HMPAO-SPECT and MRI in Acute Disseminated Encephalomyelitis

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From the case records of the Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania

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CASE PRESENTATION

On November 21, 1990, a 50-yr-old right-handed woman was admitted to this institution for further evaluation of progressive mental status changes which began 1 mo prior to admission.

CLINICAL HISTORY

The patient was well until early October 1990, when she developed symptoms of an upper respiratory infection, which lasted for about 10 days. She had been taking no significant medication. Three weeks later the patient was described as appearing fatigued, less talkative than usual, experiencing left-right confusion as well as "nearly hitting five cars" while driving. At this time her speech was not slurred, and no headache, nausea/vomiting, or visual changes were noted. Over the next few weeks, the patient's daughter noticed that her mother would now miss her mouth while brushing her teeth, appeared increasingly confused, had difficulty recognizing family members, could not get out of bed, and developed an incoherent speech pattern. MRI (1.0 Tesla) performed in another hospital showed multiple- enhancing white matter lesions with Gd-DTPA (Fig. 1A-B). To determine the etiology of these lesions, a right temporal lobe biopsy was performed in an outside clinic on November 9, 1990. The biopsy results were initially read as progressive multifocal leucoencephalopathy (PML) or as possible central nervous system lymphoma. Other laboratory studies included a slightly elevated ESR of 35, SPEP which showed polygammopathy, negative toxic screen, ACE of 29.6, non-reactive RPR, and a negative HIV titer. No evidence of a malignant lesion was detected by abdominal CT, mammogram and gynecologic exam. The patient was treated with 12 mg of Decadron and Dilantin prophylaxis. When her condition continued to deteriorate, she was transferred to this institution for further diagnostic work-up and treatment.

Physical examination on admission showed no abnormalities. Neurologic examination showed no nuchal rigidity. The patient was awake but disoriented, incoherent and perseverant. She was responsive but unable to follow commands. Her speech was slurred and encephalopathic, demonstrating fluent aphasia. On cranial nerve exam, a right upper hemianopia was noted. Fundi exam showed normal vessels. Motor exam showed a tetraspastic syndrome with bilateral positive Babinski response, and abdominal reflexes were retained. Coordination and gait were heavily impaired.

Hematocrit was 42 and white count was 8,100/mm^3. A differential blood smear showed 75% granulocytes, 20% lymphocytes and 5% monocytes. ESR was 66 mm/hr. Coagulation studies were within normal limits. Lyme antibody titer (EIA) was positive at 1:320, but was negative in cerebral spinal fluid (CSF). Rheumatoid titer was 180. ANA titer was speckled 1:320. RPR and MHATP were negative, SPEP showed moderate polyclonal hypergammaglobulemia without evidence of paraproteins. A spinal tap showed 4 red cells, 10 white blood cells (98% lymphocytes, 2% monocytes), a total protein of 147 mg/dl, and glucose of 73 mg/dl. A gram stain showed no bacteria, India ink showed no yeast, and no fungi were isolated in culture. CSF cytology revealed lymphocytes and monocytes without evidence of malignancy. CSF:Serum IgG quotient was equivocal with four homogenous bands that were not present in the serum, most likely representing oligoclonal banding.

MRI with Gd-DTPA was repeated on December 6, 1990 and showed multiple high-intensity lesions in the right temporal lobe, left frontal lobe in the subcortical region, left cortical and subcortical occipital lobe, and left parietal region (Fig. 2A-B). In comparison to the previous study, the lesions were unchanged in size with an overall decrease in the size of the areas of enhancement. No new lesions were detected.

On December 12, 1990, a SPECT scan of the brain was acquired with a dedicated triple-headed system 20 min after the intravenous administration of 20 mCi ^{99m}Tc-HMPAO. The images were acquired with a low-energy, high-resolution fan-beam collimator. Areas of increased

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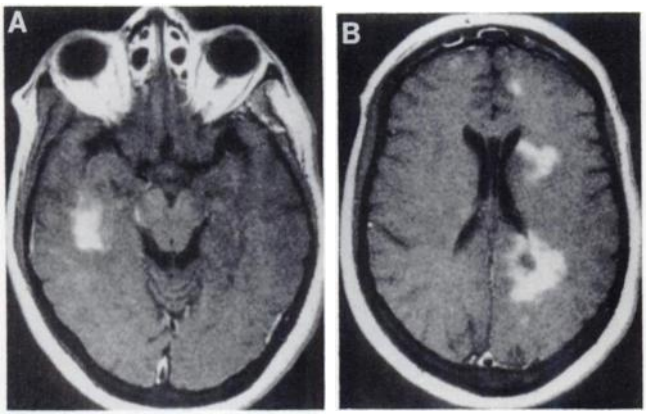

FIGURE 1. First MR (1.0T): First Gd-DTPA enhanced T1-weighted MR (TR 600/TE 15) shows intense enhancement in the right temporal lobe (A) and different regions of the left hemisphere (B).

activity in many of the white matter regions of the brain were detected. The right frontal, right temporal and left occipital were the most severely affected lobes. There was also slightly increased activity in the white matter of the left frontal and temporal lobes, indicating increased blood flow to these sides. There was significantly decreased flow to the cortical regions of both frontal lobes, left parietal lobe, right occipital lobe and the right middle and inferior temporal gyri, as well as the right thalamus (Fig. 3).

Review of the pathology slides showed extensive reactive gliosis with an intense perivascular lymphoplasmocytic infiltrate. Numerous macrophages were observed within the brain substance. Atypical astrocytes were not seen. No viral inclusions were identified. Bodian stains revealed a relative preservation of axons, while a myelin stain revealed demyelination. Special stains for PML and HSV were negative. Kappa and lambda stains did not reveal a clonal lymphoid process. After steroid treatment, a slow but significant improvement was noted.

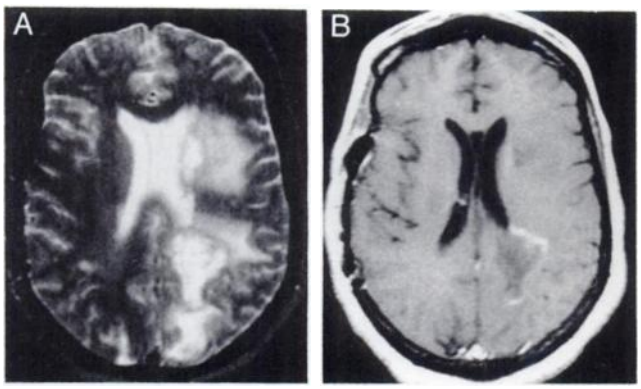

FIGURE 2. Second MR (1.5T) 4 wk later: (A) T2-weighted MR (TR 3000/TE 90) reveals large mass lesions within the left hemisphere. (B) In contrast to the first scan Gd-DTPA enhancement in the T1-weighted image (TR 600/TE 20) is decreased.

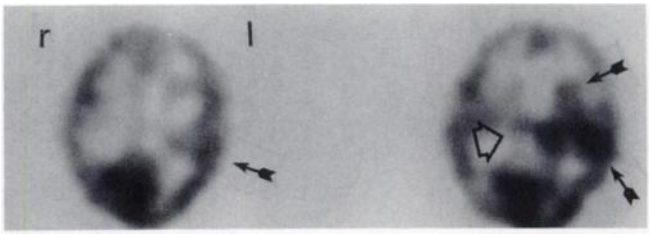

FIGURE 3. Technetium-99m-HMPAO-SPECT with marked increases of blood flow in different brain regions, most pronounced in the left parieto-temporal regions (small arrows). Note the decreased flow in the cortical regions of both frontal lobes and the asymmetry between the thalami (large arrow).

DISCUSSION

Clinical history and the results of neuroimaging studies for this patient are consistent with a diagnosis of acute disseminated encephalomyelitis (ADEM). ADEM is an inflammatory demyelinating disease of the central nervous system, classically described as a uniphasic syndrome which occurs in association with preceding immunization or systemic nonspecific infections (*1*,*2*). Incidental associations with ADEM have been noted with a wide variety of viral and bacterial infections; the most commonly implicated are measles, rubella, mumps, herpes simplex, influenza, Epstein-Barr and Coxsackie virus, as well as nonspecific infections (*1*,*3*–*5*). Clinical and pathologic evidence supports the theory that it is related to syndromes of optic neuritis, transverse myelitis, cerebellar ataxia and acute hemorrhagic leukoencephalitis (AHLE), which may follow similar precipitating events (*2*). ADEM and related syndromes are considered to be the human counterpart of experimental allergic encephalomyelitis (EAE). Features characteristic of ADEM include bilateral optic neuritis, clouding of consciousness and meningismus, loss of deep tendon reflexes, and retained abdominal reflexes in the presence of Babinski responses.

Characteristically, neurologic symptoms begin after a period of 1–3 wk of latency. The clinical course is rapid with development of multifocal neurologic symptoms within days or a few weeks. The illness may begin abruptly with high fever, motor seizures, and neurologic deterioration, finally leading to coma and death in a matter of a few hours to days. Respiratory paralysis occurs due to cerebellar tonsillar herniation, particularly in AHLE. Infrequently, the clinical course is more protacted with or without headache, fever, nausea, vomiting, loss of appetite and meningismus progressing to delirium. The specific neurologic syndrome reflects a multifocal process involving principally the white matter tracts of the cerebral hemispheres, brain stem, spinal cord, and optic nerves and may include hemiplegia, sensory deficits, ataxia and optic neuritis. Neurologic findings such as choreoathetosis also suggest involvement of gray matter structures (*1*).

The histopathologic findings in ADEM have been described in detail in the literature (*2*). The acute lesions consist of perivascular edema with inflammatory cell cuffs

within the Virchow-Robin spaces and parenchyma made of lymphocytes, histiocytes and occasionally plasma cells. There may be a proliferation of vascular endothelial cells. In the adjacent parenchyma, varying amounts of demyelination are seen with relative sparing of axons. At the edge of the lesion in the acute stages, there is microglial proliferation. Lesions may be found in the white matter of the cerebral hemispheres, brain stem, optic nerve and spinal cord, particularly in the subpial and subependymal areas. There may be involvement of the contiguous gray matter as well. These lesions are later replaced by perivenous fibrous gliosis (*2*).

The diagnosis of ADEM can usually be made with confidence in the setting of a clear cut antecedent event associated with an infection of the upper respiratory tract or other viral infection. Differential diagnosis must include multiple sclerosis (MS), CNS vasculitis, chronic meningitis, granulomatous diseases like sarcoidosis, encephalitis or brain tumors such as lymphoma. The diagnosis remains essentially clinical: no laboratory abnormality is pathognomonic.

The current favored therapy for ADEM is use of corticosteroids based on their efficacy in models of EAE, however no controlled clinical trials have been conducted. Although most patients recover completely, many suffer residual neurologic impairment.

Enhancement of demyelinating lesions with iodine agents on CT or Gd-DTPA on MRI is a common observation and usually interpreted as representing damage to the blood-brain barrier. Using chronic relapsing experimental allergic encephalomyelitis (CREAE) as a model of immune-mediated demyelination to clarify the mechanism of enhancement, it was shown that perivascular inflammation is a necessary condition for enhancement (*6*). From the similarity in morphologic and functional changes between CREAE and MS, Kermode et al. (*7*) concluded that enhancement in human disease reflects active inflammation. Miller et al. (*8*) showed that enhancement is a consistent finding in new lesions or new parts of existing lesions in nine patients using serial MRI studies with Gd-DTPA. Most lesions were enhanced for less than 1 mo, and none for as long as 6 mo. In another study, uniformly-enhancing and ring-enhancing lesions were detected. The enhancing lesions were often less extensive than the corresponding high signal on T2-weighted images (*7*). Pozzilli et al. (*9*) tried to quantify the permeability alteration of the blood-brain barrier with PET and ^{68}Ga-EDTA. Their investigation yielded a moderate but significant increase of blood-brain barrier permeability, indicating a recent damage in the MS plaques.

In ADEM, multifocal white matter damage similar to MS were found using MRI without Gd-DTPA (*10–12*). Whereas ADEM is usually a monophasic disease, MS is a multiphasic disease. Therefore, it might be expected that in ADEM all lesions would enhance in the acute stage with Gd-DTPA in contrast to MS, in which a mixture of enhancing and nonenhancing lesions is typical (*8,13,14*). Additionally, serial MRI is useful in distinguishing between MS and ADEM as shown by Kesselring et al. (*11*) and our case. New MRI lesions in MS are commonly observed after scanning intervals as short as 1 mo (*8*), whereas this is an unusual finding in ADEM (*11*). In our case, follow-up MRI revealed no new lesions and Gd-DTPA enhancement was lower than that in the first study, favouring a diagnosis of ADEM.

HMPAO-SPECT has proved useful in the diagnostic work-up of many central nervous system disorders (*15, 16*). However, its value in demyelinating disorders is unknown at this time. Previous studies in chronic MS patients have addressed the relationship among the extent of cerebral lesions shown by CT or MRI, cognitive impairments and regional blood flow and metabolism shown on SPECT and PET during stationary disease states (*17,18*). Using ratios of regional-to-whole brain activities on HMPAO scans, significant reductions were shown in both frontal lobes and the left temporal lobe, which correlate with neuropsychologic impairment. However, the authors found no areas of increased tracer activity when compared to the MRI lesions (*18*). In contrast, DiRocco et al. (*19*) described increased glucose utilization in acute lesions of EAE, similar to the results noted in a patient with progressive multifocal leukoencephalopathy (*20*). Regional increase of HMPAO uptake in inflammatory brain regions was detected in patients with encephalitis, particularly herpes encephalitis, followed by a decreased uptake in these regions in the chronic disease stage (*21,22*). The increased uptake of HMPAO in our case may not only represent blood-brain barrier damage, it also may reflect changes in tissue pH and the presence of inflammatory cells and hyperemia (*23*). This may explain that the areas of increased HMPAO uptake were larger than expected from Gd-DTPA enhanced MRI. There was no clinical or EEG evidence of seizure activity in our patient, which is known to increase HMPAO uptake ictally or postictally (*24*). The decreased cortical activity of HMPAO may reflect cortical deactivation secondary to disconnection from subcortical structures, which is described in MS patients (*18,25*).

CONCLUSION

The diagnosis of ADEM in this case demonstrates the value of Gd-DTPA enhanced MRI and HMPAO-SPECT imaging in the diagnostic evaluation of patients with inflammatory brain disease. MRI and SPECT are complementary modalities in that they provide anatomic and physiologic information about the extent and sites of involvement and their relationship to the clinical findings. Both methods may be useful in the short- and long-term monitoring of treatment regimens employed in demyelinating disorders.

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