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Fulminant Multiple Sclerosis

Gwendolyn Niebler,[1,4] Todd Harris,[3] Tom Davis,[2] and Karen Roos[1]

Summary: The authors describe the MR imaging characteristics and clinical course of a 22-year-old man with acute disseminated demyelinating disease, either Marburg multiple sclerosis or recurrent (relapsing) acute disseminated perivenous encephalomyelitis.

Index terms: Sclerosis, multiple; Demyelinating disease

Multiple sclerosis (MS) is an autoimmune demyelinating disease that typically has a relapsing-remitting course. A rare fulminant form of MS (acute fulminant MS of the Marburg type) is associated with high morbidity and mortality. We present radiographic and pathologic findings of a case of fulminant MS that resolved with aggressive immunosuppressive therapy.

Case Report

A 22-year-old man developed a flu-like illness with severe headache, low-grade fever, vomiting, and diarrhea. Five days into the illness, he became increasingly lethargic and was admitted to the hospital. Computed tomography (CT) and magnetic resonance (MR) imaging studies were obtained (Figs. 1A–1D).

The patient was treated for 10 days with intravenous acyclovir for presumed herpes encephalitis. He became increasingly obtunded and was transferred to University Hospital 1 month after the onset of symptoms.

Epidemiologic history was unrevealing. The patient was a printer who worked at the same plant for 3 years. He lived in a trailer park across from a landfill. There was no history of recent spider, tick, or mosquito bites, travel outside of Indiana, blood transfusions, intravenous drug use, or time spent in wooded areas. The patient has a single sibling, a brother, who suffered from a recurrent illness characterized by fever to 102°F (38.9°C), night sweats, and lethargy. The etiology of the patient's brother's illness is unknown. The patient's past medical history was unremarkable except for varicella (chickenpox) 3 years prior to the onset of this illness.

On admission, the patient was afebrile, stuporous, and disoriented. There was evidence of a right relative afferent pupillary defect, bilateral papilledema, and nuchal rigidity. He had a right hemiparesis with bilateral Babinski signs.

MR images obtained at the time of admission to University Hospital showed white matter lesions in the frontal and temporal lobes, the left parietal lobe, and the genu of the corpus callosum (Figs. 2A–2E). Additional lesions were present in the left internal capsule, left thalamus, left pons, and right medulla (Figs. 2F and 2G). In the right parietal lobe, there were small lesions that involved the subcortical white matter, with possible gray matter involvement. All lesions were of high signal intensity on T2-weighted images (T2WI). The large lesions were visible on T1-weighted images (T1WI) as low-signal foci with very low-signal centers. Virtually all lesions showed central enhancement with Gd-DPTA. Compared to the imaging studies done at the onset of the patient's illness, all the lesions had increased in size and degree of enhancement, but the pattern and number of lesions were unchanged.

A brain biopsy was obtained through a right frontal burr hole. Histologic sections stained with hematoxylineosin showed large plaques representing demyelination. These were diffuse and not perivenous in nature. Special stains for acid-fast bacteria and fungi were negative. Immunohistochemical stains for cytomegalovirus, herpes simplex virus, papovavirus, and *Toxoplasma* were negative. DNA probes for herpes simplex virus, cytomegalovirus, and JC virus were negative. Multiple sections of brain tissue were examined by electron microscopy, but no viral inclusions were identified.

Cerebrospinal fluid (CSF) obtained at the time of brain biopsy revealed a protein level of 186 mg/dL, four white blood cells per cubic millimeter and 2045 red blood cells per cubic millimeter. CSF T cells were normal except for a mild decrease in T suppressor cells. There were no oligoclonal bands. CSF IgG was 8.69 mg% (normal = <7 mg%). Serum electrophoresis was normal except for a borderline increase in IgM = 304 mg% (normal < 194 ± 82 mg%). Serum toxoplasmosis titer was 1:512. A test for antibodies to human immunodeficiency virus was negative. The antinuclear antibody test was negative and the Westergren sedimentation rate was 11. Serum Epstein-Barr virus titer was 1:40. There was no increase in serum acute and convalescent titers to respiratory syncytial virus, influenza A and B, adenovirus, echovirus, Coxsackie B, *Chlamydia*

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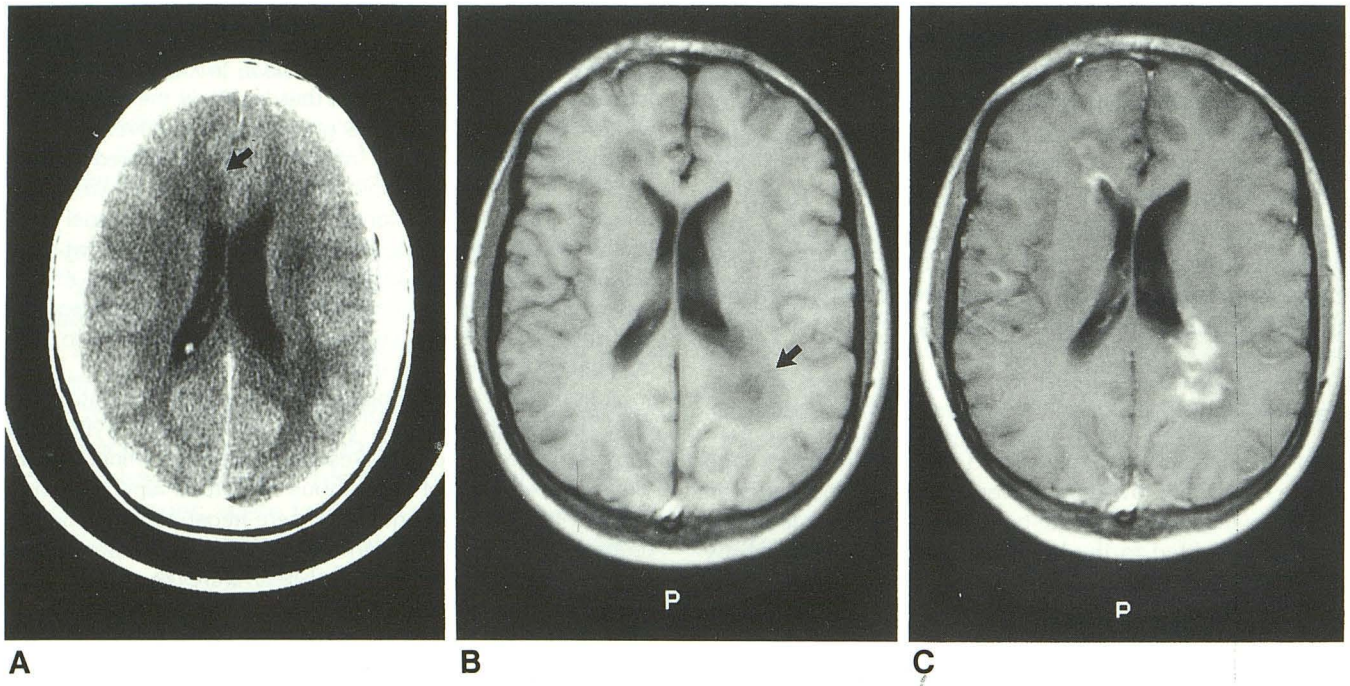
trachomatis, Epstein Barr virus, parainfluenza virus, and *Toxoplasma gondii*. Cold agglutinins for *Mycoplasma pneumoniae* were negative. Viral culture of the CSF for herpes simplex virus was negative. A Lyme disease titer was not obtained.

The patient was treated with intravenous methylprednisolone 1000 mg/day for 5 days followed by oral prednisone 80 mg/day. Seven days after the initiation of treatment, he was alert and following commands. He was able to ambulate with assistance 1 week later. A repeat postcontrast MR scan obtained 1½ weeks after initiation of treatment revealed a decrease in the size of most of the lesions with a markedly reduced degree of enhancement (Figs. 3A and 3B).

The patient was discharged on 80 mg of prednisone per day to a rehabilitation facility 3 weeks after admission. This daily dose was tapered by 10 mg per week. The patient developed optic neuritis in the left eye while on 50 mg of prednisone per day. The dose of prednisone was then increased to 100 mg per day and the daily dosage was tapered again at a rate of 10 mg every 14 days. The patient's visual acuity and pupillary examination returned



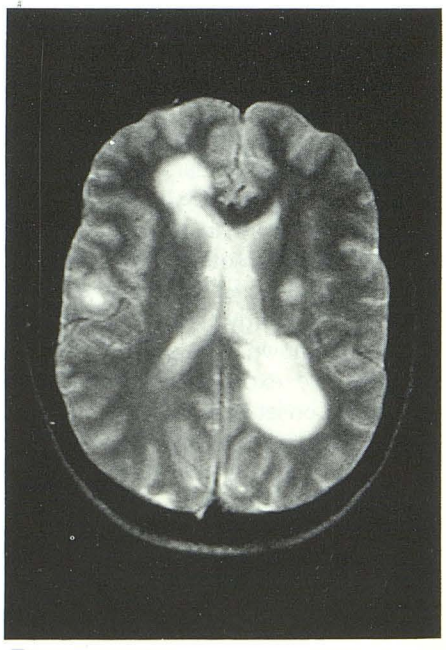


Fig. 1. *A*, A noncontrasted CT obtained at the onset of the patient's illness (at outside hospital) demonstrates periventricular white matter (PVWM) low-density lesions, especially in the right frontal region (*arrow*).

B, Axial 500/13/2(TR/TE/excitations). Unenhanced T1WI image obtained at the same stage in the patient's illness as the CT in *A*. In addition to the right frontal lesion, the left parieto-occipital PVWM lesion is more noticeable (*arrow*).

C, Axial 500/13. Gd-DTPA-enhanced T1WI image obtained at the same time as *A* and *B* shows the enhancement of both the right frontal and left parieto-occipital lesions.

D, Axial 2000/100. T2WI image obtained at the same time as *A–C* shows extensive abnormal increased signal in the periventricular and deep white matter.

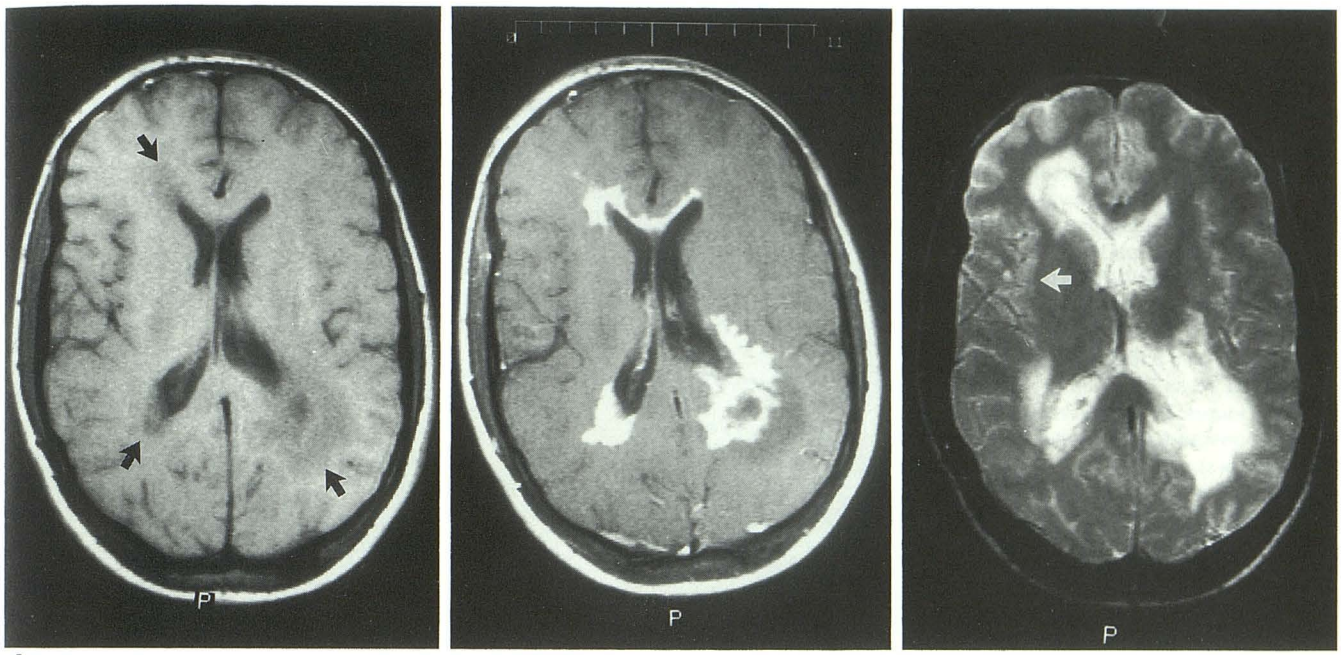


Fig. 2. *A*, Axial 800/20/1. Unenhanced T1WI image obtained at University Hospital 1 month after onset of symptoms shows an increase in low-signal abnormalities in frontal and parieto-occipital periventricular white matter (PVWM) (*arrows*) compared to Figure 1B.

B, Axial 800/20. Gd-DTPA-enhanced T1WI image obtained at the same time as *A* shows marked PVWM enhancement with prominent callosal involvement. Note the increase in degree of enhancement and size of the lesions compared to Figure 1C.

C, Axial 2500/80. T2WI image obtained at the same time as *A* and *B* reveals an increase in the abnormal signal in the PVWM, the genu of the corpus callosum, and left internal capsule compared to Figure 1D. The *arrow* indicates lack of insular involvement.

to normal. There was mild pallor of the right optic disc, but the left eye was normal. Nine months after discharge, the patient developed an acute bout of optic neuritis in the right eye and was again treated with pulse methylprednisolone therapy. He is presently maintained on 15 mg of prednisone per day.

Discussion

The MR scan demonstrated a disease process almost exclusively confined to white matter with both supra- and infratentorial involvement. There was marked breakdown of the blood-brain barrier as evidenced by intense contrast enhancement. Herpes simplex type I typically involves the temporal lobes, causing both gray and white matter disease, and has a predilection for insular cortex (1). In this case, the majority of the disease was located outside of the insula. Lyme disease, a spirochetal infection that may involve the central nervous system (CNS), might have imaging findings similar to our case. MR of CNS Lyme disease has revealed multifocal white matter disease involving the cerebrum and brain stem (2). Multiple ring-enhancing lesions have been described in a patient with Lyme disease. However, our patient's history, physical examination, and disease progression were not consistent with this diagnosis. Neoplastic considerations for the radiographic disease pattern included lymphoma. Primary intracranial lymphoma often presents as hyperdense or isodense lesion on noncontrasted CT. Enhanced CT or MR shows homogeneous, or less commonly, ring-enhancing lesions (3). The brain biopsy ruled out this diagnosis.

The clinical course, radiographic findings, and microscopic examination of brain tissue were suggestive of a fulminant demyelinating process. Adrenoleukodystrophy, which causes widespread demyelination, was considered and excluded based on the patient's age, history (acute onset and intact adrenals), and MR. Progressive multifocal leukoencephalopathy, a viral demyelinating disease associated with immunosuppression, was also considered. However, our patient had no clinical or laboratory evidence of immunosuppression and the electron microscopic examination of the brain biopsy excluded this diagnosis.

The differential diagnosis was narrowed to acute disseminated encephalomyelitis (ADEM)

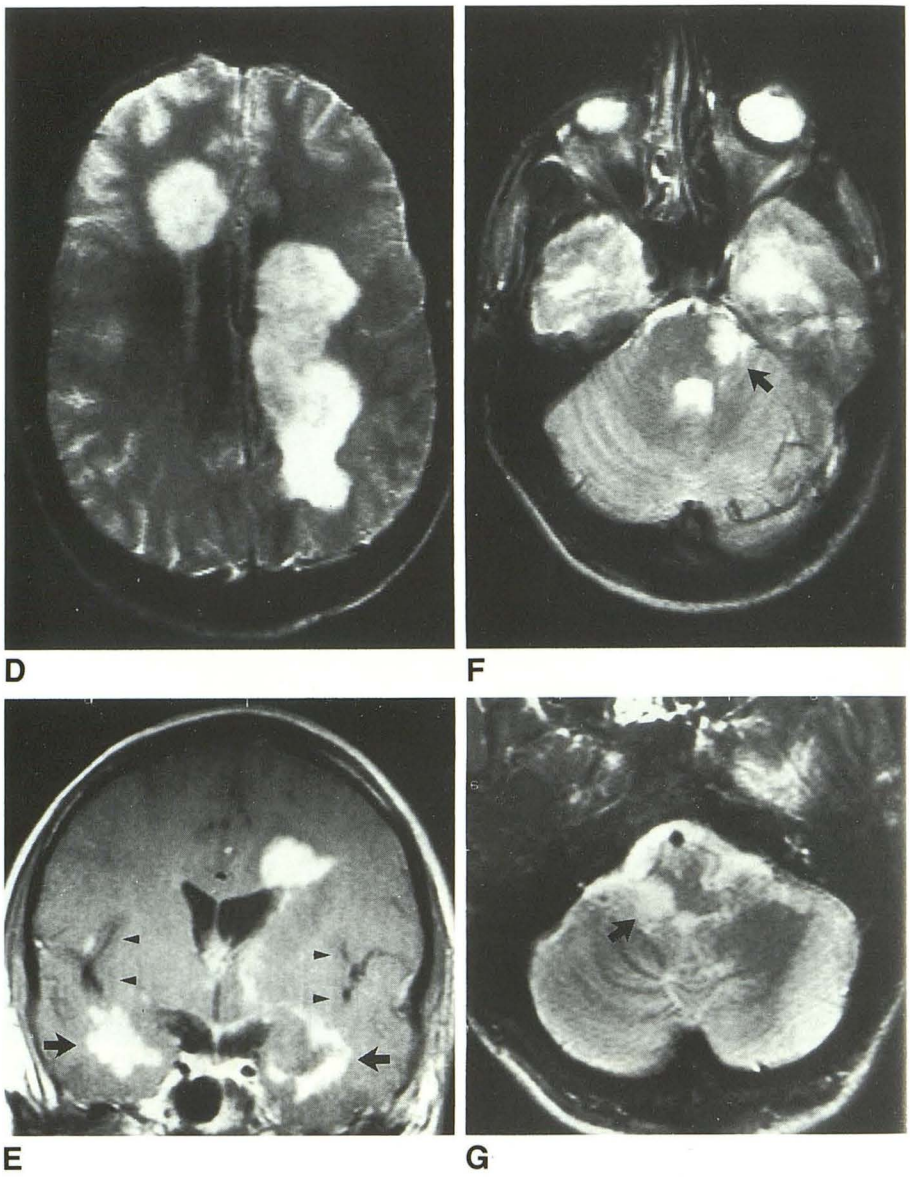


Fig. 2. —*Continued. D*, Axial 2500/80. T2WI image above the lateral ventricles obtained at the same time as Figures 2*A*–2*C* indicates large confluent left parietal and right frontal plaques.

E, Coronal 800/20. Gd-DTPA-enhanced T1WI image obtained at the same time as Figures 2*A*–2*D* shows white matter disease of the temporal lobes (*large arrows*) and right parietal operculum. There is also a left PVWM lesion. *Arrowheads* indicate minimal insular involvement.

F and *G*, Axial 2500/80. T2WI images of posterior fossa obtained at the same time as Figures 2*A*–2*E* reveal lesions in the left pons and right medulla respectively (*arrows*).

and fulminant MS based on clinical, neuroimaging and pathologic findings. ADEM is a demyelinating disease that develops subsequent to a viral infection or following vaccination against viral diseases and may represent CNS damage caused either by direct infection by the virus, damage by a viral toxin or, most likely, an autoimmune reaction. MS is an acquired inflammatory demyelination of the CNS. ADEM and MS may represent different manifestations of the same pathologic process. ADEM is usually a monophasic acute disease, whereas MS is usually a polyphasic chronic disease. It is unusual for MS to present in a highly malignant form; however, when it does, diffuse CNS symptoms can evolve over a few weeks. Coma and death generally occur in a few weeks to months, often without a period of remission (4–7).

Unfortunately, a single MR examination usually does not allow one to distinguish between MS and ADEM and follow-up studies are required (8–9). ADEM and MS may have multifocal white matter lesions represented by areas of increased signal on T2WI images. The lesions of both diseases may enhance with gadolinium and this has been correlated with clinical disease activity in MS.

The diagnosis of acute MS in this patient is suggested by the MR evidence of multiple irregularly enhancing lesions in the periventricular and subcortical white matter areas, the clinical course including two subsequent episodes of optic neu-

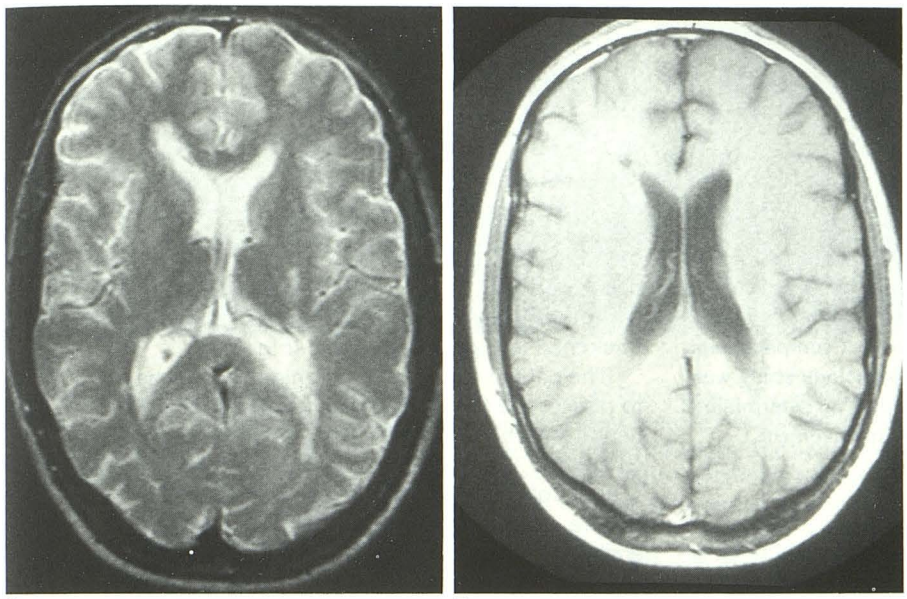


Fig. 3. *A*, Axial 2500/80. T2WI image obtained 1½ weeks after initiation of treatment with high-dose methylprednisolone reveals decreased size of periventricular lesions.

B, Axial 800/20. Gd-DTPA-enhanced T1WI image obtained at the same time as *A* shows marked decrease in enhancement of periventricular lesions.

ritis and the pattern of diffuse, not perivenous, demyelination on microscopic examination of the brain biopsy. In ADEM, the areas of demyelination are predominantly perivenous in distribution. The microscopic differences between the fulminant and the typical form of MS are that in the fulminant form of MS, the plaques are all of the same age, and there is a tendency toward a merging of the areas of demyelination resulting in large plaque formation (10).

We followed the recent recommendations of the Mayo Clinic for the therapy of acute exacerbations of MS, with a slight modification, in managing the patient. For the treatment of moderate to severe relapsing-remitting MS, intravenous methylprednisolone 1000 mg/day for 5 days followed by prednisone 60 mg/day on a tapering schedule over 18 days, is recommended (11). We used a longer course of daily prednisone therapy because our patient developed an additional acute exacerbation of the disease, characterized by optic neuritis, during the initial attempt to taper the daily prednisone dose. The patient survived with minimal neurologic deficit.

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