

CLINICAL PROBLEM-SOLVING

On the Threshold — A Diagnosis of Exclusion

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In this Journal feature, information about a real patient is presented in stages (boldface type) to an expert clinician, who responds to the information, sharing his or her reasoning with the reader (regular type). The authors' commentary follows.

A 48-year-old airline mechanic from Belize presented to the emergency department with fever and altered mental status.

Two weeks earlier, fever, myalgias, and dry cough had developed. His maximal daily temperature reached as high as 41.1°C, and one week before coming to the emergency department, the patient awakened unable to speak. At a hospital in Belize, he was febrile and aphasic without other focal neurologic findings. The results of computed tomography (CT) of the brain were normal. Examination of the cerebrospinal fluid revealed a protein level of 157 mg per deciliter and a glucose level of 44 mg per deciliter (2.4 mmol per liter) but no cells or microorganisms. The patient received treatment with chloroquine and acyclovir for the next five days but did not improve and was flown to Chicago for further care.

On examination, the patient was agitated and unable to speak or follow verbal commands. The blood pressure was 132/74 mm Hg, the pulse 82 beats per minute, and the respiratory rate 20 breaths per minute. The temperature was 39.5°C. The results of the general examination were normal, without meningismus. A neurologic examination revealed global aphasia but was otherwise normal except for an equivocal extensor plantar response on the right. The optic fundi appeared normal.

Fever with aphasia and an absence of other neurologic abnormalities suggest an inflammatory process involving a discrete area of the dominant cerebral cortex in the temporoparietal or frontal region, or both. The apparently sudden onset of aphasia suggests a vascular process, such as a septic embolism, vasculitis, or hemorrhage into an abscess or neoplasm. In a patient from Central America, neurocysticercosis must also be considered. Has the patient had seizures? Other primary infections that might occur in an immunocompetent patient include viral encephalitis (especially due to herpes simplex virus), acute disseminated encephalomyelitis, and tuberculosis — but the reported absence of cells in the spinal fluid argues against these diagnoses. Because the patient's immune status is unknown, I would also be concerned about fungal disease, toxoplasmosis, and other opportunistic infections.

I would reexamine the patient, looking particularly for signs of infective endocarditis (such as Roth's spots or splinter hemorrhages). I would also obtain additional images of the brain, preferably with magnetic resonance imaging (MRI), obtain blood cultures and malaria smears, and test for the human immunodeficiency virus (HIV).

The white-cell count was 10,300 per cubic millimeter, with 80 percent polymorphonuclear leukocytes. The hematocrit, platelet count, electrolyte levels, levels of urea nitrogen and creatinine, liver-enzyme levels, smears for malaria, and results of the urinalysis, toxicologic screen, chest radiography, and the test for HIV were normal. Blood cultures were obtained. The findings on contrast-enhanced CT of the brain were normal.

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Examination of cerebrospinal fluid revealed 15 red cells and 30 white cells per cubic millimeter (21 lymphocytes and 9 neutrophils); the protein level was 140 mg per deciliter, the glucose level 33 mg per deciliter (1.8 mmol per liter), and the serum glucose level 100 mg per deciliter (5.5 mmol per liter). But the results of Gram's staining, a smear for acid-fast bacilli, India-ink preparation, and a test for cryptococcal antigen were negative.

The patient was hospitalized, and treatment was begun with intravenous ceftriaxone, vancomycin, and acyclovir.

The normal results of the patient's imaging studies are perplexing. A cortical infarct, abscess, or mass should be visible by now, one week after the onset of aphasia. Is it certain that the patient is aphasic? Mutism associated with cerebellar or brain-stem disease (for which CT may be a less reliable method of diagnosis) can be confused with aphasia.

Lymphocytic pleocytosis with hypoglycorrachia suggests tuberculous, fungal, or carcinomatous meningitis, any of which can cause stroke due to contiguous vascular involvement. Has the patient lost weight or had prior systemic symptoms?

I would immediately perform MRI of the brain and a tuberculin skin test. In addition to bacterial, fungal, and mycobacterial cultures, I would test the cerebrospinal fluid with the polymerase chain reaction (PCR) for herpes simplex virus and *Mycobacterium tuberculosis*. Pending the results of these studies, broad-spectrum antibiotics, including acyclovir, should be continued.

A neurology consultant agreed that the patient was globally aphasic, with no other focal neurologic findings. MRI of the brain revealed increased signal intensity along the left sylvian fissure and the adjacent left frontal lobe, with localized leptomeingeal enhancement (Fig. 1). The neuroradiologist's impression was that the focus of the differential diagnosis should be "meningoencephalitis versus vasculitis."

Additional information was obtained. Three months before the current illness, the patient had been aphasic for several days without other symptoms. At that time, he was flown to Houston, where MRI abnormalities in the left frontal cortex were reported as "consistent with possible vasculitis." He was treated with phenytoin prophylactically. His aphasia subsequently resolved, and he stopped taking phenytoin one month later. In the ensuing

six weeks before his current presentation, he was reportedly well.

His history was otherwise remarkable only for infrequent migraine headaches that occurred over a period of 20 years, without associated neurologic symptoms, and recurrent oral ulcers. He did not use tobacco, alcohol, or drugs. He had not lost weight.

A relapsing course of symptoms such as the patient had over three months argues against most of the infectious disorders initially considered. Noninfectious inflammatory processes, such as sarcoidosis or vasculitis, are possible. The history of oral ulcers is intriguing, but no other clinical findings suggest systemic lupus erythematosus or Behcet's disease. Giant-cell arteritis is very improbable in a patient of this age. Primary central nervous system (CNS) angiitis, a granulomatous vasculitis limited to the nervous system that may cause either focal or diffuse neurologic impairment (and lymphocytic pleocytosis), is rare but must be considered.

I would perform tests for antinuclear and anti-neutrophil cytoplasmic antibodies and also try to obtain further information about the patient's previous evaluations in Houston and Belize. If initial cultures are negative, I would repeat the lumbar puncture.

On the second through fifth hospital days, the patient had a temperature as high as 40.0°C. The results of a neurologic examination showed no change.

Blood and cerebrospinal fluid cultures revealed no growth after 72 hours. Transesophageal echocardiography showed no abnormalities. Tests of serum and cerebrospinal fluid for syphilis and a tuberculin skin test were negative. Assays for toxoplasma IgG and *Borrelia burgdorferi* antibodies were negative. An electroencephalogram showed nonspecific diffuse slowing. The results of tests for antinuclear and anti-neutrophil cytoplasmic antibodies, protein electrophoresis, and evaluation of complement levels were normal. The sedimentation rate was 69 mm per hour.

On the sixth hospital day, a repeated lumbar puncture showed 130 red cells and 510 white cells per cubic millimeter (61 percent lymphocytes and 39 percent neutrophils), with negative results on Gram's staining, an acid-fast smear, an India-ink preparation, and cytologic evaluation. Protein and glucose levels in the cerebrospinal fluid were not

measured; oligoclonal bands were absent. Ceftriaxone and vancomycin were discontinued. A treatment regimen of isoniazid, rifampin, pyrazinamide, ethambutol, and pyridoxine was begun.

Considering the diagnostic importance of hypoglycorrachia in a febrile patient with lymphocytic pleocytosis, the level of glucose in the spinal fluid should be measured again. Fungal meningitis is very improbable in an immunocompetent patient. A prolonged, relapsing clinical course is unusual in tuberculous or carcinomatous meningitis, but I agree with the recommendation of empirical antituberculosis treatment, and I would search for a primary cancer.

CT of the neck, chest, abdomen, and pelvis revealed no abnormalities. The serum level of angiotensin-converting enzyme (ACE) was normal.

Cerebrospinal fluid PCR tests were negative for *M. tuberculosis*, cytomegalovirus, the Epstein-Barr virus, herpes simplex virus, herpes zoster virus, and enteroviruses. Tests of serum for antibodies to the California, eastern equine, western equine, and St. Louis encephalitis viruses were negative. Acyclovir was discontinued.

On the sixth through ninth hospital days, the patient's condition remained unchanged. His temperature was as high as 40°C daily, and he remained unable to communicate. Treatment with doxycycline was begun, pending the results of serologic studies for rickettsia and brucella.

The normal results on CT imaging of the body reaffirm the probability that the disease is limited to the brain. A normal serum level of ACE does not rule out the diagnosis of sarcoidosis, but isolated CNS sarcoid is very rare. Coverage with doxycycline is appropriate because the patient's clinical findings and cerebrospinal fluid findings are consistent with brucellosis. Rickettsial diseases seem highly improbable, with the possible exception of Q fever (caused by *Coxiella burnetii*).

Unless the patient has a dramatic response to the current antibiotic therapy, I would push for brain biopsy. I doubt that cerebral angiography would be definitive.

On the 10th hospital day, cerebral arteriography revealed marked attenuation, narrowing, and irregularities of the left middle and anterior cerebral arteries, with decreased parenchymal blush (small-

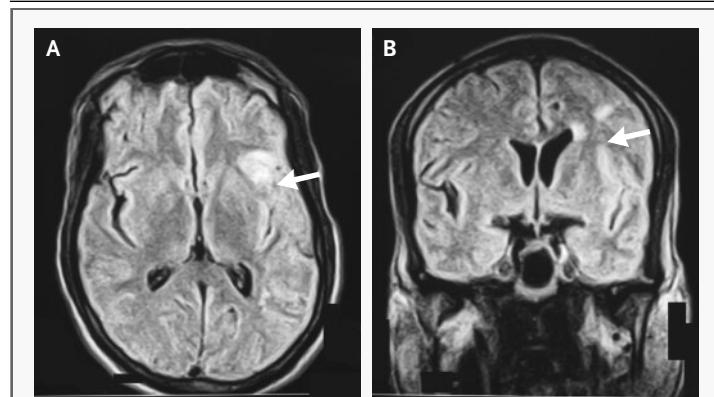


Figure 1. Axial (Panel A) and Coronal (Panel B) Magnetic Resonance Images of Left Frontotemporal Parietal Abnormality (Arrows).

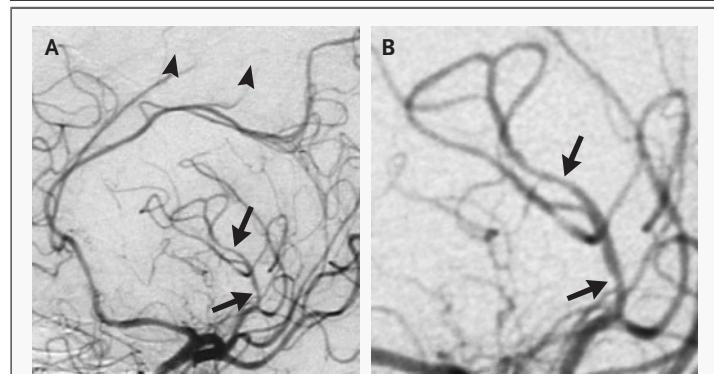


Figure 2. Cerebral Angiogram.

Panel A shows irregular narrowing of the middle cerebral artery (arrows) and decreased parenchymal blush in the distribution of the middle and anterior cerebral arteries (arrowheads). Panel B is a magnification of the same area.

vessel perfusion) in those regions (Fig. 2). The neuroradiologist's impression of the findings was "focal asymmetric cerebral angiitis, primary versus secondary to meningoencephalitis." Treatment with felodipine was begun.

The angiographic findings correlate with the patient's clinical findings, but the underlying cause of the vascular abnormalities remains unclear. We must consider systemic vasculitides, drug-induced vasculitis (e.g., due to amphetamines), and neoplasms (including lymphoma), but none of these diagnoses seem likely. The patient's high fever — not a common finding in primary CNS angiitis —

mandates that we rule out infection with vasculotropic organisms such as herpesviruses, fungi, and other organisms, including *M. tuberculosis*, that are known to cause secondary CNS angiitis.

On hospital days 10 through 17, the patient's temperature spiked to 40°C daily despite antituberculosis therapy and treatment with doxycycline, phenytoin, and felodipine. He remained aphasic. All cultures were negative.

On hospital day 18, intravenous methylprednisolone therapy was begun for probable primary CNS angiitis, on the advice of a consulting rheumatologist. The neurology consultant recommended brain biopsy.

The patient has shown no signs of improvement after almost two weeks of broad-spectrum antibiotic therapy, and the diagnosis remains unclear. As I have already noted, I agree with the recommendation for brain biopsy.

On hospital day 19, an open left-frontal brain biopsy was performed. Grossly, the dura was thickened and adherent to the arachnoid and the pia. The adjacent cerebral cortex was noted to feel rubbery. Biopsy specimens were obtained from the cortex and leptomeninges.

During the next 48 hours, low-grade fever (38.3°C) persisted, but the patient's condition appeared improved, and he began to speak haltingly. Serum titers of antibodies to rickettsia and brucella were negative. Doxycycline was stopped.

Microscopical examination of biopsy specimens revealed noncaseating granulomas and an intense lymphocytic infiltrate involving small blood vessels, the leptomeninges, and the adjacent cerebral cortex (Fig. 3). Tissue and cerebrospinal fluid smears for bacteria, acid-fast bacilli, parasites, fungi, and malignant cells were negative. PCR testing was negative for *M. tuberculosis*, cytomegalovirus, herpes simplex virus, varicella-zoster virus, human herpesvirus 6, and JC and BK viruses.

We have now done all we can to make a diagnosis. The granulomatous histologic findings are non-specific. However, I believe we can rule out viral, fungal, and rickettsial causes with confidence. Given the patient's relapsing clinical course; the negative tuberculin test, acid-fast smears, and DNA tests on multiple spinal-fluid and brain-tissue specimens; and the lack of clinical improvement after

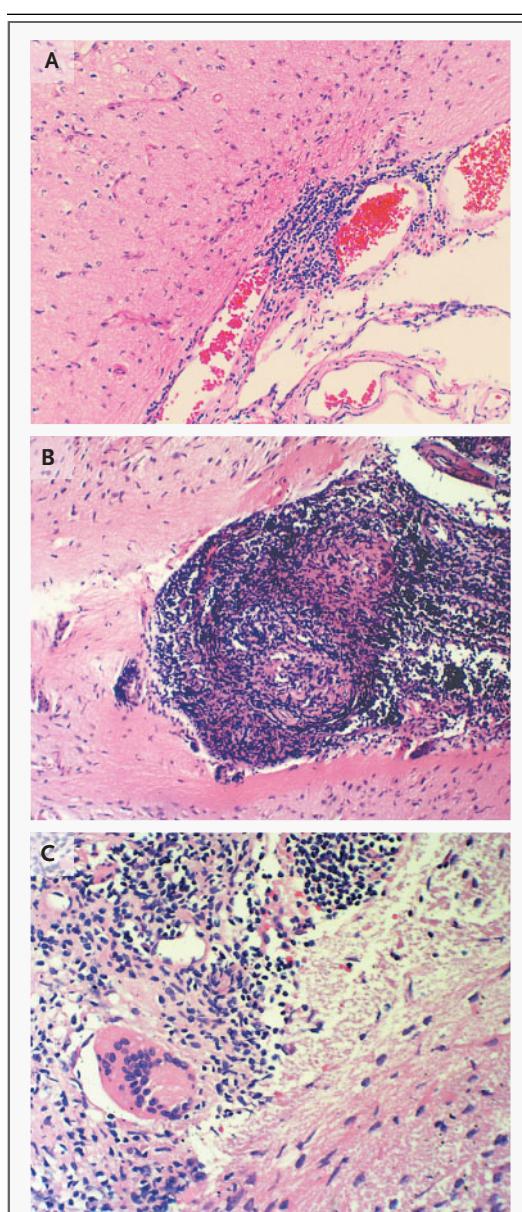


Figure 3. Brain-Biopsy Specimen (Hematoxylin and Eosin).

Panel A shows a lymphocytic infiltrate involving the leptomeninges, adjacent cerebral cortex, and small blood vessels with noncaseating granulomas. Panels B and C show higher-power magnifications of the granulomas.

two weeks of antituberculosis therapy, the diagnosis of tuberculosis seems so unlikely that I believe that empirical antituberculosis therapy can be discontinued. There is no evidence of neoplasm or systemic vasculitis. By a process of exclusion, primary CNS angiitis is the most likely diagnosis.

I would treat the patient with corticosteroids and follow his response clinically and with MRI.

During the following week, the patient's fever resolved, and he became more interactive verbally, but he remained markedly dysphasic (with poor comprehension, repetition, and naming facilities). Treatment with prednisone (60 mg daily) and the antituberculosis therapy were continued. The results of bronchoscopic biopsy and transbronchial biopsies were normal. In light of the patient's persistent severe verbal disability, the rheumatology consultant recommended the addition of high-dose cyclophosphamide therapy for primary CNS angiitis. The consultants in neurology and infectious diseases agreed but also recommended full antituberculosis treatment for 12 months.

An intravenous infusion of 1300 mg of cyclophosphamide was given.

The evidence to support the addition of cyclophosphamide as first-line therapy for primary CNS angiitis is not strong. In this case, the patient's condition is already improving, and we must consider the potential toxicity of cyclophosphamide. My recommendation would be to treat with corticosteroids alone and follow the patient carefully.

All cultures remained negative. On hospital day 35, the patient was discharged to his home in Belize while receiving daily prednisone and antituberculosis therapy, with plans for a second infusion of high-dose cyclophosphamide in the next month. At the time of discharge, he appeared greatly improved but remained dysphasic.

Three weeks later, the laboratory reported positive cerebrospinal fluid cultures for isoniazid-sensitive *M. tuberculosis*. Cultures of brain and lung tissue were sterile. Cyclophosphamide was stopped. Antituberculosis therapy was continued, and prednisone therapy was tapered gradually.

One year later, the patient is doing well.

Hats off to those who insisted on treatment for tuberculosis despite the patient's unusual clinical presentation and multiple negative tests. That decision may well have been lifesaving.

COMMENTARY

During the primary infection, *M. tuberculosis* disseminates widely before cell-mediated immune mech-

anisms either kill or contain the organisms.¹ In the latter event, caseous tubercles containing live bacilli (so-called Rich foci) can be found in the CNS many years after the primary infection.² If one of these foci ruptures, typically when host immunity wanes, tuberculous meningitis (rupture into the ventricle or subarachnoid space) or tuberculoma (rupture into the brain or spinal cord) will develop. We speculate that our patient's initial aphasia resulted from rupture of a caseous tubercle into his frontotemporal cortex. After improving temporarily, he worsened as the infection and local inflammatory response spread to involve the adjacent blood vessels and meninges.

This clinical syndrome — tuberculous meningoencephalitis with granulomatous vasculitis — is rarely seen today in immunocompetent adults native to North America. However, it remains an important concern in people living in or emigrating from countries with a high prevalence of tuberculosis.³ The prevalence of tuberculosis in Belize, for example, is about 10 times that in the United States.

The diagnosis of CNS tuberculosis is notoriously difficult to make.¹ Half of afflicted patients show no clinical signs of pulmonary (or other extraneuronal) involvement. Typical symptoms (e.g., headache and low-grade fever) are nonspecific. Progressive worsening is the rule, but relapsing clinical courses, as in this patient, have been reported.⁴ Abnormal neurologic findings may be absent (in stage 1 disease) or striking (stupor, coma, or dense hemiplegia in stage 3 disease), but most patients present with stage 2 disease, accompanied by signs (confusion, cranial-nerve palsies, or hemiparesis) that mimic many other disorders.^{5,6} Abnormalities on CT and MRI scanning are common (in 70 to 80 percent of patients) but nonspecific; hydrocephalus, meningeal or parenchymal enhancement, mass lesions, or infarction may be seen.^{7,8} Cerebrospinal fluid may be normal on examination early in the clinical course, and 25 percent of patients never have what would be considered the classic cerebrospinal fluid profile (lymphocytic pleocytosis, elevated protein levels, and low glucose levels). Smears for acid-fast bacilli in cerebrospinal fluid are positive in only 20 percent of cases,¹ and the sensitivity of PCR testing (30 to 80 percent) has been disappointing.^{9,10} The gold standard test — spinal-fluid culture for *M. tuberculosis* — requires several weeks to complete and is negative in as many as half of all patients who improve

clinically with antituberculosis treatment. Thus, the diagnosis requires both a high index of suspicion and the knowledge that, as Zuger and Lowy have stated, "All pre-mortem means of diagnosing [CNS tuberculosis] must be assumed to be fallible."¹

As the discussant noted, primary CNS angiitis is very rare; there were only 108 cases reported in the English-language literature over a 40-year period.^{11,12} Such so-called zebra diagnoses should always prompt skepticism, because a common presentation of a rare disease is less likely than a rare presentation of a common disease. This rule of thumb is especially germane to our case, because primary CNS angiitis is a diagnosis of exclusion: it cannot be made until all other secondary causes are disproved, especially infectious diseases, such as tuberculosis, that may worsen if treated mistakenly with corticosteroids alone. Fortunately for our patient, his physicians knew this. Untreated CNS tuberculosis is invariably fatal. With treatment, 70 to 85 percent of patients survive, half of them with no residual neurologic disability.⁵

Even if primary CNS angiitis were considered

the more probable diagnosis, a "threshold approach" to clinical problem-solving could have avoided the discussant's (potentially disastrous) treatment error in this case.¹³ Under conditions of diagnostic uncertainty, empirical treatment is indicated for all diagnoses whose probability exceeds their treatment threshold. (This term refers to the probability of disease at which there is no clear advantage for either empirical treatment or no treatment.) For CNS tuberculosis, this threshold probability is very low because the potential harm of antituberculosis drugs is very small (risk of fatal hepatitis, approximately 0.1 percent)¹⁴ and their potential benefit very great.⁵ In other words, empiric antituberculosis treatment should be given even if the probability of CNS tuberculosis is very low and another diagnosis seems more plausible. Once this critical decision is made to "cover" the patient for tuberculosis, the decision also to begin corticosteroid treatment is an easy one. Corticosteroids are not only the mainstay of treatment for primary CNS angiitis¹²; they are also recommended (as adjunctive treatment) for CNS tuberculosis.¹⁵

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