Clinical, Neurodiagnostic, and MR Findings in Children with Spinal and Brain Stem Multiple Sclerosis

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PURPOSE: To describe the clinical, neurodiagnostic, and MR findings in seven children with brain stem and spinal multiple sclerosis. **METHODS:** Spinal or brain stem multiple sclerosis was diagnosed in seven children between 1986 and 1992. All patients had neurologic and MR examinations as well as neurodiagnostic testing, including spinal fluid analysis and brain stem and auditory evoked potentials. **RESULTS:** Three children had clinical findings and masslike lesions in the brain stem (two) or spinal cord (one) suggestive of neoplasm, which prompted biopsy (two) or radiation therapy (one). Five of six patients with spinal involvement had cord swelling with increased signal on T2-weighted images over at least three cord segments, and two children had essentially holocord involvement. Three children had normal cranial MR at presentation. **CONCLUSIONS:** Multiple sclerosis involvement of the brain stem and spinal cord may be associated with extensive swelling and MR signal changes suggestive of neoplasm without typical cerebral white matter abnormalities. Serial clinical and neuroimaging examinations may be necessary to make a definitive diagnosis of multiple sclerosis in children.

Index terms: Sclerosis, multiple; Magnetic resonance, in infants and children

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Multiple sclerosis (MS), the most common demyelinating disease in adults, is rare in children, accounting for fewer than 3% of all cases (1). "Typical" MS patients present with recurrent neurologic signs and symptoms, especially optic neuritis. Cranial magnetic resonance (MR) is confirmatory and shows high-signal lesions on T2-weighted images in the corpus callosum and periventricular white matter. Because MS is much less common in children than in adults, the diagnosis may not be entertained in children who present with the acute onset of neurologic signs and symptoms, particularly in the absence of cerebral white matter lesions on cranial MR. As in adults, MS in children may present with masslike lesions on MR that suggest neoplasia, sometimes leading to invasive diagnostic tests. Imaging diagnosis of MS is difficult when MR findings are limited to the brain stem and spinal cord. We present clinical and MR findings in seven children with brain stem and/or spinal MS at presentation, three of whom underwent surgical biopsy or radiation therapy before final diagnosis of MS.

Patients and Methods

Seven children, five girls and two boys, from 2 to 18 years of age (mean age, 9 years), had the final diagnosis of spinal or brain stem MS made by experienced pediatric neurologists based on a combination of MR, clinical, and laboratory criteria between 1986 and 1992 (Table). Six of seven patients had remitting and relapsing symptoms and clinical evidence of two separate central nervous system lesions. According to Poser's criteria (2), these patients would be considered "definite" MS, although Poser's criteria apply to patients between the ages of 10 and 59, which excludes four of these six patients. Patient 7 has had only one clinical attack and one anatomic central nervous system lesion, but is considered to have "probable" MS based

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Clinical and MR findings in pediatric MS

Patient	Age, y/ sex	Clinical Presentation	Laboratory Data Summary				MR Findings	Biopsy/Radiation	Outcome
			OB	Cells/ Protein	VEP	BAEP			
1	2/F	Ptosis, nystagmus, ataxia, cranial nerve 7 palsy	−	+/+	+	+	Head MR—hyperintense lesions (T2-weighted images) involving pons, midbrain, and thalami	No. 1 stereotactic—normal tissue biopsy	Six-year follow-up—unable to walk, multiple cranial nerve deficits, nasogastric feedings
							Head MR (11 months later)—progressive hyperintense lesions (T2-weighted image) in brain stem and centrum semiovale	No. 2 stereotactic—inflammation biopsy	
							Head MR (6 years later)—multiple stable hyperintense lesions (T2-weighted image) in centrum semiovale		
							Brain stem atrophy		
2	4/M	Upper and lower extremity weakness	NA	NA	NA	−	No initial head MR. Spine MR—swollen cervical cord (C-2 to C-5); diffuse increased signal T2-weighted images	Open cord/biopsy—gliosis vs low-grade astrocytoma	Six-year follow-up—mild visual impairment, right upper extremity spasticity
							Head MR (5 years later)—typical hyperintense white matter lesions of MS on T2-weighted images		
3	8/F	Optic neuritis, subsequent cranial nerve deficits, and upper extremity weakness	−	−/−	−	+	Initial head MR—Nl Spine MR (3 years later)—swollen cervical cord (C-2 to C-7), increased signal T2-weighted image, diffuse Gd^+ enhancement		Organic brain syndrome, intermittent quadriparesis, multiple cranial nerve deficits
							Head MR (3 years later)—high signal lesions (T2-weighted image) pons, cerebellum, corpus callosum, periventricular white matter with Gd^+ enhancement, diffuse atrophy		
							Head MR (5 years later) stable		

(*Table continues*)

Table continued

Patient	Age, y/ sex	Clinical Presentation	Laboratory Data Summary				MR Findings	Biopsy/Radiation	Outcome
			OB	Cells/ Protein	VEP	BAEP			
4	6/F	Left side weakness, dysphagia, subsequent optic neuritis, incontinence, clonus	−	−/−	+	+	Initial head MR—left temporal edema, probable infarct	. . .	Seven-year follow-up—left hemiparesis, bilateral paraesthesias, incontinence, blindness, nystagmus
							Spine MR (4 years after presentation)—swollen cervical cord (C-4 to C-6), diffuse increased signal T2-weighted image; diffuse nodular enhancement		
							Head MR (7 years after presentation)—left temporal and pons encephalomalacia; no supratentorial white matter lesions		
5	12/F	Intractable vomiting followed by nystagmus, ataxia, cranial nerve 6 palsy. Six months later, optic neuritis	−	*/+	−	−	Head MR—hyperintense T2-weighted image, round lesion in dorsal medulla; no enhancement Spine MR—normal	Radiation therapy	Two-year follow-up—quadriparesis, incontinence, multiple cranial nerve deficits
							Head MR (18 months after presentation)—enhancement of optic chiasm and nerves without swelling		
							Spine MR (20 months after presentation)—diffuse swelling, increased signal T2-weighted image, and diffuse Gd^{+} enhancement C-1 to T-7 Head MR—new periventricular white matter lesions compatible with MS		
							Spine MR (26 months after presentation)—diffuse myelomalacia and central syrinx without enhancement C-1 to L-1 Head MR—atrophy, multiple periventricular and corpus callosum plaques		

(*Table continues*)

Note.—OB indicates oligoclonal banding; VEP, visual evoked potential; BAEP, brain stem auditory evoked potentials; NA, not obtained; +, positive test; −, negative test; and *, malignant neuroectodermal cells seen.

Table continued

Patient	Age, y/ sex	Clinical Presentation	Laboratory Data Summary				MR Findings	Biopsy/Radiation	Outcome
			OB	Cells/ Protein	VEP	BAEP			
6	14 /F	Cardiomyopathy—subsequent transverse myelitis and optic neuritis Recurrent left-side weakness	−	−/+	+	NA	Head MR—Nl × 3 (2-year period). Spine MR—Cord swelling, increased signal T2-weighted image C-6 to T-11; patchy enhancement T-4 to T-10 Spine MR (3 months later)—cord swelling, increased signal T2-weighted image and Gd^+ enhancement C-3 to T-5 with cystic change Spine MR (11 months later)—swelling, increased signal T2-weighted image T-1 to T-6 with Gd^+ enhancement, cystic change at T-3	. . .	Two-year follow-up—optic atrophy, wheelchair bound, urinary retention
7	18 /M	Weakness, decreased sensation in lower extremities	NA	+/+	−	NA	Head MR—no evidence of MS Spine MR—no swelling, increased T-2 signal at T-6 (focal), no Gd^+ enhancement	. . .	Complete recovery

Note.—OB indicates oligoclonal banding; VEP, visual evoked potential; BAEP, brain stem auditory evoked potentials; NA, not obtained; +, positive test; −, negative test; and *, malignant neuroectodermal cells seen.

on his age, presentation with transverse myelitis, and absence of other causes to explain his neurologic presentation. Children with "typical" cerebral white matter lesions of MS and without spinal or brain stem involvement on cranial MR at the time of initial clinical presentation were not included in this study. Clinical evaluation included serial neurologic examination as well as spinal fluid analysis. Visual and brain stem auditory evoked potentials were also obtained. MR of the head and spine was performed in six children and MR of the head and brain stem only in one. T1-weighted (600/20/1 [repetition time/echo time/excitations]) and T2-weighted (2400/20–90/1) images of the head were obtained in all patients. T1- and either T2- or T2*-weighted (600/15, 20° flip angle) images of the spine were obtained in six children. Examinations were performed on either a 0.5-T (one patient) or 1.5-T (six patients) system. Two patients did not initially receive intravenous contrast because it was not available. The other five patients all received intravenous contrast (gadopentatate dimeglumine or gadodiamide, 0.1 mmol/kg). Clinical follow-up time ranged from 18 months to 6 years. Thirty-five cranial MR scans were performed (mean, 5; range, 1 to 11) in the seven patients. The two patients (patient 2 and 7) with the most benign clinical outcomes each had only 1 cranial MR. The other five patients, all of whom are severely neurologically impaired, had a total of 33 cranial MR scans, averaging 7 each. The six patients who had spine MR had a total of 11 scans. Patients 5 and 6 had 3 and 4 spine MR examinations, respectively.

Results

A summary of the clinical, laboratory, and MR imaging data is found in the Table. Six patients had spinal MS, four had brain stem involvement, and three had both spinal and brain stem lesions. Two patients had a history of viral prodrome before development of MS. Patient 4 had an apparent viral pharyngitis, and patient 6 had a lengthy hospitalization for viral myocarditis. Patient 1 presented with brain stem involvement within 48 hours of a wasp sting, implicating a possible allergic mechanism. Two patients with isolated brain stem and thalamic MS showed diffuse brain stem, pontine, and thalamic involvement (patient 1) and a focal, 1-cm medullary mass (patient 5). Brain stem lesions were isointense to brain on T1-weighted images and hyperintense to brain on proton density- and T2-weighted images, without cystic change. The focal medullary mass lesion (Fig 1) did not enhance with intravenous contrast, and there was minimal mass effect. Neoplasm was suspected because of the rounded appearance of the mass, the lack of other cerebral parenchymal lesions, and apparently malignant cells in the cerebrospinal fluid (CSF). (Clinical and MR-positive spinal MS subsequently developed in this child.) In patient 1, diffuse brain stem swelling, apparent mass effect, and multiple cranial nerve deficits led to the diagnosis of brain stem glioma, and computed tomography–guided biopsies were performed.

Spinal MR was focally abnormal, with increased signal on the T2-weighted image without cord swelling or enhancement, in only one patient with spinal MS. This patient (patient 7) presented with acute transverse myelitis and a midthoracic sensory level. The other five patients with spinal involvement all had cord swelling on T1- and T2-weighted images and diffusely increased T2 signal over at least three spinal segments at the time of initial spine MR. Four of these five patients had diffuse, heterogeneous cord enhancement in the areas of T2 signal abnormality (patient 2 had spine MR before the availability of intravenous MR contrast). Two patients had almost holocord involvement (patients 5 and 6). No cystic changes were seen initially in any of the cord lesions, although the two patients with near holocord involvement subsequently developed diffuse myelomalacia/syrinx (patient 5) and cystic change (patient 6). Paramagnetic contrast administration did not define additional brain stem or spinal cord lesions not detected on proton density– or T2-weighted images. Neither was it helpful in directing biopsy, because both patients 1 and 2 were studied before its availability.

Three patients had normal cranial MR findings at the time of presentation. In one of these children (patient 8) cerebral white matter and brain stem lesions typical of MS subsequently developed. Three children were never shown to have supratentorial white matter lesions suggestive of MS on cranial MR, despite serial examinations in two of them. Four of seven patients were eventually found to have multiple white matter lesions suggestive of MS on cranial MR. Cerebral atrophy developed in two of these four patients. Cranial MR in these four patients became positive from 5 months (patient 1) to 5 years (patient 2) after initial clinical presentation. Two patients underwent three biopsy procedures of the brain stem (stereotactic) or spinal cord (open) because of suspected neoplasia. Patient 1 had two biop-

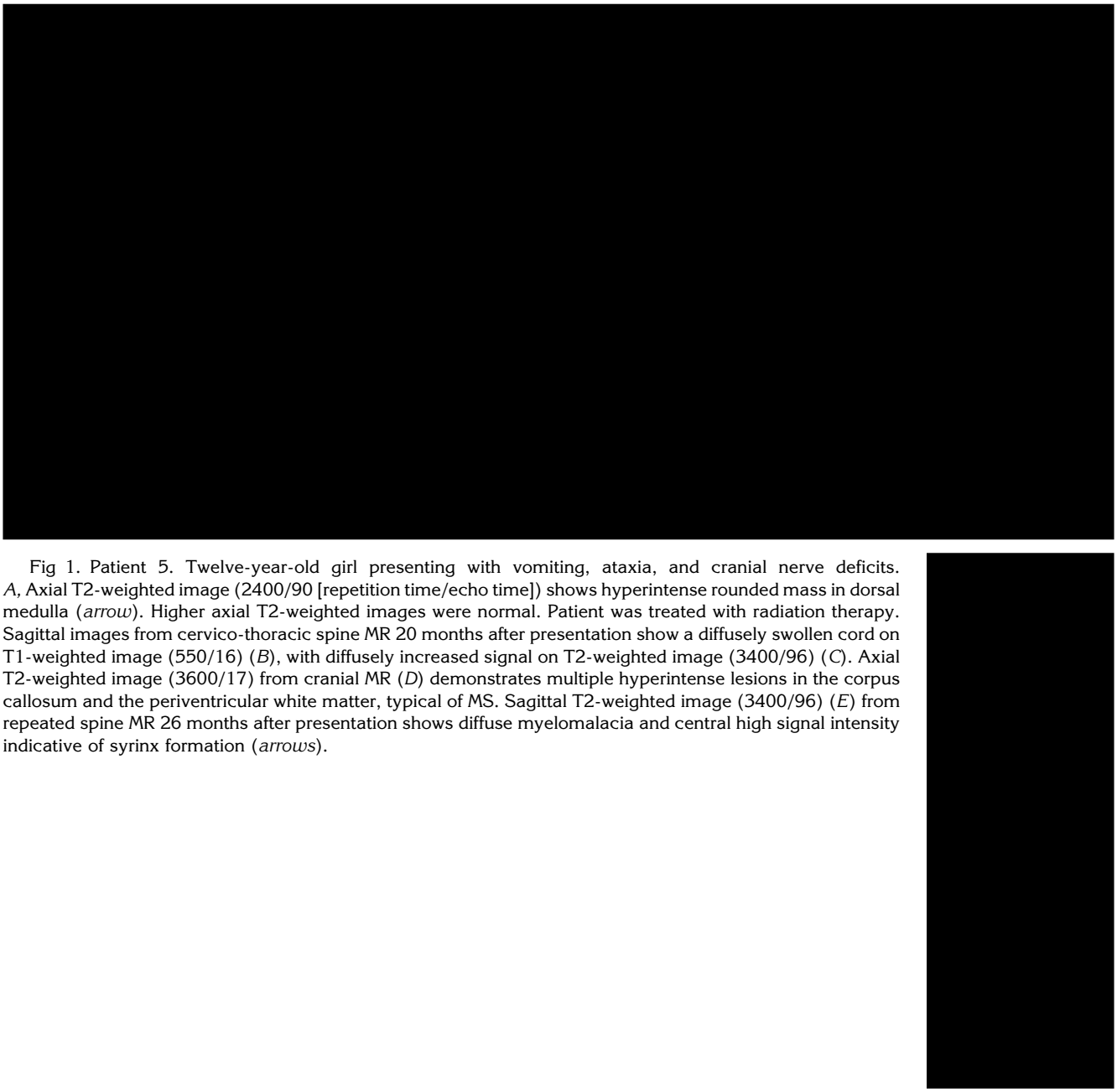

Fig 1. Patient 5. Twelve-year-old girl presenting with vomiting, ataxia, and cranial nerve deficits. *A,* Axial T2-weighted image (2400/90 [repetition time/echo time]) shows hyperintense rounded mass in dorsal medulla (*arrow*). Higher axial T2-weighted images were normal. Patient was treated with radiation therapy. Sagittal images from cervico-thoracic spine MR 20 months after presentation show a diffusely swollen cord on T1-weighted image (550/16) (*B*), with diffusely increased signal on T2-weighted image (3400/96) (*C*). Axial T2-weighted image (3600/17) from cranial MR (*D*) demonstrates multiple hyperintense lesions in the corpus callosum and the periventricular white matter, typical of MS. Sagittal T2-weighted image (3400/96) (*E*) from repeated spine MR 26 months after presentation shows diffuse myelomalacia and central high signal intensity indicative of syrinx formation (*arrows*).

sies because of progressive neurologic symptoms, with normal results from the first biopsy. Patient 5 received radiation therapy without biopsy after cerebrospinal fluid cytology showed apparently malignant cells.

Discussion

Pediatric MS accounts for 0.4% to 3% of reported cases (1, 3). Whereas the median age of presentation in adults is 30 years, the average age in children is 13 years. There are several reports of MS in young children, with the youngest reported patient (MS diagnosed at autopsy) presenting at the age of 10 months (4). Maeda et al described an infant who presented clinically at age 13 months with right hemiparesis and extensive white matter changes on computed tomography and MR findings suggestive of a leukodystrophy (5).

Our youngest patient was 2 years old at initial presentation. Unlike MS in adults, in which only a small female preponderance exists, childhood MS presents at least twice as often in girls as in boys (1, 3).

MS in characterized by exacerbations and remissions of neurologic dysfunction. Causative factors include infection, trauma, pregnancy, emotional stress, and allergic reactions. Although no definite etiologic or pathophysiologic differences are found in children compared with adults, precipitating infections may be seen more commonly in children than in adults (6), as noted in two of our cases.

The diagnosis of MS in children is difficult unless the child presents initially with optic neuritis. Only one child in our series presented with optic neuritis. There is no single definitive diagnostic test. Supportive laboratory data include the presence of increased cerebrospinal fluid protein, white blood cells, and especially oligoclonal bands indicating increased immunoglobulin production in the cerebrospinal fluid. Cerebrospinal fluid is said to be positive for the presence of oligoclonal bands in 90% of adults with definite clinical MS (7, 8). Cerebrospinal fluid in children with MS is less frequently positive for oligoclonal bands, which were found in only one of our patients despite serial testing (9, 10). Evoked-potential testing is sensitive to conduction abnormalities in the auditory and visual systems, but the tests are not specific for MS. Abnormal visual evoked potentials are seen in 75% of patients with definite clinical MS; abnormal brain stem auditory evoked potentials are seen in 67% (7). Five of seven children tested in our series had positive auditory or visual evoked potentials (Table).

The long-term prognosis in children with MS is uncertain (1, 3). In this small series, the presence of brain stem and extensive (greater than three segments) spinal cord involvement appeared to indicate a poor prognosis. All five of our patients with either brain stem or extensive spinal cord involvement are significantly disabled. Previous large clinical studies of children with MS (1, 2), however, have not shown a worse prognosis in children than in adults, but both of these series were published before the widespread availability of MR imaging. It will require the multicenter study of a much larger group of children with MS to determine whether brain stem and spinal cord involvement are more common in children than in adults, and whether such involvement indeed indicates a poor prognosis.

Abnormal findings on MR are seen in 70% to 95% of patients with definite clinical MS, and MR has become an important diagnostic tool in confirming the clinical diagnosis (7). All seven of our patients had abnormal MR at the time of clinical presentation, although none had cerebral white matter abnormalities typical of MS at the time of initial clinical presentation. Osborne et al noted frequent involvement of the brain stem and spinal cord in adolescents with MS; three of their patients with spinal involvement had no evidence of cerebral involvement on cranial MR (11). At autopsy, MS lesions are typically found scattered through the cerebrum, brain stem, and spinal cord and involve both gray and white matter. MS plaques, however, may be present in the spinal cord with little or no cranial involvement. As in our patients, when the cord is involved, cervical disease is seen most commonly (12).

The combination of clinical and MR findings was suggestive of neoplasm at the time of initial presentation in three of the seven children in this series. Large MS plaques simulating tumor are known to occur, and may be more common in children than in adults (13). Confounding this issue is the fact that tumors and MS may coexist in the same patient (10, 11). In addition, several authors have reported cases with the initial clinical diagnosis of MS that subsequently proved to have tumor or chronic encephalitis (10). Acute MS plaques are characterized by cellular infiltration. Astrocytosis may be seen in the adjacent or remote white matter (12). The biopsy specimens in our patients were not thought characteristic of demyelination, and even with retrospective review an experienced neuropathologist was unable to differentiate gliosis from tumor on the tissue obtained from open cervical cord biopsy (patient 2) (Fig 2).

Previous authors have suggested that spinal MS lesions tend to be focal, hyperintense on T2-weighted images, and usually without marked cord swelling (11, 14). However, five of six patients in our series with spinal MS had three or more spinal segments involved with diffusely increased signal on T2-weighted images and concomitant cord swelling. Two patients had virtual holocord involvement. In four of five patients who were given contrast,

Fig 2. Patient 2. Four-year-old boy with progressive upper- and lower-extremity weakness. Sagittal cervical spine MR shows swelling of the cervical cord on T1-weighted image (500/20) (*A*), with increased signal within the cord on T2-weighted image (*arrows*) (*B*). Cord biopsy revealed gliosis versus low-grade astrocytoma. Repeated spine MR 5 years after presentation shows return of cord signal and size to normal on T1-weighted image (400/12) (*C*). Cranial MR at this time demonstrates multiple hyperintense lesions in the periventricular white matter and corpus callosum on an axial T2-weighted image (2500/90) compatible with MS (*D*).

diffuse heterogeneous cord enhancement was seen. Only one patient (patient 6) had cystic changes within the involved cord, although in patient 5 diffuse myelomalacia and cen tral syrinx developed 26 months after initial presentation.

The differential diagnosis of the MR abnormalities seen in spinal MS includes transverse myelitis, acute disseminated encephalomyelitis, cord infarction, acquired immunodeficiency syndrome–related myelopathy, and neoplasm. Differential diagnosis of isolated brain stem MS with multiple cranial neuropathy primarily includes brain stem glioma or encephalitis as in both of our patients with brain stem MS. Helpful diagnostic findings on MR in patients with acute spinal or brain stem MS are the paucity of cystic changes and lack of an exophytic mass, which are symptoms frequently seen in pilocystic astrocytomas of childhood. Chronic MS, however, produces encephalomalacia and myelomalacia, which could simulate cystic change in a tumor.

MS should be considered in the differential diagnosis in children with the acute onset of neurologic symptoms and MR findings compatible with acute demyelination or tumor. Clinical evaluation in these patients should include careful examination for optic neuritis, determination of brain stem auditory and visual evoked potentials, and examination of the cerebrospinal fluid for the presence of oligoclonal bands. Cranial MR should be performed in all of these children to search for the abnormal white matter signal changes characteristic of MS. Despite a high degree of clinical suspicion and ancillary diagnostic tests, biopsy may be necessary to distinguish demyelination from tumor. Stereotactic or even open biopsy, as in two of our patients, may not be sufficient to differentiate demyelination from low-grade tumor, and follow-up clinical and neuroimaging examinations may be necessary to make a definite diagnosis of MS in children.

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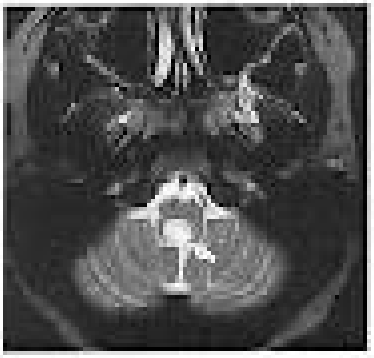

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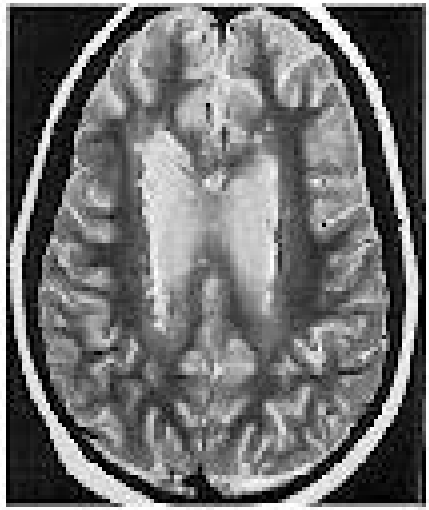

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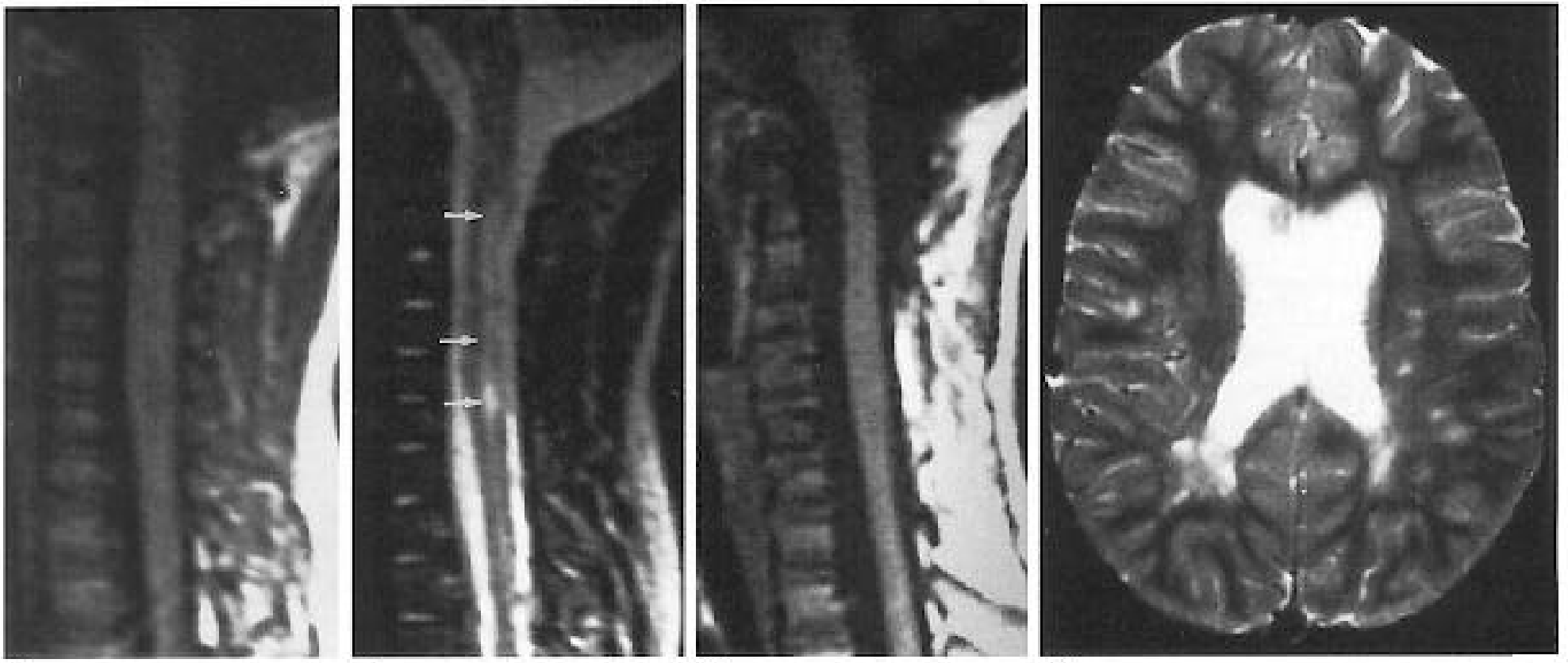
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