A 23-year-old man was admitted to the hospital because of complex partial seizures that had become generalized.

The patient, who was from El Salvador, had been well until the age of 15 years, when he had three seizures during a two-month period. He was told that the seizures were caused by a "parasite." A medication, which has not been identified, was prescribed, and there was no recurrence. At the age of 16 years, he had a series of episodes of "panic," each lasting as long as three days. Soon after these episodes, he emigrated to the United States after a four-week stay in Mexico.

Ten months later, a tonic–clonic seizure occurred. The patient was evaluated at this hospital at the age of 17 years. The results of neurologic and hematologic examinations, blood chemical analyses, and screening of the serum for toxic substances were negative; radiographs of the chest were normal. Computed tomographic (CT) scanning of the brain, performed without the administration of contrast material, showed no change in the calcific lesion, adjacent to the choroid fissure. A lumbar puncture was performed (Table 1). An electroencephalogram was normal, both while the patient was awake and while he was asleep. Radiographs of the chest remained normal. Isoniazid, rifampin, and pyridoxine were administered. The patient was subsequently lost to follow-up for five years.

At the age of 23 years, the patient returned to this hospital. He reported that his seizures had begun when he was 15 years old, after he had been struck on the right side of the head by his father and had lost consciousness. The seizures were preceded by an aura of warmth on the right side of the head; occasionally, he had brief myoclonic jerks before losing awareness. His brother added that the patient would look to the right and then fall, stiffen, and shake for several minutes. Tongue biting and incontinence accompanied the seizures, which were followed by confusion and sometimes combativeness for as long as 30 minutes. The seizures occurred as often as six times weekly but usually occurred two or three times a week. The patient had had only minor injuries as a result of the falls. He had been taking 200 mg of carbamazepine three times daily, presumably on a regular basis, during the two weeks before this presentation. He also reported having generalized fatigue, malaise, and severe headaches. He was admitted to the Epilepsy Service.

The patient’s birth and development had been normal. He did not have a history of encephalitis or feve-
brile convulsions and did not use tobacco, alcohol, or illicit drugs. He was unmarried and, because of his symptoms, was unemployed. He resided with his brother. There was no family history of seizures or other neurologic disease.

The temperature was 36.6°C, the pulse 76, and the respirations 18. The blood pressure was 130/75 mm Hg.

A general physical examination revealed no important abnormalities. On neurologic examination, the patient was fully alert and oriented; his speech was fluent. The retinas were normal. The cranial-nerve functions were intact. Motor strength was 5/5 throughout, with normal bulk and tone. Sensation, tendon reflexes, coordination, stance, and gait were normal.

The urine was normal. Hematologic and blood chemical tests (Table 2) and a lumbar puncture (Table 1) were performed. Magnetic resonance imaging (MRI) of the head, performed without the use of contrast material, showed a focus of abnormal magnetic susceptibility in the medial portion of the left temporal lobe, as well as mucosal thickening in the right sphenoid and ethmoid sinuses. Radiographs of the chest were normal. A CT scan of the brain, obtained without the administration of contrast material, revealed a calcific lesion within the tip of the left temporal lobe (Fig. 1). A positron-emission tomographic (PET) study of the brain, performed after the intravenous injection of $^{18}$F-fluorodeoxyglucose, showed reduced accumulation in the left temporal lobe. No evidence of normal $^{18}$F-fluorodeoxyglucose uptake was observed elsewhere in the brain.

The dose of carbamazepine was reduced, and then the drug was withdrawn. Continuous video electroencephalographic monitoring for a period of five days showed six typical seizures, each of which was characterized by an initial spike, followed by rhythmic activity in the left temporal region; interictal epileptiform discharges were recorded in a similar pattern. There was no obvious background abnormality in the left temporal region.

Carbamazepine therapy was resumed at the usual dose, and the patient was discharged on the sixth hospital day. He subsequently had one or two seizures per week.

A diagnostic procedure was performed.

DIFFERENTIAL DIAGNOSIS

DR. EDWARD B. BROMFIELD*: This patient had had partial, or focal, seizures since adolescence. The tendency of these seizures to begin with the same type of aura suggests that they arose from a single cortical area. Partial seizures, which are classified as

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**Table 2. Results of Hematologic, Blood Chemical, and Serologic Studies.**

<table>
<thead>
<tr>
<th>Variable</th>
<th>At Age of 17 Yr</th>
<th>At Age of 23 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>39.3</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular volume ($\mu m^3$)</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Partial-thromboplastin time</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dl)*</td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Urea nitrogen</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>Sodium (mmol/liter)</td>
<td>139</td>
<td></td>
</tr>
<tr>
<td>Potassium (mmol/liter)</td>
<td>3.2</td>
<td></td>
</tr>
<tr>
<td>Chloride (mmol/liter)</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Carbon dioxide (mmol/liter)</td>
<td>32.3</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine (µg/ml)</td>
<td>5.9†</td>
<td></td>
</tr>
<tr>
<td>Test for IgG antibodies to toxoplasma</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Test for cysticercosis</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Test for syphilis</td>
<td>Negative</td>
<td></td>
</tr>
</tbody>
</table>

*To convert the value for glucose to millimoles per liter, multiply by 0.05551.

†The value for carbamazepine is within the therapeutic range.

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*Director, Electroencephalography Laboratory and Epilepsy Program, Brigham and Women’s Hospital; assistant professor of neurology, Harvard Medical School — both in Boston.
partial even if they become generalized, are more common than seizures generalized at onset. In patients with partial epilepsy, the temporal lobe, particularly its medial portion, is often the site at which seizures are generated. The most common underlying pathological lesion is mesial temporal sclerosis, which is characterized by a specific pattern of neuronal loss, gliosis, and axonal reorganization in the hippocampal formation, but other lesions in this region can have similar clinical manifestations. The development of modern neuroimaging techniques, beginning with CT scanning in the mid-1970s and especially MRI in the 1980s, has revolutionized our ability to identify and treat these lesions.

May we review the radiographic findings?

DR. R. GILBERTO GONZALEZ: Neuroimaging studies were performed over a period of several years. On the CT scan of the head that was obtained on admission to the Epilepsy Service, the only abnormality is a high-density, apparently calcified focus in the medial portion of the left temporal lobe (Fig. 1). The lesion appears to be unchanged from that seen on the previous CT scan. On the T₂-weighted images from the MRI studies, there is a focus of hypointensity in the same region, which is consistent with the presence of calcification.

We also performed a pulse-sequence study with sensitivity to magnetic susceptibility in order to help differentiate between the presence of blood products and calcification. The focus of hypointensity did not appear to be enlarged on the pulse-sequence study, a finding that confirmed its calcific nature. On the coronal T₁-weighted image, the calcification appeared to be near or within the left choroid fissure.

DR. BROMFIELD: Before I discuss the differential diagnosis of this lesion, I must decide whether it caused the patient's epilepsy. The first step in localizing the focus of a seizure is to take a detailed history. The ability to identify the site of onset of a seizure on the basis of clinical manifestations began with the pioneering efforts of Jackson in the late 19th century and expanded with surgical studies conducted by Penfield and colleagues in the middle of the 20th century; it has exploded during the past two decades with the increased availability of long-term video electroencephalographic recording. We have also learned, however, that clinical findings do not always pinpoint the site of a seizure, since many common manifestations of seizures reflect spread of the electrical discharge from a clinically silent cortical area. In the present case, the usual warning was a sensation of warmth on the right side of the head. Unilateral sensory phenomena (with the exception of head pain) reliably indicate a site in the contralateral hemisphere. One cannot assume, however, that within that hemisphere the seizure arose in the primary sensory cortex of the postcentral gyrus; it may instead have spread to that region from the temporal lobe or elsewhere. Even areas outside the parietal lobe, such as the second sensory area of the frontal operculum, can generate such somatosensory phenomena.

When a partial seizure begins to generalize, deviation of the head and eyes toward the right — as reported in this case — suggests that the seizure originated in the left hemisphere (although when temporal-lobe seizures do not become generalized, the head usually turns toward the side of onset of the seizure). Seizures arising from the medial temporal lobe are commonly associated with a visceral, cognitive, or psychic aura and with oral movements after loss of consciousness. Such features did not accompany this patient's seizures. Furthermore, there was no reliable history of isolated simple partial or complex partial seizures, which are almost always more frequent than secondarily generalized seizures in cases of epilepsy involving the medial temporal lobe. It is possible, however, that the patient and those around him did not remember the more subtle events.

In the hospital, the withdrawal of medication would have made secondary generalization more rapid and frequent, possibly masking the early features of the seizures. The prolonged episodes of panic that occurred several years before the current admission could have been a manifestation of simple partial seizures, but a duration of two to three days would suggest simple partial status epilepticus, a very rare condition. Furthermore, the panic did not immediately precede loss of awareness, which would be expected in the case of a true epileptic aura.

In the absence of definitive phenomenologic data, we must rely on ancillary testing, primarily electroencephalographic studies. Localization of both ictal and interictal abnormalities to the left temporal region is very helpful, and if clinical findings suggest involvement of the left hemisphere, the likelihood of a focus in the left temporal lobe is high. The presence of glucose hypometabolism in the left temporal lobe on PET, which is seen in 70 to 80 percent of patients with temporal-lobe epilepsy who have undergone surgery, also supports the possibility of a focus in the left temporal lobe. For these reasons, the calcification seen in the left medial temporal region on the MRI and CT scans is probably of causative importance. Finally, one should not be dissuaded by the small size of the lesion; even very small lesions can cause intractable epilepsy, as was illustrated at one of these discussions three years ago.

Cerebral calcification can have a metabolic, neoplastic, vascular, congenital or developmental, traumatic, or infectious or noninfectious inflammatory cause. The isolated nature of the lesion in the case under discussion, however, should allow me to narrow this list of possibilities.

Metabolic processes, such as hypoparathyroidism and other disorders of calcium and phosphorus metabolism, can result in bilateral calcification, which
typically involves the basal ganglia and can therefore be dismissed from further consideration. The same is true of other systemic diseases that are occasionally associated with cerebral calcification, such as systemic lupus erythematosus.\textsuperscript{13}

A neoplasm of low-grade malignancy must be carefully considered in this case. Tumors that are found during surgery for chronic epilepsy often lack radiologic characteristics that are typical of other tumors, including edema, mass effect, and contrast enhancement. Furthermore, their radiologic appearance does not change over the course of many years.\textsuperscript{14} The types of tumor identified on pathological examination include low-grade astrocytomas, oligodendrogliomas, gangliogliomas, and the more recently recognized dysembryoplastic neuroepithelial tumors.\textsuperscript{12,14,15} Calcification can be a manifestation of any of these tumors, especially on CT scans,\textsuperscript{16} but on MRI scans they typically appear as heterogeneous masses rather than as a uniform focus of calcification, such as that seen in the case under discussion.

Vascular lesions that may give rise to epilepsy include infarcts, primary intracerebral hemorrhages, and congenital vascular anomalies. This patient’s history rules out all but the last category, which comprises arteriovenous malformations, venous angiomas, capillary telangiectasias, and cavernous angiomas. Arteriovenous malformations consist of anomalous vessels that have the characteristics of both arteries and veins, with intervening parenchymal tissue, and that are visible on MRI or conventional angiography; MRI scans characteristically show multiple flow voids. Since these features are not present in the case under discussion, an arteriovenous malformation is unlikely, although a small, thrombosed malformation cannot be ruled out. Magnetic-susceptibility studies are helpful in cases in which vascular lesions are suspected.

Venous angiomas have a linear or radial appearance and typically do not cause seizures or calcify. Capillary telangiectasias usually appear in the brain stem and do not cause seizures. Cavernous angiomas are present in about 0.5 percent of the general population and are frequently associated with epilepsy when they are symptomatic.\textsuperscript{17} The lesions are characteristically heterogeneous and do not appear as a solid, calcified focus; typically, there is a hyperintense center with a hypointense rim, corresponding to the presence of hemoglobin-breakdown products from previous small, usually asymptomatic hemorrhages.\textsuperscript{2,17,18} Other surgically important lesions are thrombosed aneurysms of the internal carotid artery or of the circle of Willis, but these are rarely associated with epilepsy and would not be intraparenchymal at a distance from the relevant signal voids on MRI scans. In this case, therefore, the lesion is probably not of vascular origin.

Hamartomas, among other congenital lesions, can appear on CT scans as isolated, nonenhancing foci of calcification. On MRI scans, however, they usually are associated with anomalies now recognized as areas of dysplastic cortex.\textsuperscript{18}

Traumatic lesions rarely calcify, and when they do, the calcification is generally seen in an area of bleeding associated with a cerebral contusion. The history of head trauma in this case does not strongly suggest such an injury, and the density of the calcification and the absence of associated encephalomalacia make this an unlikely explanation for the lesion. Cranial irradiation is another form of trauma that can lead to cerebral calcification, but there was no history of it in this case.\textsuperscript{19}

With respect to possible infectious or noninfectious inflammatory causes of the calcified lesion, the patient’s fatigue, malaise, and headache at the time of the third presentation at this hospital raise the possibility of an active infection, although infection of the central nervous system is improbable, since the cerebrospinal fluid was normal and the lesion had been stable for many years. Among specific causes, viral, bacterial, mycobacterial, or parasitic infections merit consideration.

Multiple areas of calcification may develop after neonatal herpes or cytomegalovirus encephalitis, and a single case of an isolated, calcified temporal-lobe focus in an adult who had had herpes encephalitis has been reported.\textsuperscript{20} The history in the present case, however, does not suggest either of these viral diagnoses. There is also no clinical evidence of syphilis, which would be associated with abnormal findings in the cerebrospinal fluid and a positive serologic test, or any other bacterial process.

The possibility of a mycobacterial lesion, however, merits serious consideration. The patient’s positive tuberculin skin test indicates that he was exposed to tuberculosis, but positive tests are common among immigrants from developing countries and do not necessarily indicate the presence of symptomatic disease either at the time of the evaluation or in the past. The long course of the patient’s illness and the absence of abnormal findings in the cerebrospinal fluid eliminate tuberculous meningitis from consideration. Although isolated tuberculomas can occur, usually they are more than 2 cm in diameter and are enhanced with the use of contrast material, and they rarely calcify.\textsuperscript{21,22} Other granulomatous diseases, such as sarcoidosis, are also unlikely, given the normal cerebrospinal fluid and the absence of contrast enhancement.

Toxoplasmosis is a common parasitic disease that often results in cerebral calcification when it occurs in newborns, but there are almost always multiple calcified foci. In older children and adults, cerebral infection is usually associated with immunosuppressive disorders, particularly the acquired immunodeficiency syndrome. The lesions in those cases, however, are frequently multiple and usually enhance, and the clinical course is much shorter than that in the
present case. Trematodes such as schistosoma and paragonimus, both of which are found in Asia and Africa rather than Central America, may infect the cerebrum but typically also invade other organs, such as the liver or lungs, and usually cause seizures only in the acute stage of the disease. Giardia, a common intestinal parasite in developing countries, was found in this patient, but this organism does not cause cerebral infection.

Cysticercosis may be the most common cause of symptomatic epilepsy in the world. The disease is caused by the larval form of the pork tapeworm, *Taenia solium*, and is endemic in much of Central America and South America, as well as Asia. It is associated with poor sanitation and is acquired through consumption of infected food or by fecal-to-oral transmission. The infected food may be pork, but more commonly transmission occurs through consumption of fruits and vegetables grown in soil fertilized with contaminated pig or human waste.

*T. solium* is the only tapeworm for which humans can be both the intermediate host, harboring the larval form of the worm, and the definitive host, harboring the adult form. The embryos, or oncospheres, are ingested and absorbed through the intestinal blood vessels into the venous circulation. They pass through the lungs and then embolize systemically, ultimately lodging in skeletal muscle, the eyes, and the central nervous system. In the central nervous system, the oncospheres may lodge in the gray matter, at the junction of the gray and white matter, or in the subarachnoid space. In tissue, the embryos develop into encapsulated larval forms called cysticerci, which are filled with clear fluid and contain a viable scolex. When contaminated meat is ingested by humans, the cysticerci may attach to the intestinal mucosa and develop into mature tapeworms 2 to 8 m in length. The worms are composed of hundreds of proglottids, each of which contains oncospheres that repeat the cycle when the proglottid is shed in feces.

Cerebral lesions typically evolve from an active to a transitional form and then to an inactive form. On CT or MRI scans, the active form appears as a thin-walled, fluid-filled cyst with a mural nodule (the live scolex); it causes no inflammatory reaction. The transitional form is a more proteinaceous, encapsulated cyst with ring enhancement; this cyst becomes a transitional form and then to an inactive form. When contaminated meat is ingested by humans, the cysticerci may attach to the intestinal mucosa and develop into mature tapeworms 2 to 8 m in length. The worms are composed of hundreds of proglottids, each of which contains oncospheres that repeat the cycle when the proglottid is shed in feces.

**CLINICAL DIAGNOSIS**

Neurocysticercosis, with epilepsy.

**DR. EDWARD B. BROMFIELD’S DIAGNOSIS**

Neurocysticercosis, inactive, with temporal-lobe epilepsy.

**PATHOLOGICAL DISCUSSION**

Dr. Jean-Paul Vonsattel: The patient underwent a left temporal craniotomy. Three fragments of brain tissue were obtained from the junction of the hippocampus and the amygdala. The largest fragment was 3.5 by 2.3 by 1.7 cm. Two of these fragments were grossly normal, but the third contained a round, firm nodule, 3.0 mm in diameter, filled with granular, tan-yellow material and surrounded by a capsule and attached parenchyma.

Histopathological examination revealed a cyst (Fig. 2) that was circumscribed by a collagenous capsule, 0.2 mm thick, and attached to a portion of the hippocampus. The lumen of the cyst contained acellular, eosinophilic debris (Fig. 3), with scattered, round, basophilic concretions, as well as a dense, homogeneous, refractive cuticle that was serpentine in shape and that rested on a less dense but thicker layer stuffed with calcified particles. Beneath the second layer were spaces containing debris. The serpentine fragment was probably the remnant of a desiccated scolex,
although it was not possible to confirm the identification of the parasite.

A dense, lymphoplasmacytic infiltrate that included rare eosinophils, macrophages containing hemosiderin, and Russell bodies involved the capsule (Fig. 4) and the parenchymal vessels (Fig. 5).

The portion of the hippocampus near the capsule was gliotic, with focal neuronal loss (Fig. 6). Some of the remaining neurons were encrusted with granular, ferruginous material. There were also foci of perivascular or vascular chronic inflammation.

These findings are consistent with a diagnosis of cysticercosis involving the cerebrum, with features that are characteristically observed 2 to 10 years or even longer after infestation. The central nervous system is involved in 90 percent of cases of human cysticercosis. The presence of a single cerebral cysticercus in this case is unusual, however, since in 80 percent of the cases multiple cysts are found.

Four types of central nervous system cysts are encountered in cysticercosis. Parenchymal cysts are usually found in the cerebral cortex, including the cor-
tical–subcortical junction; the white matter is rarely involved. Meningeal cysts form in the meninges overlying the base of the brain more often than in the meninges overlying the convex surface, sometimes causing hydrocephalus and strokes. Ventricular cysts are usually located in the fourth ventricle and cause intermittent hydrocephalus and, occasionally, sudden death. Spinal cord cysts are rare.

The host can tolerate the worm as long as the embryo is alive. It usually dies two to six years after infection, and the ensuing disintegration of the parasite triggers a vigorous tissue reaction. The dead parasite eventually decays into grumose or eosinophilic, desiccated material. The final stage of this process is characterized by the presence of a calcified nodule, presumably the result of dystrophic calcification of the necrotic larva.

The patient has been free of seizures since his left temporal lobectomy.

If the development of seizures is related to an inflammatory process, how does it increase excitability?

The mechanism is not known, but one hypothesis is that the lesion disturbs the microenvironment of the surrounding neurons, either by affecting neurotransmitters or by stimulating axonal reorganization in ways that favor excitation over inhibition. Inflammation does not always accompany the lesions that cause seizures, however.

Several studies suggest that the sensitivity of serologic testing decreases considerably late in the course of the disease, especially when only a single lesion is present.

ANATOMICAL DIAGNOSES

Neurocysticercosis, left temporal lobe, end-stage, with calcification.

Epilepsy.

REFERENCES


