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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 35-1985

PRESENTATION OF CASE

A 30-year-old woman was admitted to the hospital because of progressive encephalopathy.

There was a history of "migraine headaches" since childhood, with premenstrual exacerbations; the headaches improved when a hysterectomy was performed 10 months before entry because of dysmenorrhea and menorrhagia. Three years before admission there was the abrupt onset of a severe occipital headache with nausea and vomiting, for which she was seen at another hospital and treated with intramuscularly administered meperidine. She was otherwise well until three weeks before entry, when she experienced another severe occipital headache of abrupt onset, with nausea, vomiting, abdominal cramps, and the passage of several diarrheal stools. Physical examination at another hospital was reported to show no abnormality. Meperidine and hydroxyzine were injected, and she was discharged home feeling improved. That night she was awakened from sleep by another occipital headache with bitemporal radiation, followed by nausea, vomiting, and photophobia. On the next morning she returned to the same hospital. Examination was again reported to be negative, and she was admitted.

The urine was normal. The hematocrit was 42.2 per cent; the white-cell count was 12,800, with 75 per cent neutrophils, 2 per cent band forms, 17 per cent lymphocytes of which 6 were atypical cells, and 6 per cent monocytes. The platelet count was 360,000. The urea nitrogen was 9 mg per 100 ml (3 mmol per liter), the glucose 111 mg per 100 ml (6.16 mmol per liter), the bilirubin 0.4 mg per 100 ml (7 μmol per liter), the calcium 9.3 mg per 100 ml (2.3 mmol per liter), and the protein 6.0 g (the albumin 4.1 g and the globulin 1.9 g) per 100 ml. The sodium was 142 mmol, and the potassium 3.6 mmol per liter. The serum aspartate aminotransferase (SGOT) and the alkaline phosphatase were normal. A computed tomographic (CT) scan of the brain, performed before and after the injection of contrast material, was normal. A lumbar puncture yielded clear, colorless cerebrospinal fluid under an initial pressure of 120 mm; the fluid contained 2 red cells and 1 lymphocyte per cubic millimeter; the protein was 54 mg per 100 ml.

The patient was given meperidine and prochlorperazine. Headache, nausea, and vomiting persisted, and on the third hospital day examination revealed that the left pupil was nonreactive and the left hand was weak. On the fifth hospital day the patient continued to vomit. An electrocardiogram demonstrated quadrigeminy. Vomiting persisted, and on the seventh hospital day the headache worsened. On the following day propranolol was begun. On the ninth hospital day the patient said that her vision was blurred, with "spots and sparkles." Chlorpromazine, with caffeine, and a mixture of phenobarbital, ergotamine tartrate with caffeine, and belladonna alkaloids were administered. On the 11th hospital day the patient was lethargic and unable to locate her bedside medications; she reported tingling and numbness in the left hand. On the next hospital day she was confused and cried frequently. She complained of photophobia and was unable to put on her bathrobe. On the 13th hospital day she again vomited and reported dizziness, blindness, and weakness of the left arm; she was unable to brush her teeth without assistance. Examination disclosed evidence of left–right confusion. On the following day the patient's headache resolved, although she continued to complain of blindness, dizziness, and weakness. All medications were discontinued except for acetaminophen.

On the 15th hospital day the temperature rose to 37.5°C. The patient fell over while sitting up in bed. A psychiatric consultant observed that she was drowsy, with rhythmic, jerking movements of the right upper extremity. She was disoriented, with left–right confusion and poor concentration, and did not know the ages of her children. A left ptosis was present; she was unable to look past the midline to the right, and right central facial weakness was observed. The right grasp was weak. Diazepam was injected by vein. On the next day the temperature rose to 37.4°C. A neurologic consultant found evidence of cortical blindness and a left Babinski sign; the other findings were unchanged except that there were no further abnormal movements of the right upper extremity. The erythrocyte sedimentation rate was 2 mm per hour. Another lumbar puncture yielded cerebrospinal fluid that contained 2 red cells, 2 lymphocytes, and 1 mononuclear cell per cubic millimeter; the glucose was 75 mg per 100 ml (4.2 mmol per liter), and the protein 55 mg per 100 ml. Another CT scan of the brain showed diffuse gyriform enhancement of the cerebral convolutions. An electroencephalogram revealed bilateral diffuse slowing in the delta and theta range. On the 17th

hospital day the temperature rose to 37.9°C. The patient appeared worse and was incontinent of urine. The pupils were 8 mm; a left Babinski sign persisted. The urea nitrogen was 5 mg per 100 ml (2 mmol per liter), the glucose 130 mg per 100 ml (7.2 mmol per liter), and the calcium 9.7 mg per 100 ml (2.4 mmol per liter). The sodium was 136 mmol, the potassium 3.7 mmol, the chloride 104 mmol, and the carbon dioxide 28 mmol per liter. Dexamethasone was begun. On the following day the temperature rose to 37.9°C, and she lapsed into a monosyllabic state. On the 19th hospital day the temperature rose to 38°C. The patient was sweaty and obtunded; she opened her eyes when addressed but did not obey commands. Tremors were again observed in the right upper extremity. Examination showed spastic quadriparesis with bilateral hyperreflexia and bilateral Babinski signs. On the following day another CT scan of the brain, performed with double-dose contrast material, disclosed areas of irregular gyral enhancement; decreased absorption was evident in the left frontal, occipital, and right posterior parietal regions; poor visualization of the sylvian fissures suggested a diffuse mass effect. She was transferred to this hospital.

The patient was right-handed. There was a history of measles at the age of three years. She used marijuana several times weekly and had taken a contraceptive pill for 10 years until the time of the hysterectomy. She was treated on two occasions for pelvic inflammatory disease. She smoked 1½ packs of cigarettes daily and drank small amounts of alcohol. Two children, aged 8 and 10 years, and the patient's parents were well. Her maternal grandmother died of cancer; her maternal grandfather was living and had rheumatoid arthritis. A maternal aunt was said to have had five or six episodes of viral meningitis in the past 10 years. A brother had Reiter's syndrome. There was no history of seizures, loss of consciousness, prior changes in the visual fields, or psychiatric illness, antecedent herpetic or other viral illness, exposure to mosquitoes, ticks, or sick animals, intravenous drug abuse, exposure to known toxins, or recent travel except to Maine in April, five months before entry.

The temperature was 38.1°C, the pulse was 128, and the respirations were 22. The blood pressure was 110/60 mm Hg.

On examination the patient was a pale, thin, sweating, obtunded woman with extensor posturing of the extremities except for a flexed position of the left arm. An erythematous papulopustular folliculitis was observed in both axillae. No lymphadenopathy was found. The ears, mouth, and throat were normal; no oral ulcers were seen. The neck was supple; the carotid pulses were ++, without bruits. The lungs were clear, and the heart, breasts, abdomen, and extremities were normal; pelvic and rectal examinations were negative.

Neurologic examination disclosed that she occasionally sighed deeply and sometimes moved the right leg. A fine resting tremor was noted over the upper portion of the body bilaterally. Roving eye movements were observed; there was no response to visual threat from either side, and opticokinetic nystagmus was absent. The optic disks were sharp and flat; no hemorrhage or evidence of chorioretinitis was observed. The right pupil was 7 mm and the left 6 mm; both reacted to light. Extraocular movements were intact in response to the doll's-head maneuver, but the movements were disconjugate. Mild central right facial weakness was observed. The remaining cranial nerves were intact insofar as testing was possible. Muscle tone was increased in all limbs, with a mixed pattern on the right side, predominance of flexor postures in the left arm, and extensor postures in the left leg. The patient grimaced in response to noxious stimuli applied to all extremities and made abortive withdrawal movements. The triceps and ankle reflexes were +, the brachioradialis ++, and the biceps and knee jerks +++ bilaterally; the right plantar response was flexor, and a left Babinski sign was present.

The urine was normal. The hematocrit was 40.3 per cent; the white-cell count was 18,900, with 74 per cent neutrophils, 16 per cent lymphocytes, 2 per cent atypical lymphocytes, and 8 per cent monocytes. The platelet count was 478,000, and the erythrocyte sedimentation rate 2 mm per hour. The prothrombin time was 9.8 seconds, with a control of 10.2 seconds; the partial thromboplastin time was 23.2 seconds. A stool specimen gave a negative test for occult blood. The urea nitrogen was 11 mg per 100 ml (3.9 mmol per liter), the glucose 126 mg per 100 ml (6.99 mmol per liter), the bilirubin 0.5 mg per 100 ml (9 μmol per liter), the uric acid 1.3 mg per 100 ml (0.077 mmol per liter), the triglyceride 82 mg per 100 ml, the cholesterol 206 mg per 100 ml (5.33 mmol per liter), the calcium 10.3 mg per 100 ml (2.57 mmol per liter), the phosphorus 4.7 mg per 100 ml (1.5 mmol per liter), and the protein 7.3 g (the albumin 4.8 g and the globulin 2.5 g) per 100 ml. The sodium was 134 mmol, the potassium 3.8 mmol, the chloride 100 mmol, the carbon dioxide 24 mmol, and the osmolality 274 mOsm per liter. The SGOT was 36 U per milliliter (0.29 μmol · sec^{-1} per liter), the lactic dehydrogenase (LDH) 192 U per milliliter (3.21 μmol · sec^{-1} per liter), the creatine kinase (CK) 189 mU per milliliter (3.15 μmol · sec^{-1} per liter), the amylase 4 U, and the alkaline phosphatase 22 IU (0.37 μmol · sec^{-1}) per liter. A specimen of arterial blood, drawn while the patient was breathing room air, disclosed that the partial pressure of oxygen (PaO_2) was 96 mm Hg, the partial pressure of carbon dioxide ($PaCO_2$) 34 mm Hg, and the pH 7.47. An electrocardiogram demonstrated a normal rhythm at a rate of 75, with a PR interval of 0.10 second, believed consistent with the Lown–Ganong–Levine syndrome; nonspecific ST-segment and T-wave abnormalities were noted. X-ray films of the chest were normal. A CT scan of the brain (Fig. 1) disclosed a heterogeneous, patchy area of low density in the left parie-

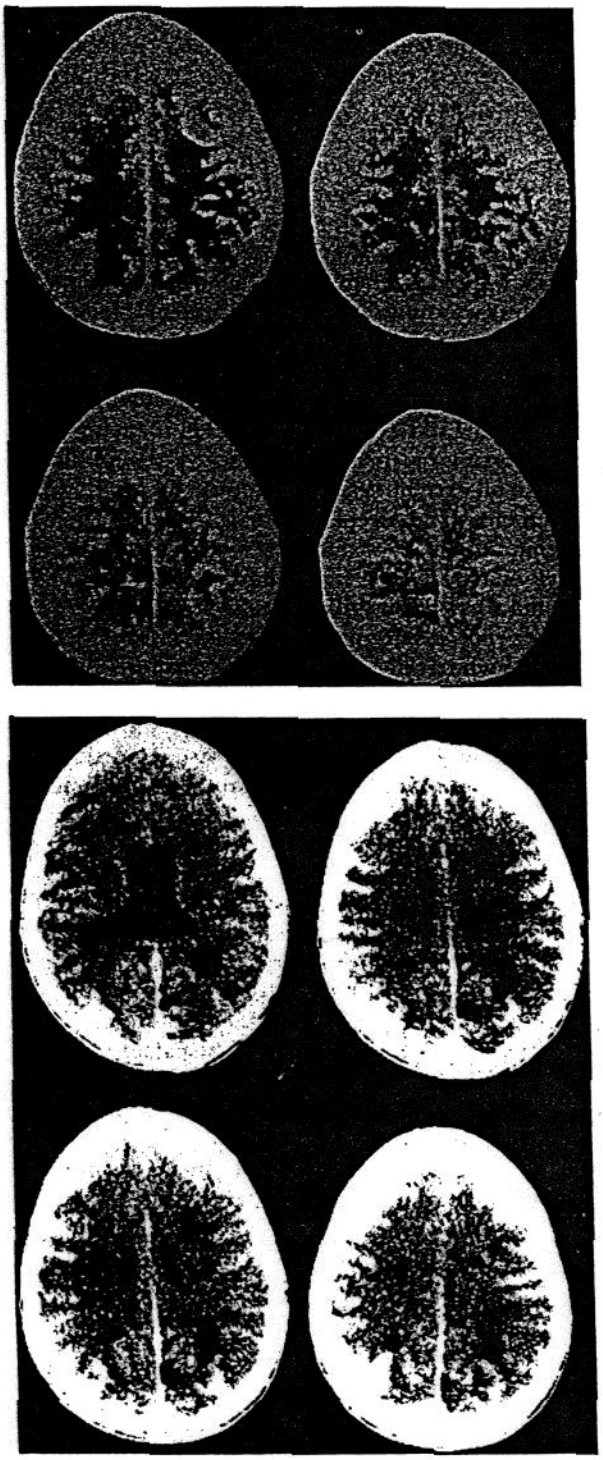

Figure 1. CT Scan of the Brain Obtained on the First Hospital Day — Upper Cranial Sections (Top), One-Hour Delay, High-Iodine, Showing Abnormal Generalized Gyriform Enhancement with Focal Left Frontal, Right Parietal, and Bilateral Parieto-Occipital Changes.

Diffuse swelling is seen. The mid-cranial sections (bottom) depict pronounced right parieto-occipital gyral enhancement and white-matter low absorption in the left frontal and parieto-occipital areas.

tal, left frontal, and left periatrial regions. After the administration of contrast material multiple patchy areas of enhancement were observed in the frontal, parietal, and occipital regions bilaterally, and abnormal enhancement was observed in the perisulcal regions of both cerebral convexities; there was no contrast enhancement of the low-density areas in the left frontal and parietal regions. A screening test on the blood for toxic substances was positive only for phenobarbital, 2.2 μg, and acetaminophen, 10.1 μg per milliliter. A serologic test for syphilis, an LE-cell test, a test for heterophil agglutinins, and tests for hepatitis B surface antigen and antibody, rheumatoid factor, antinuclear antibodies, and anti-native DNA were negative. Serum immunoelectrophoresis showed normal precipitin arcs, and an agarose-gel electrophoresis gave a normal pattern. A lumbar puncture yielded clear, colorless cerebrospinal fluid under an initial pressure of 245 mm; the fluid contained 2 red cells and 6 lymphocytes per cubic millimeter; the glucose was 89 mg per 100 ml (4.9 mmol per liter), and the protein 32 mg per 100 ml. An electroencephalogram disclosed continuous generalized, irregular moderate-to-high-voltage slow activity, most prominent anteriorly; without appreciable asymmetry. A cerebral arteriographic study (Fig. 2), done by means of a right femoral approach, showed focal narrowing of multiple vessels in both the anterior and the posterior cerebral circulatory systems bilaterally but none in the distributions of the external carotid arteries.

A diagnostic procedure was performed.

Differential Diagnosis

Dr. Robert H. Ackerman*: We have the problem of a 30-year-old woman with a history of migraine headaches since childhood, whose recent illness began with two bouts, within 24 hours, of severe occipital headache, nausea, and vomiting. Worsening of the headache and recurrent vomiting characterized the first week of the illness despite vigorous treatment with a number of medications used to ameliorate migraine. The headache persisted for two weeks. On the third day at another hospital the left pupil was nonreactive and the left hand was weak. Except for photophobia and some "spots and sparkles" in her visual fields she had no neurologic signs or symptoms until the 11th hospital day, when she experienced lethargy, inability to locate her bedside medications, and tingling and numbness of the left hand. Over the next week there was rapid progression of the neurologic complaints and findings. They included nonlocalizing cerebral disturbances characterized by disorientation, poor concentration and dizziness, right parietal signs of dressing apraxia and right–left confusion, occipital

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blindness, right and left corticobulbar or corticospinal impairment, and brainstem pupillary and oculomotor deficits. By the third week after the onset of the illness she had become obtunded and had a spastic quadriparesis. Steroids were started. Three days later she was transferred to this hospital.

Examination on admission showed that she was obtunded and had extensor or decorticate posturing of the extremities, consistent with bihemispheric and upper brainstem disturbances. Although she was wakeful, opticokinetic nystagmus and response to visual threat were absent, indicating interruption in her visual pathways. These disturbances were probably due to posteriorly situated lesions, since the pupils reacted to light, demonstrating that the anterior visual system was intact. The eyes roved spontaneously and moved fully in response to the doll's-head maneuver, which means that the medial longitudinal fasciculus and its widespread brainstem connections were spared. The previously noted right-gaze palsy, unreactive left pupil, and right Babinski sign had resolved, indicating some reversibility of the process. The neck was supple, which is evidence against the diagnosis of meningitis in an awake patient.

The clinical course, then, was consistent with the evolution of a multifocal process affecting the central nervous system. It began with a nonspecific prodrome and developed with minimal evidence of involvement outside the central nervous system except for a leukocytosis in the blood and incidental cardiac and dermatologic findings. Although the process eventually involved both cerebral hemispheres and the brainstem, the only definite abnormality found in three spinal taps was an increase in the cerebrospinal pressure three weeks after the onset, at the time of admission to this hospital. A process that involves the leptomeninges or the ventricular ependymal surface will cause a cerebrospinal fluid pleocytosis and an elevated protein content.

In approaching the differential diagnosis from the clinical point of view we can dismiss at the outset the question of migraine as a major process in this case, despite a history of migraine headaches since childhood and a similar episode of headache, nausea, and vomiting three years earlier. Unexplained neurologic deficits are often attributed to migraine in patients with a history of headaches. Part of the attraction of migraine may be its mystery. Although it is one of the oldest known medical disorders, we still do not understand its pathophysiology. Little concrete evidence supports the prevalent idea, however valid, that the prodrome and headache phases of typical migraine are due to constriction of large cerebral vessels followed by dilatation of external carotid branches or the more recent concept that migraine is related to microcirculatory disturbances mediated by projection fibers from the locus ceruleus. "Migraine" is the Greek word for "hemicrania." The alternating unilateral nature of the headache is the cardinal diagnostic feature, although in common migraine the headache can be generalized. When migraine is associated with neurologic deficits they generally are referable to one hemisphere or the other or to the brainstem itself, but they do not affect multiple widespread regions of the brain, as they did in this case. In addition, the deficits in migraine have their onset in close relation to the headache, and

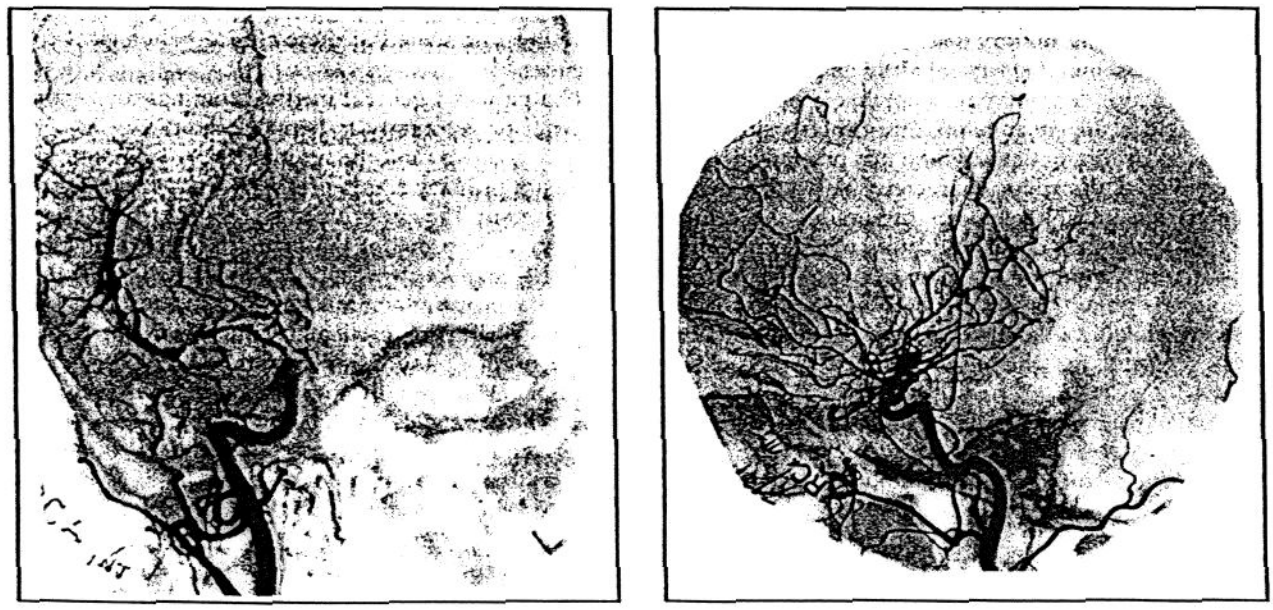

Figure 2. Right Carotid Angiograms, Anteroposterior (Left) and Lateral (Right) Views, Showing Diffuse Proximal and Distal Segmental Arteritis.

only uncommonly does the headache persist for 14 days. These temporal and topographic features help to distinguish so-called malignant migraine from the disease under discussion.

Of the encephalopathic processes that might explain this patient's course we must consider an infectious encephalitis. As calculated from data in the case record the onset occurred in September, when there was an increased frequency of eastern equine encephalitis in Massachusetts as a result of the large mosquito population fostered by a wet spring. Eastern equine encephalitis can begin with headache, nausea, and vomiting but usually is associated with a temperature of at least 39 to 40°C and a markedly abnormal cerebrospinal fluid. Moreover, there is only a short interval between the onset of the headache and the neurologic deficits. This patient was never very febrile. Her temperature ranged from approximately 37.5 to 38°C, and 11 days elapsed before her neurologic deterioration became fulminant. In eastern equine encephalitis clinically demonstrable disease usually occurs in subjects younger or older than the patient under discussion.

The picture in this case also could be that of herpes simplex encephalitis, which can be difficult to distinguish from other types of encephalitis unless anosmia, olfactory hallucinations, temporal-lobe seizures, electroencephalographic evidence of abnormalities over the temporal lobes, or memory dysfunction occurs early in the course. Against the diagnosis of herpes simplex encephalitis in this case are the location of the first signs of involvement in areas other than the temporal lobes, the absence of increased intracranial pressure as a prominent feature of the clinical course, and the normal cerebrospinal fluid at a time when the disease was fulminant.

An acute inflammatory demyelinating process, such as acute disseminated encephalitis or its hyperacute version, acute necrotizing hemorrhagic encephalitis, can produce an encephalopathic process similar to that seen in this patient. These are postinfectious or postvaccinial disorders characterized by foci of demyelination in white matter throughout the central nervous system. Typically, a history of an exanthematous disease, mumps, or an upper respiratory tract infection is obtained. Rarely, no history of a prior illness is available. A delayed hypersensitivity mechanism seems to be the underlying pathophysiologic process.

I have been discussing primarily parenchymal causes of progressive encephalopathy. The possibility of a vascular cause must also be entertained in this case. The course was progressive, occurred in a limited time frame, and did not have the long-term episodic characteristics of recurrent cerebral emboli complicating an atrial myxoma, rheumatic valvular disease, or nonbacterial thrombotic endocarditis. Moreover, there were no predisposing factors to suggest the latter two processes. In a young woman with an unexplained medical disorder vasculitis is a tempting diagnosis. By this term one usually refers to an immune-mediated disorder, such as systemic lupus erythematosus or polyarteritis nodosa. Lupus is not a vasculitis, strictly speaking, since the fibrinoid degeneration that characterizes the vascular change occurs without an inflammatory reaction. Polyarteritis nodosa, cranial (giant-cell) arteritis, and granulomatous angiitis are the principal nervous system disorders associated with primary inflammation in the vessel walls. Polyarteritis is more common in the peripheral than the central nervous system. The absence of systemic involvement and the normal results of immunologic studies rule out both lupus and polyarteritis in this patient. Cranial arteritis involves the extracranial carotid arteries and their branches. It occurs in much older patients and is associated with anemia and an elevated erythrocyte sedimentation rate. Only rarely does it involve the intracranial vessels. Granulomatous angiitis is an uncommon disorder that typically occurs in older patients and affects much smaller vessels (less than 500 μm) than cranial arteritis, and these vessels in the leptomeninges or the brain usually are arterioles or venules. Occasionally, granulomatous angiitis involves large cerebral vessels as well.[1] The clinical course of granulomatous angiitis is consistent with the course in this case, but the cerebrospinal fluid findings are often abnormal. The cause of granulomatous angiitis is unknown. Up to 1976, however, it had occurred in association with lymphoma in 5 of 23 reported cases and in association with herpes zoster infection in 4 of them.[2] An immune disturbance has been thought to facilitate vascular invasion by an infectious agent (especially varicella zoster virus) or to mediate an inflammatory process. Although granulomatous angiitis is rare, at least two previous cases have been presented at these clinicopathological conferences.[3,4]

The patient's general medical findings are against an arteritis secondary to hematogenous spread of an infectious agent, and the normal cerebrospinal fluid is against a primary meningitis with secondary vascular involvement. If an arteritis was present I would expect it to have been one of the primary forms that I discussed — in other words, polyarteritis nodosa, cranial arteritis, or granulomatous arteritis.

Venous-sinus or cortical venous thrombophlebitis can result in a picture similar to that in the case under discussion, but usually there is more rapid evolution of cerebral deficits once neurologic changes occur. When brainstem signs are present they are secondary to alterations in intracranial pressure. The cerebrospinal fluid formula is abnormal, and there may be a history of a parameningeal infectious process, recent childbirth, use of birth-control pills, or a hematologic abnormality.

On purely clinical grounds, then, the most likely diagnoses are an acute inflammatory demyelinating process or a primary inflammatory disorder of

the intracranial vessels. May we review the CT scans, Dr. Davis?

DR. KENNETH R. DAVIS: The plain CT scan obtained at another hospital on the day of the onset of the illness was described as negative. The CT scan done on the 16th day of the illness at that hospital, performed with and without contrast material, was interpreted as showing diffuse gyral enhancement. The CT scan without contrast material on the 20th day from the onset of the illness, obtained at this hospital, demonstrates a diffuse low-absorption abnormality in the parietal, parieto-occipital, and frontal lobes. There is a diffuse mass effect in the frontal lobes superiorly, with obliteration of the sulci and compression of the ventricles. No low-absorption abnormality is seen in the temporal lobes. A CT scan performed on the same day with a high dose of contrast material and one-hour delay (Fig. 1) discloses a diffuse gyriform enhancement in the perisulcal regions of the parieto-occipital, parietal, and frontal regions. Focal areas of enhancement are seen in the posterior parieto-occipital regions. Focal areas of low absorption are visible in the left frontal and parieto-occipital white matter.

DR. ACKERMAN: The CT scans indicate the widespread nature of the pathologic process in the cerebral hemispheres, with a predilection for the white matter posteriorly and superiorly. The process was least marked in the anterior temporal lobes. Marked gray-matter changes occurred only in the right parieto-occipital region.

The low-absorption-value changes in the white matter are compatible with many of the diseases that I have already discussed, including eastern equine encephalitis, acute necrotizing hemorrhagic encephalitis, and granulomatous angiitis. The nonspecificity of the CT findings, however, must be emphasized. If the history had indicated a period of cardiopulmonary arrest, the changes could be consistent with hypoxic encephalopathy. If the patient had been younger, the course had been more chronic, and headache had not been a feature, the CT findings could suggest subacute sclerosing panencephalitis. The CT abnormalities are not those found with migraine. Low-absorption-value changes in the white matter have been reported in patients with migraine, but they are unifocal and nonprogressive. When migraine results in fixed neurologic deficits, the CT findings are those of infarction in an identifiable vascular territory in the cortex and subjacent white matter.

The gyral enhancement seen in this case probably reflected breakdown of the blood–brain barrier. Although such enhancement is sometimes called "luxury perfusion," it more often results from breakdown of the blood–brain barrier. The term "luxury perfusion" can be used only when one knows that a relative or absolute hyperemia is present and represents an increase in blood flow out of proportion to the altered metabolic needs of the tissue. We do not often see evidence of hyperemia on CT scans in patients with a necrotizing lesion or infarction. To prove that enhancement is due to changes in flow and not to impaired integrity of the blood–brain barrier a second CT scan is required one to two hours after the initial scan to demonstrate that contrast material is no longer present in the tissues. Steroids will suppress contrast enhancement due to breakdown of the blood–brain barrier, and that might be the explanation for the decreased gyral enhancement in the scan obtained after admission to this hospital as compared with the previous one.

Therefore, I must account for the clinical, electroencephalographic, and CT evidence of a diffuse multifocal encephalopathy that started with headache, but only after 11 days became manifest as fulminant involvement of the cerebral hemispheres and brainstem, and caused a pleocytosis in the blood but no abnormality in the cerebrospinal fluid formula. The temporal and spatial distribution of the disease, as evidenced by the clinical and CT findings, makes the most likely diagnoses acute necrotizing hemorrhagic encephalitis and granulomatous angiitis. In contrast to eastern equine encephalitis, which always causes abnormal cerebrospinal fluid, in these two diseases the spinal fluid formula occasionally remains normal. In the early report of Adams, Cammermeyer, and Denny-Brown[5] acute necrotizing hemorrhagic encephalitis seemed to have a predilection for occurrence in the summer or fall, an observation that is relevant to this case. The young age of the patient is also consistent with that diagnosis. At this point, in view of the clinical and CT findings, acute hemorrhagic necrotizing encephalitis would be my leading diagnosis.

May we see the arteriograms now, Dr. Davis?

DR. DAVIS: The bilateral carotid and vertebral angiograms (Fig. 2), performed three weeks after the onset of the illness and one day after the CT scan at this hospital, demonstrate a diffuse abnormality of the large vessels at the base of the brain and also of the smaller distal middle, anterior, and posterior cerebral arteries. There is irregular segmental narrowing of the vessels, with delay of peripheral flow. The external carotid and ophthalmic arteries appear normal. Films taken in the venous phase reveal no abnormality. The vertebral angiograms also show abnormal areas of segmental narrowing of the basilar, posterior cerebral, superior cerebellar, and posterior inferior cerebellar arteries. Flow into more distal branches of these vessels is diminished.

DR. ACKERMAN: The arteriograms show multiple areas of narrowing, beading, and sausage-shaped dilatation of vessels overlying the convexity of the brain. These segmental changes are nonspecific signs that can be found in a number of primary and secondary disorders affecting the pial vessels, which lie in the subarachnoid space and receive an investiture of pia as they enter the brain. As a secondary disorder beading can be found in patients with carcinomatous, infectious, or chemical meningitis. With carcinomatous

meningitis there is encasement of the vessels by the neoplastic process. In infectious meningitis an inflammatory response can occur in the vessel wall. With chemical meningitis, such as occurs after subarachnoid hemorrhage, focal spasm of the cerebral vessels can produce this arteriographic picture. The cerebrospinal fluid findings in this case serve to rule out the diagnoses of carcinomatous meningitis, a virulent infectious process in the subarachnoid space, and subarachnoid hemorrhage. Blood in the subarachnoid space typically causes spasm between 4 and 15 days after the hemorrhage. This interval is appropriate for the period between the onset of the headache and the neurologic signs in the patient under discussion. However, the degree of spasm after subarachnoid hemorrhage is related to the amount of blood in the subarachnoid space, and one would not expect to find extensive vasospastic changes without evidence of blood on an early CT scan or in the cerebrospinal fluid. Acute hemorrhagic necrotizing encephalitis, the diagnosis that I favored previously, does not cause gross bleeding into the subarachnoid space and should not produce spasm of the pial vessels, even though a few hundred or thousand red cells might be counted on microscopical examination of the cerebrospinal fluid. The angiographic picture is compatible with the necrotizing arteritis that is found occasionally in methamphetamine abusers,[6] but we have no history of drug abuse in this case.

A primary vascular process emerges as the most likely diagnosis. Arteriosclerosis should be considered in the differential diagnosis of the arteriographic findings in this case but is not relevant clinically in view of the age of the patient, the course, and the normal lipid values. I have ruled out polyarteritis nodosa because of the lack of systemic findings and its infrequent involvement of the central nervous system alone.[7] Cranial arteritis does affect vessels of the size seen on the arteriograms but has only rarely been demonstrated to involve them intracranially. Wilkinson and Russell[8] found no evidence of intracranial involvement in 12 carefully studied cases of cranial arteritis. Moreover, the erythrocyte sedimentation rate is almost invariably elevated unless, as studies in our laboratory have shown, whole-blood viscosity is increased. Granulomatous angiitis typically involves vessels smaller than those seen on the arteriograms of this patient. Moreover, it affects veins as well as arteries. The arteriograms in this case show involvement only of arteries. The overall clinical, laboratory, CT-scan, and arteriographic picture, then, is not typical of any of the diseases that I have discussed.

I am left having to postulate that the patient had a primary arteritis with features of both cranial arteritis and granulomatous angiitis. The process presumably involved small intracerebral vessels, causing the CT evidence of subcortical disease, as occurs in granulomatous angiitis, and also involved larger vessels in the subarachnoid space, giving the arteriographic picture of beading, as occurs in external carotid branches in cranial arteritis. In this case the arteriograms demonstrated no extracranial involvement. Three cases with similar findings have been reported.[9-11] I suggest that the diagnostic procedure was a biopsy and that it showed giant-cell arteritis. However, we must keep in mind the fact that segmental involvement of the vessels can result in a negative biopsy in patients with central nervous system angiitis. In three of seven reported cases of granulomatous angiitis the biopsy specimen was normal.[10]

DR. EDWARD P. RICHARDSON, JR.: Dr. Boom, you saw this patient as a consultant. Do you wish to comment?

DR. W. HENRY BOOM: We saw her on the evening of her transfer from the other hospital and were struck by the slow progression of the disease, the absence of fever, the bilateral cortical involvement, the benign appearance of the cerebrospinal fluid, the relatively nonfocal findings on the CT scan, and the normal erythrocyte sedimentation rate. We believed that the acute viral infectious causes being considered, such as herpes Type I and eastern equine encephalitis, were very unlikely. The possibility of a postinfectious encephalitis remained, but there was very little in the history to suggest that she had had a viral respiratory tract infection or other viral syndrome that preceded the central nervous system disturbance. We considered the possibility of primary central nervous system vasculitis, but with a sedimentation rate of 2 mm per hour without evidence of hyperviscosity or other factors resulting in low sedimentation rates we regarded that diagnosis as less likely. We did not think that an acute infectious process could explain the clinical course.

CLINICAL DIAGNOSES

? Primary central nervous system vasculitis.
? Postinfectious encephalitis.

DR. ROBERT H. ACKERMAN'S DIAGNOSIS

Primary giant-cell arteritis of brain, with features of cranial arteritis and granulomatous angiitis.

PATHOLOGICAL DISCUSSION

DR. RICHARDSON: The diagnostic procedure was a biopsy. The specimen included a portion of the superficial temporal artery, a branch or continuation of the middle meningeal artery with a portion of dura included, and a fragment of the temporal lobe, in which the appearance of a small meningeal vessel suggested that there might be a pathologic process in its wall. Examination of all these biopsy specimens showed no evidence of disease. We concluded that the biopsy samples included portions of vessels not involved by the process. The evidence that Dr. Ackerman has reviewed in his discussion unequivocally points to the presence of angiitis involving intrinsic vessels of the central nervous system, even though the biopsies were negative. The lesions in the vessel walls are typically granulomatous, with lymphocytes, larger mononucle-

ar inflammatory cells, and multinucleated giant cells, and they involve the entire thickness of the wall. The disease is generally designated granulomatous angiitis of the central nervous system.

The disease is rare. In 1968 Kolodny and his colleagues[1] reported four cases with postmortem examination from this hospital. The pathological features are generally consistent from case to case. The inflammatory process involves the walls of vessels of varying size. The vascular lesions are characteristically segmental, a feature that correlates well with the angiographic findings in these cases and explains why a biopsy might fail to include an affected portion of a vessel. Ordinarily, various forms of central nervous system angiitis are distinguishable, but we have seen one case in which there was suggestive evidence of an angiitis of small cerebral vessels together with giant-cell arteritis of the type seen in cranial arteritis. That case, in which the diagnosis was based on a biopsy of a small muscular meningeal artery, was discussed at a clinicopathological conference by Dr. Jay P. Mohr.[9] Moore and Cupps[12] have given an informative review of the neurologic aspects of inflammatory vascular disease.

Another feature of this case that should be emphasized is the response to treatment. This patient was given cyclophosphamide and prednisone and started to improve. After another 2½ weeks in the hospital she was discharged to a rehabilitation hospital near her home, and Dr. Sakmar will give us further follow-up information.

Dr. Thomas P. Sakmar: Three weeks after the initiation of therapy the patient was awake and alert, turned toward voices, opened her eyes on command, and articulated short phrases. She moved all extremities spontaneously and reacted in a purposeful manner to painful stimuli. She had cortical blindness. She was maintained on 60 mg of prednisone and 50 mg of cyclophosphamide daily. An attempt to taper the cyclophosphamide to an every-other-day schedule one month after discharge resulted in recrudescence of neurologic dysfunction and recurrence of vasculitic changes demonstrable on another cerebral angiographic study. The doses were temporarily increased and later tapered again. On a regimen of prednisone, 70 mg every other day, and cyclophosphamide, 75 mg every other day, her rate of neurologic recovery increased somewhat. At about three months after the onset of therapy she was alert and understood speech, with normal comprehension, and could talk in short sentences with a moderate expressive aphasia. The strength in her right leg and left arm was nearly normal, but her right arm and left leg remained weak. She could distinguish light from dark. After five months of treatment the patient's condition had improved so that she was able to return home from a rehabilitation hospital. Currently, her vision and speech continue to improve. She can walk alone with the aid of a left leg brace and cane. She has difficulty with right–left discrimination. Immunosuppressive therapy with cyclophosphamide and prednisone has been continued.

Dr. Richardson: Dr. Davis will tell us about the follow-up CT scan and angiographic examination.

Dr. Davis: There was a follow-up CT scan without contrast material shortly after admission to this hospital, four days after the first CT scan and 3½ weeks from the onset of the illness. Marked progression of the low-absorption changes in the left frontal, left parieto-occipital, and centrum-semiovale regions is seen. Less striking change is shown in the frontal temporal regions.

Follow-up angiograms (Fig. 3), obtained 5½ weeks

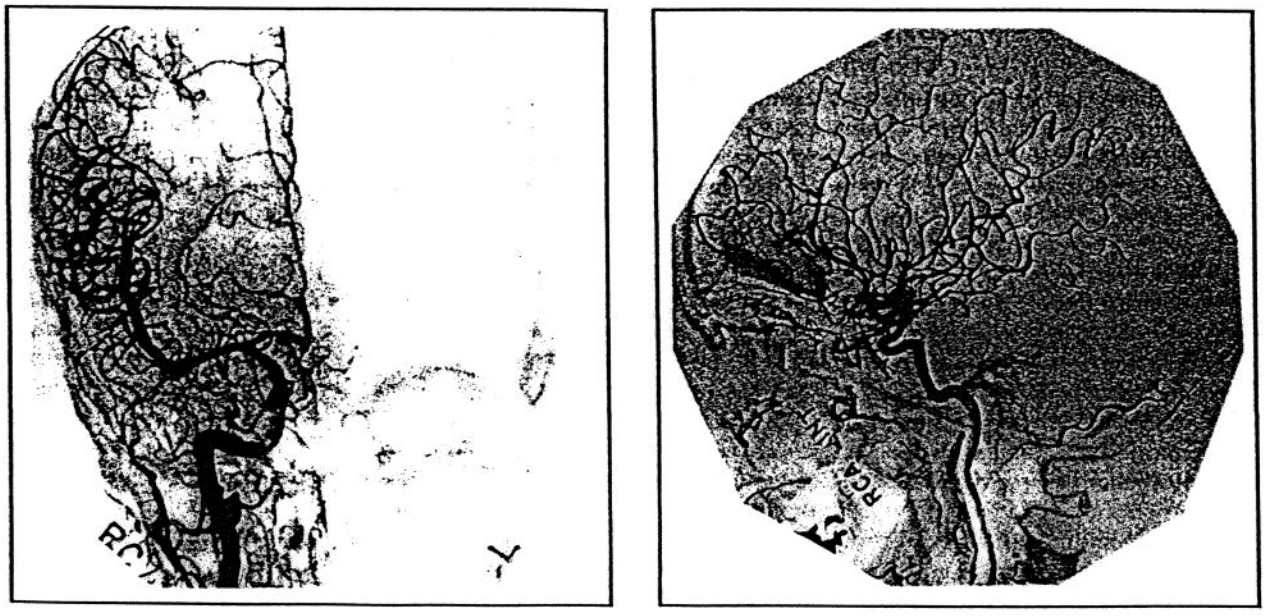

Figure 3. Right Carotid Angiograms, Anteroposterior (Left) and Lateral (Right) Views, Obtained 2½ Weeks after Admission, Showing Generalized Improvement but with Residual Diffuse Abnormality.

from the onset of the patient's illness and 17 days from the date of the first angiographic study, show considerable improvement in the caliber of all the carotid and vertebral basilar vessels, both proximally and distally. There is, however, slight residual irregularity. The flow to the more peripheral branches is increased but is still somewhat delayed.

DR. RICHARDSON: Dr. Haley, a cerebrovascular research fellow in the Laboratory of Cerebral Blood Flow and Metabolism, will report on positron emission tomographic studies in this patient, the results of which correlate well with the clinical course and the CT-scan findings.

DR. E. CLARKE HALEY: Cerebral blood flow and oxygen metabolism were studied during continuous inhalation of ^{15}O-labeled carbon dioxide and molecular oxygen, respectively (Fig. 4). At approximately the time of the first arteriographic examination qualitative studies showed a relative depression in cerebral blood flow and oxygen metabolism in the parieto-occipital region as compared with more anterior structures and in the left cerebral hemisphere as compared with the right. At the time of the second arteriographic examination cerebral blood flow in the left hemisphere was closer to that on the right, but it remained relatively depressed in the parieto-occipital region; oxygen metabolism was relatively depressed in the high left parietal area as compared with the right, as well as in both parieto-occipital regions. Arterial sampling was done during this study so that the data could be quantitated. Cerebral blood flow (CBF) and the cerebral metabolic rate of oxygen metabolism ($CMRO_2$) were low bilaterally. Representative values from the high parietal regions showed CBF to be approximately 35 ml per 100 g per minute bilaterally; $CMRO_2$ at this level measured 0.8 ml per 100 g per minute on the left side and 1.4 ml per 100 g per minute on the right side. In the parieto-occipital regions CBF was 9 ml per 100 g per minute on the left side and 20 ml per 100 g per minute on the right side; $CMRO_2$ values were below measurable levels on the left side and 1.1 ml per 100 g per minute on the right side. The marked depression in oxygen metabolism in the left high parietal and parieto-occipital regions is consistent with infarction in these areas. On the basis of previous data from our laboratory on the meaning of such changes in cerebral blood flow and oxygen metabolism we believe that the tissues with better preserved oxygen metabolism are viable.[13,14]

DR. ACKERMAN: This case illustrates the nonspecificity not only of clinical findings but also of the results of special procedures. The CT scan does not demonstrate pathologic changes themselves but shows only structural changes from which the nature of a pathologic process may be inferred if one knows the clinical history and findings. As special-procedure testing becomes increasingly diverse and noninvasive it must be considered to be an extension of the eyes, ears, and fingers and thus of the bedside evaluation rather than an exercise remote from clinical medicine. Ten years ago the special-procedure alternatives available for diagnostic purposes were few. Technology at that time was employed to confirm or reject the bedside formulation. Today the alternatives are increasingly numerous, and each has several modes of application that must be selected according to the clinical problem at hand. As new technologic procedures that examine different physiologic and anatomical features of disease become available, special procedures are ordered not just to confirm or reject a bedside diagnosis but to help to formulate it. Occasionally, as in cases such as this one, the aggregate technologic information when analyzed in the context of the clinical findings is sufficient to allow one to arrive at a final diagnosis.

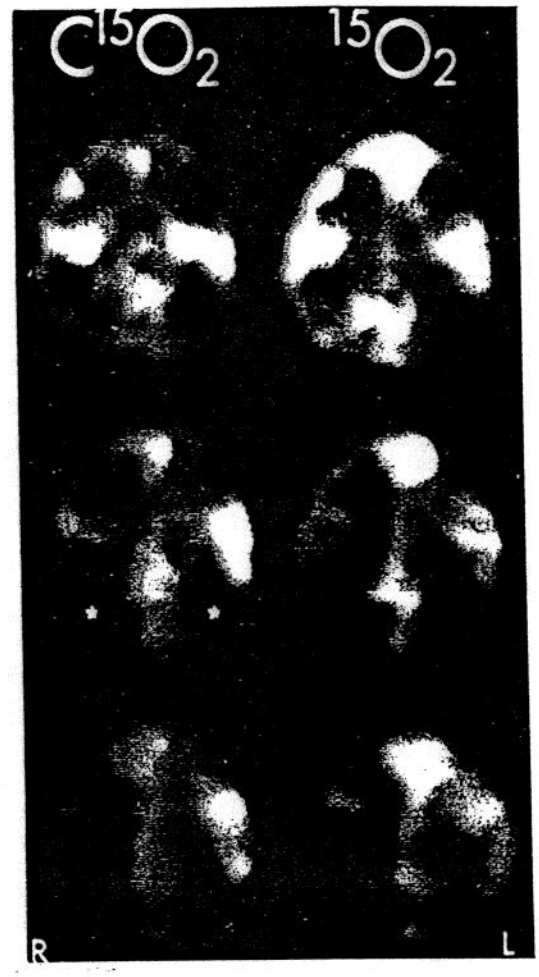

Figure 4. Transverse-Section Images of Cerebral Blood Flow and Oxygen Metabolism Made during Continuous Inhalation of $C^{15}O_2$ and $^{15}O_2$, Respectively.

Brightness is proportional to physiologic activity. In each image the anterior region is above. In each column the lower plane is at the top. In the lower two cuts a relative depression of cerebral blood flow and oxygen metabolism is seen in the left hemisphere and in the parieto-occipital regions (*) bilaterally.

ANATOMICAL DIAGNOSIS

Angiitis of central nervous system.

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