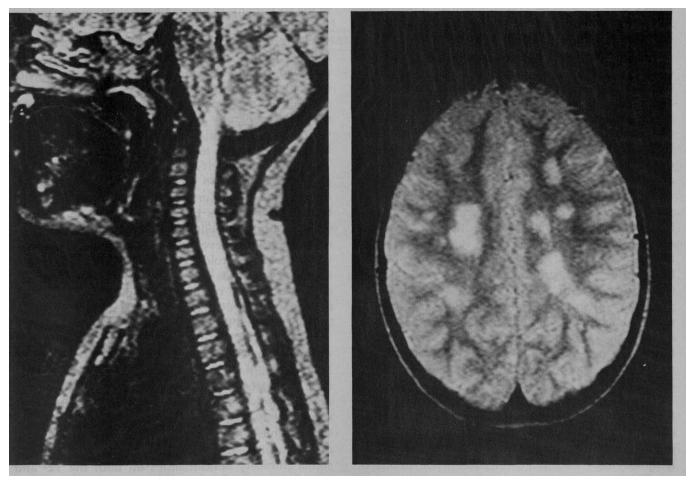


FIGURE 3

Patient #11: T2-weighted sagittal MR of the spinal cord demonstrating widening of the cervical area and high signal intensity from the cervicomedullary to high thoracic regions.

FIGURE 4

Patient #12: Axial plane T2-weighted MR showing multiple high signal areas from the cerebral white matter.

TABLE 2 Patient Demographics

Pt	Age	Race	Sex	Month	Prodrome	Course
1	3	W	F	Nov	Mycoplasma	MP
2	7	В	М	May	Varicella	MP
3	8	W	Μ	May	EBV	MP
4	8	W	Μ	Aug	Aseptic meningitis	PP
5	5	W	М	Feb	URI	PP
6	2	W	F	May	?	PP
7	2	W	F	July	DPT	MP
8	5	W	М	Aug	Gastrointestinal	MP
9	3	W	Μ	July	Upper respiratory infection	PP
10	6	В	М	Sep	EBV	MP
11	1	Ι	F	Sep	EBV	MP
12	4	W	W	Sep	?	PP

Course of illness is defined as either monophasic (MP) or polyphasic (PP).

Journal of Child Neurology / Vol. 3 / July 1988 209

weeks after nonspecific, presumably viral infections, including upper respiratory (2) or gastrointestinal (1) illness, and aseptic meningitis (1).

All patients with clinical or MR imaging lesions above the spinal cord had some degree of encephalopathy, ranging from irritability to obtundation (Table 3). Headache and altered mental status were prominent early complaints. Ataxia was present in 75% of patients, but often lagged behind the encephalopathy by several days. Seizures occurred in only two patients (#4, 6), neither of whom have required long-term anticonvulsant therapy.

Visual problems occurred in four patients. Two patients (#2, 9) developed optic neuritis with acute loss of visual acuity and papillitis. In both cases, this occurred as other symptoms had stabilized or begun to improve. Normal visual function was restored following the administration of steroids. One patient (#8) had an internuclear ophthalmoplegia. The fourth patient (#6) suffered from recurrent papilledema with visual blurring and enlarged blind spots in association with episodes of intracranial hypertension. Control of her intracranial pressure has resulted in restoration of normal visual function despite mild optic atrophy.

CSF findings varied widely (Table 1). Three patients had no detectable abnormalities on routine studies, and one other demonstrated only mild hypoglycorrhachia. More commonly, a mild to moderate lymphocytosis was noted. Significant elevations of myeline basic protein were noted in two patients (#9, 12); four other patients had detectable levels. The degree of elevation of the myelin basic protein concentration did not correlate with clinical course or outcome. Oligoclonal bands were not detected in any

TABLE 3

of the six patients in whom this evaluation was undertaken.

Three patients with mild clinical courses made full recoveries without immunosuppression. The other nine patients, including both patients with optic neuritis, received steroids. While individual regimens varied, methylprednisolone sodium succinate was generally initiated at 2 to 4 mg/kg/day, with a change to oral prednisone after one week, followed by complete tapering over four to six weeks. Three patients received more intense immunosuppression. Patient #8 received one month of daily intravenous methylprednisolone sodium succinate before tapering was begun. Two patients (#6, 12) initially improved with steroid therapy, but either relapsed (#6) or developed new symptoms (#12) on withdrawal of steroids. Both were pulsed with short courses of steroids and had azathioprine (2 mg/kg/ day) added for maintenance immunosuppressive therapy without evidence of clinical recurrence for up to eight months thus far.

Neuroimaging Studies

Eleven of 12 patients had abnormalities on MR scanning compared to 3 of 7 on CT (Table 4). The CT abnormalities were limited to low-density lesions in the cerebellar hemispheres. MR more readily demonstrated these abnormalities, and identified other, often multiple, areas of involvement (Table 5). High signal intensity abnormalities on both the T2- and spin density-weighted studies were the most prominent early changes. Lesions of the brainstem and cerebellum were most common (six each), with less frequent cortical (four) and spinal cord (three) involvement. Multiple areas of involvement were seen in

Clinical Symptoms in Patients with Parainflammatory Leukoencephalomyelitis

Pt	Encephalopathy	Paresis	Ataxia	Seizures	Headache	Ophthalmology
1	+		+		+	_
2	+		+	_	+	_
3	+		+		+	_
4	+		+	+		+
5	+	_	+		_	
6	+			+	+	+
7			+			—
8	+	_	_			+
9	_		+			+
10	—	+		—		
11	_	+				—
12	+	+	+			

The degree of encephalopathy ranged from malaise and irritability to obtundation. Ophthalmologic involvement included optic neuritis (2), papilledema (1), and ophthalmoplegia (1).

Pt	CT	MRI	BAER	SSEP	EEG
1		+		+	Diffuse slowing
2	+	+	NP	NP	L temp slowing
3	-	+	_	+	NP
4	-	+	NP	NP	Occipital slowing
5		+	+	NP	Posterior slowing
6	_	+	+	_	Normal
7	NP	_	NP	NP	NP
8	+	+	-	NP	Posterior slowing
9	NP	+	NP	NP	NP
10*	NP	+	NP	NP	NP
11	**	+	NP	+	NP
12*	NP	+	NP	NP	NP

TABLE 4 Electrophysiologic and Imaging Studies

Key: NP = not performed; + indicates the presence or – absence of abnormality. * Patients had NCV +/- EMG studies. ** Patient 11 had myelography with CT.

seven patients. Infratentorial and spinal cord lesions correlated well with clinical symptoms. Cortical lesions typically were not associated with specific localizing signs, even when multiple lesions were present. Neither the presence nor extent of the cortical lesions correlated with the degree of encephalopathy or the occurrence of seizures. Eight patients were evaluated with serial MR imaging. Improvement in MR abnormalities did correlate with clinical improvement; however, high signal intensity abnormalities on T2-weighted images generally persisted despite resolution of neurologic deficits. In case #8 the high-intensity signal abnormalities in the pons progressed to an area of low signal intensity on T1weighted images consistent with cystic necrosis. This coincided with the clinical picture of spastic quadriplegia. Even small lesions around the fourth ventricle resulted in mild distortion of the ventricle, but did not produce obstructive hydrocephalus. Transient

TABLE 5 Location of MRI Lesions

	Location of Lesions						
Pt	Cortex	Cerebellum	Brainstem	Spinal Cord			
1			+				
2	+	+					
3		+					
4		+	+				
5	+	+	+				
6	+		+				
7							
8		+	+				
9		+	+				
10		<u> </u>	_	+			
11		_		+			
12	+						

communicating hydrocephalus was noted in two patients.

Electrophysiologic Studies

Electroencephalography was performed on six patients. One patient had diffuse slowing; five had occipital slowing, associated with abnormalities of the brainstem and cerebellum on MR imaging.

Brainstem auditory evoked potentials were abnormal in two of five patients (#5, 6), both with brainstem signs. In patient #5, a deterioration of the wave forms correlated with a clinical recurrence three months after the initial neurologic symptoms had begun to resolve.

Four patients were evaluated with somatosensory evoked potentials; abnormalities were present in three (#1, 3, 11), all with brainstem or cervical spinal cord lesions. Although auditory brainstem and somatosensory-evoked potential abnormalities corresponded to clinical and MR lesions of the brainstem, they were not predictive of long-term outcome.

Two patients (#10, 12) had normal conduction studies; one (#10) also had electromyographic evidence of denervation in the fifth and sixth cervical roots consistent with his clinical myelitis.

Discussion

Inflammation of the nervous system following acute illness, immunization, or other noxious stimuli has long been recognized.¹ Either the peripheral or central nervous system may be involved; more rarely, simultaneous involvement of both may occur.^{2,3}

There is a wide spectrum of the severity of central nervous system (CNS) disease, which includes acute cerebellar ataxia, acute disseminated encephalomyelitis, and acute hemorrhagic leukoencephalopathy. Cerebellar ataxia is generally benign, self limited, and most commonly associated with varicella.

There is also considerable variability in the severity of pathologic features of parainflammatory leukoencephalomyelitis. Perivascular demyelination with axonal sparing is seen with acute demyelinating encephalomyelitis. Neuronal necrosis with a polymorphonuclear cellular infiltrate and vasculitis with vessel wall necrosis and fibrin exudates are more typical of acute hemorrhagic leukoencephalopathy.⁴ Clinically, our patients ranged from mild ataxia with spontaneous recovery and no detectable lesion on MR imaging (#7), to involvement of multiple sites in the CNS with a chronic encephalopathy and vasculitis requiring long-term immunosuppressive therapy (#6). Evidence of neuronal necrosis, presumably secondary to vascular inflammation, was also evident in patient #8, in which the early demyelinating changes progressed to cystic degeneration despite aggressive corticosteroid therapy. The variability of the site and extent of lesions on neuroimaging studies correlate with the known pathologic variability of this disease.

CT of postinfectious demyelinating processes, first described by Reich,⁵ has generally revealed areas of decreased density in the white matter that is consistent with the pathologic findings,^{6,7} although clinical correlation is less reliable.⁸ Often the findings are subtle or misleading, which may delay appropriate diagnosis.⁹ Acutely, there may be edema that may mimic a brainstem tumor.¹⁰ Improvement of the CT abnormalities may coincide with clinical improvement.^{11,12}

MR imaging is a powerful tool for the evaluation of white matter diseases in adults and children. It is more sensitive than evoked potential studies in patients with suspected multiple sclerosis, exclusive of lesions involving the spinal cord or optic nerves.¹³ The MR imaging findings in two children with disseminated encephalomyelitis have been described.¹⁴ Our experience highlights the increased sensitivity of MR imaging over CT in these parainflammatory disorders. The finding of increased signal intensity on T2-weighted images is felt to be representative of increased water content associated with demyelination or edema. Serial MR evaluation in several cases has proved a useful adjunct to the clinical examination in documenting the course of the illness. While some studies have highlighted the reversibility of radiologic abnormalities suggesting edema, our experience suggests that many of the acute changes persist, a finding more supportive of demyelination with subsequent gliosis. Less commonly (case #8), there may be progression to tissue necrosis with cystic changes characteristic of acute hemorrhagic leukoencephalopathy. Earlier reports have stressed the good correlation between clinical symptoms and the location of MR lesions. In our experience, however, supratentorial lesions often did not produce specific localizing symptoms.^{15,16} This is more consistent with the experience in multiple sclerosis, where clinically silent lesions are often noted on neuroimaging studies and at autopsy. Lesions of the cerebellum are more common and also more likely to be symptomatic. The classic periventricular lesions seen with multiple sclerosis appear to be uncommon in parainflammatory leukoencephalomyelitis.¹⁷

Although no controlled trials regarding steroids or other immunosuppressive agents have been published, there are abundant anecdotal reports of clinical improvement with steroid administration. In Ziegler's report,¹⁸ two patients transiently worsened on withdrawal of steroids, an experience that has been noted by ourselves and others. Two of our patients (#6, 12) have had recurrent disease; however, the proximity of the two attacks suggests that they may represent only a single, albeit prolonged, reaction to the initial infection. Immunosuppressive therapy may blunt this response, which may be reactivated on withdrawal of this medication, resulting in dependence on immunosuppressive therapy. These two patients remain on azathioprine with no evidence of continuing or recurrent problems thus far.

Summary

Many terms have been used to classify the encephalitides that follow acute illness, including acute disseminated encephalomyelitis, acute hemorrhagic leukoencephalopathy, postinfectious cerebellarataxia, and steroid responsive or parainfectious encephalitis. We have adopted the term parainflammatory leukoencephalomyelitis to encompass the spectrum of clinical entities induced by a wide variety of events and resulting in what is apparently a single pathologic process.

Increased availability of MR imaging should improve the certainty with which this diagnosis is made. Long-term, longitudinal studies should further help the relationship between the parainflammatory demyelinating syndromes.

The role of immunosuppressive therapy remains unclear; however, once initiated, some patients may require sustained therapy to prevent reactivation of the inflammatory response.

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