Whipple’s disease presenting with isolated neurological symptoms

Case report

ADAM P. BROWN, M.D., JUDY C. LANE, M.D., SHIGEO MURAYAMA, M.D., AND DENNIS G. VOLLMER, M.D.

Department of Neurosurgery, Washington University School of Medicine, St. Louis, Missouri; and Division of Neurological Surgery, Department of Neurology, and Division of Neuropathology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

Whipple’s disease is infrequently considered in the differential diagnosis of patients presenting with progressive neurological deterioration. This is in part a result of the relative rarity of this entity and in part due to the more frequent initial presentation of the disease with gastrointestinal, musculoskeletal, or cardiovascular symptoms. A case is described in which the neurological symptoms of progressive dementia and weakness were seen in the relative absence of non-neurological symptomatology. The diagnosis of Whipple’s disease was made from a brain biopsy. The neuropathology of Whipple’s disease of the central nervous system is described and the importance of considering it as a treatable entity in the differential diagnosis of progressive neurological deterioration, despite the absence of systemic symptomatology, is stressed.

KEY WORDS • Whipple’s disease • dementia • brain biopsy

ALTHOUGH Whipple’s disease is generally recognized as a multisystem chronic granulomatous disease preferentially involving the digestive system, it can present as a primary neurological disorder in rare cases.1,8,9,21 With this presentation, the most common neurological symptoms include progressive dementia, ophthalmoplegia, seizures, myoclonus, gait disturbance, hypothalamic dysfunction, and coma. When confined to the central nervous system (CNS) or when systemic spread includes the CNS, Whipple’s disease can exhibit a fulminant course.1 Diagnosis with rapid and appropriate treatment is imperative at this time since the disease usually progresses to death within 6 to 12 months;1,9,10 death has been reported as early as 1 month after the onset of symptoms.10 Unfortunately, the diagnosis of CNS Whipple’s disease cannot be ascertained and confirmed noninvasively.

We present a case of primary CNS Whipple’s disease with a complex clinical course, ultimately diagnosed by brain biopsy. We emphasize the importance of considering Whipple’s disease in the differential diagnosis of progressive atypical dementia and discuss the pertinent neuropathological findings in this disorder.

Case Report

This 45-year-old white man was referred to the neurosurgical service at North Carolina Memorial Hospital (NCMH) with a 2-year history of progressive dementia, weakness, ataxia, and weight loss. He presented initially with complaints of impotence and insomnia. Two weeks before that he had noted the onset of diffuse weakness.

Examination. Physical examination was remarkable for a II/VI systolic ejection murmur. Neurological examination demonstrated a “bizarre” affect, dysarthria, end-gaze nystagmus, hyperreflexia, bilateral Babinski signs, dysmetria, and a wide-based gait. Laboratory studies revealed anemia, an elevated erythrocyte sedimentation rate, mildly elevated liver function tests, a negative hepatitis screen, and a negative dementia screen (B12, folate, thyroid panel, heavy metals). The patient was started on a course of ferrous sulfate.

Course. Seven months later he was admitted to his local hospital with headache, mental status changes, ataxia, anorexia, and diarrhea. Examination revealed a deficit of recent memory and marked worsening of
gait. Opening pressure on lumbar puncture was 23 cm H₂O. Total nucleated cells were 80/high-powered field with 90% polymorphonuclear cells. Cerebrospinal fluid (CSF) analysis revealed a protein level of 72 mg/dl and a glucose content of 45 mg/dl. Electromyography and nerve conduction velocities demonstrated a demyelinating polyneuropathy with chronic reinnervation changes. Magnetic resonance (MR) imaging revealed diffuse cerebral atrophy and an increase of signal intensity in the pons and brachium pontis on T₂-weighted images. Broad-spectrum antibiotics were instituted for 1 week, although final CSF bacterial, mycobacterial, and fungal cultures were negative. A tentative diagnosis of demyelinating disease was made.

Three months later the patient was once again admitted to the hospital. There had been a rapid decline in his mental function and he had become hostile. Low-grade fevers had been present, and his weakness and weight loss continued. Pertinent findings on neurological evaluation included proximal muscle weakness, persistent CSF pleocytosis without oligoclonal bands, and increased serum angiotensin converting enzyme (ACE) levels. Serological studies for human immunodeficiency virus and syphilis were negative. A tuberculin skin test was nonreactive. An electrocardiogram showed a new left bundle branch block, and an echocardiogram revealed aortic valve thickening with mild insufficiency. Biopsy of bone marrow and an erythematous plaque on the left hip demonstrated multiple noncaseating granulomas. A chest x-ray film revealed biapical pleural thickening. He was started on a course of prednisone for presumed sarcoidosis and antituberculin therapy pending cultures.

One month later the patient began to experience seizures and was readmitted. He was postictal on examination but otherwise unchanged. Electroencephalography revealed periodic epileptiform discharges in the right hemisphere. His seizures were clinically controlled with phenytoin. Antituberculin therapy was discontinued after cultures were found to be negative. Prednisone was stopped because of the lack of clinical evidence for sarcoidosis.

Over the next several months the patient became more aggressive and belligerent. He was referred to the neurosurgical service at NCMH. Examination revealed a II/VI systolic murmur, a new soft diastolic murmur, and continued decline in mental status, strength, and gait. The CSF analysis was unchanged except that ACE levels had normalized. Cerebral MR imaging revealed a focal lesion with high signal intensity in the right temporal lobe on T₂-weighted images (Fig. 1). Cerebral angiography revealed no evidence of vasculitis or significant large vessel stenosis. Echocardiogram demonstrated worsened left ventricular function.

In the context of progressive neurological deterioration without a definitive diagnosis, the patient was taken to the operating room for a right temporal leptomeningeal biopsy. The area of biopsy included the region of high signal intensity noted on the preceding MR image. No perioperative complications occurred.

Pathological Examination. The biopsy tissue consisted of leptomeninges, cortex, and white matter. The specimen was prepared for frozen sections, smears, and permanent sections for both light and electron microscopy. On light microscopy, smear specimens demonstrated perivascular accumulation of macrophages. The macrophages had multilobulated lumina and were stuffed with yellow granules. Lymphocytes were also present. Frozen section analysis demonstrated leptomeningeal infiltration by inflammatory cells. The gray and white matter showed considerable gliosis. Frozen section diagnosis was leptomeningitis with gliosis of the brain, which was confirmed on the permanent sections; however, numerous macrophages were noted in the leptomeninges, cerebral cortex, and white matter. The macrophages contained intensely periodic acid-Schiff (PAS)-positive material which was perivascular in distribution (Fig. 2). These macrophages were also intensely positive with methenamine-silver, but negative with Ziehl-Neelsen stain for acid-fast bacilli and Brown-Brenn Gram stain.

Epon-embedded toluidine blue-stained semithin sections, prepared for electron microscopy, demonstrated gliotic gray matter with perivascular accumulation of macrophages containing multiple intracytoplasmic osmiophilic dark granules. Ultrastructurally, these dark granules consisted of lipofuscin and unique membrane-bound inclusions containing numerous membranous profiles (Fig. 3). Transitional forms from these unique inclusions to lipofuscin were also observed (Fig. 3 left). Whipple's disease bacilli were not present.

The neuropathological diagnosis was that of partially treated cerebral Whipple's disease.
Whipple’s disease with isolated neurological symptoms

**Discussion**

Whipple’s disease is named for George H. Whipple who first described an intestinal lipodystrophy in 1907. Subsequently, the disease has become known as a multisystem chronic granulomatous disorder. Most often it presents with weight loss (in 70% to 100% of cases), diarrhea (in 70% to 80% of cases), acute polyarthritis (in 50% to 90% of cases), abdominal pain (in 50% to 70% of cases), hypotension (in 60% to 65% of cases), cardiopathy (in 40% to 60% of cases), lymphadenopathy (in 45% to 55% of cases), and hyperpigmentation (in 25% to 50% of cases). A 6:1 male predominance exists, with the peak age of onset at 40 to 49 years.

Whipple’s disease confined to the CNS is a rare occurrence. This presentation is seen in less than 5% of all cases of Whipple’s disease. The triad of progressive dementia, myoclonus, and external ophthalmoplegia (with sparing of the pupils) is highly suggestive of the diagnosis. Hypothalamic involvement is also common, including insomnia/hypersomnia, hyperphagia, and polydipsia. Schwartz, et al., stated that convergence nystagmus is virtually diagnostic of CNS Whipple’s disease.

The confusing and nonspecific clinical presentation seen here is typical for primary CNS Whipple’s disease. The slowly progressive dementia was the most prominent aspect of the clinical course. However, other signs and symptoms consistent with CNS Whipple’s disease were also present. These included weakness, ataxia, seizures, nystagmus, dysmetria, weight loss, and hypothalamic dysfunction. Prospectively, the systemic man-

![Image](https://example.com/image1.png)

**Fig. 2.** *Left:* Photomicrograph demonstrating numerous macrophages in the leptomeninges (M), and brain parenchyma. Prominent perivascular cuffing (asterisk) is evident. PAS. *Right:* High magnification of the area indicated by the asterisk shown left. PAS.

![Image](https://example.com/image2.png)

**Fig. 3.** *Left:* Electron micrograph of the biopsy specimen revealing a macrophage around a blood vessel. Lipofuscin (L), unique membrane-bound inclusions with numerous membranous profiles (arrowheads), and transitional forms (arrows), are ubiquitous. *Right:* Higher magnification of the unique membranous inclusion shown left. Dense bodies (D) are present in the middle of the membranous profiles.
ifestations were few. Fever and weight loss were the primary symptoms; diarrhea, hyperpigmentation, and anemia were also noted. Cardiac involvement was present, manifested by the development of murmurs and worsening echocardiograms.9,14,17

Throughout the lengthy evaluation of this patient, a number of other diagnoses were entertained. Granulomatous disease, both sarcoïdosis and tuberculosis, was suggested by elevated serum ACE levels, along with granulomas of the skin and bone marrow. Demyelinating disease was also suspected based on the multiplicity of the neurological findings and the white matter changes on MR images. Finally, other forms of infectious disease were suggested by fevers and CSF pleocytosis.

Because of the progressive nature of the neurological deterioration in the absence of a definitive diagnosis, a brain biopsy was obtained. The biopsy revealed the diagnostic features of CNS Whipple’s disease: 1) accumulation of macrophages staining intensely with PAS and methenamine-silver but negative for acid-fast bacilli staining, and 2) ultrastructural demonstration of unique membrane-bound inclusions at different stages of degradation.3

Recent evidence suggests that the granulomatous infiltrations are a direct and specific reaction to the Whipple’s disease bacillus. Delayed hypersensitivity is thought to be the underlying mechanism for granuloma formation.25 During active disease, electron microscopy of affected tissue reveals bacillus-like inclusions within macrophages, as well as free bacilli in the infected area. After appropriate antibiotic therapy, a unique membrane-bound inclusion replaces the bacterial-like inclusion. Bacilli are no longer seen, but PAS positivity remains. The PAS-positive material probably represents undigested bacterial wall fragments, although various theories have been proposed for the staining characteristics.2,12,16 Our patient was treated intermittently with broad-spectrum antibiotics and antituberculous agents. His subsequent biopsy was consistent with partially treated Whipple’s disease.2,16

As in all previous cases, no organism was cultured. Researchers have theorized that the inability to culture the bacillus is due to an outer membrane external to the cell wall of the Whipple’s disease bacillus.7

The mechanism for Whipple’s dementia has not been well characterized. Neuronal involvement by the bacillus has been described by Sieracki, et al.,25 although it is infrequent. Other authors have spoken of involvement with microglia.13,20,21 Lampert, et al.,13 noted that stuffed microglia frequently surround nerve cells causing a definite loss of neurons.13 Furthermore, granulomas have been noted to destroy brain parenchyma and cause moderate gliosis.26 The cause of dementia is perhaps due to this disruption of brain tissue.

A progressive demyelinating peripheral neuropathy has been described infrequently in Whipple’s disease.8 Neurophysiology demonstrated demyelination in this patient. The MR images suggested central demyelinat-

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Address reprint requests to: Adam P. Brown, M.D., Department of Neurosurgery, Washington University School of Medicine, Campus Box 8057, 660 South Euclid Avenue, St. Louis, Missouri 63110.