

Intracerebral Whipple's Disease Diagnosed by Stereotactic Biopsy: A Case Report and Review of the Literature

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OBJECTIVE AND IMPORTANCE: This case demonstrates the rare occurrence of intracerebral Whipple's disease in a patient lacking classic systemic manifestations of the disease. Because of the nonspecific presentation and the typically deep-seated location of cerebral lesions in these patients, definitive diagnosis is frequently problematic. We present the first reported use of stereotaxy-guided brain biopsy to confirm the diagnosis of isolated intracranial Whipple's disease.

CLINICAL PRESENTATION: The patient was a 36-year-old man who presented with a 4-month history of progressive lethargy, hypersomnia, behavioral changes, and weight gain. The results of the physical examination were remarkable only for findings of hypogonadism. Subsequent laboratory evaluation confirmed the diagnosis of hypogonadotrophic hypogonadism, with low levels of testosterone, luteinizing hormone, cortisol, and prolactin.

INTERVENTION: A magnetic resonance image of the brain demonstrated hyperintense lesions on T2-weighted images in the regions of the right fornix, hypothalamus, and putamen that subsequently enhanced with intravenously administered contrast medium. A biopsy was then obtained from the right putaminal lesion under stereotactic guidance. Histopathological analysis of the tissue revealed findings consistent with intracerebral Whipple's disease that were subsequently confirmed using electron microscopy.

CONCLUSION: Intracerebral Whipple's disease should be included in the differential diagnosis of patients presenting with progressive dementia and cognitive decline. In these patients, lesions have typically been observed in the hypothalamus, cingulate gyrus, basal ganglia, insular cortex, and cerebellum. As evidenced by our case, stereotaxy affords clinicians the attractive option of a minimally invasive technique by which to obtain tissue from such deep-seated areas. A review of this rare neurosurgical entity is presented. (Neurosurgery 44:203-209, 1999)

Key words: Brain biopsy, Dementia, Hypogonadism, Stereotaxy, Whipple's disease

Whipple's disease is characterized by a widespread chronic granulomatous infiltration of the gastrointestinal, cardiac, pulmonary, and nervous

systems. Originally described in 1907 as "intestinal lipodystrophy," this entity is now recognized as an infectious disorder caused by the rod-shaped bacillus

Tropheryma whippelii. Central nervous system (CNS) involvement is well described in systemic Whipple's patients and occurs in 10 to 20% of cases (8). On rare occasions, neurological manifestations may be the first and only herald of the disease process. The nonspecific symptomatology combined with the rarity of this entity often leads to difficulties and delays in the management of these patients. We present a rare case of isolated intracerebral Whipple's disease that ultimately required stereotaxy-guided brain biopsy before definitive diagnosis and treatment could be rendered.

CASE REPORT

A 36-year-old right-handed Greek man presented with a 4-month history of generalized lethargy, behavioral changes, and brief sporadic periods of hypersomnia. These were described as episodes of spontaneous sleep onset with speech arrest and unarousability. His family reported that the patient also had become increasingly withdrawn, unmotivated, and listless during the previous 3 months. No history of nausea, vomiting, bowel or bladder incontinence, fever, chills, or trauma was reported. There were no episodes of rhythmic or stereotyped movements noted. He denied any significant previous medical problems and was in a state of good health before the onset of symptoms. He was receiving no medications and denied any recreational drug or alcohol consumption. He did report a weight gain of 20 to 30 pounds during a period of 2 months as well as a 2-month history of impotence and decreased libido.

At admission, the patient was afebrile and normotensive. A neurological examination revealed Cranial Nerves II through XII to be intact. The results of a fundoscopic examination were unremarkable, without evidence of papilledema. Although the patient was drowsy and had a blunted affect, he was able to fully cooperate with the examination. No sensory or motor deficits were discovered. All reflexes were brisk. The patient's gait was steady, and the results of his

Romberg test were negative. No evidence of cerebellar dysfunction was elicited. The results of the physical examination were significant only for features of hypogonadism (decreased size of testes, loss of muscle mass).

An endocrinological consultation was thus obtained. Hormonal assay demonstrated an abnormally low serum testosterone level of 42 ng/ml (normal range, 270-1070 ng/ml). Cortisol, prolactin, and luteinizing hormone levels were similarly depressed (0.8-1.8 ng/dl). The remainder of the laboratory examination showed a mild anemia, a negative dementia panel (B12, folate, thyroid panel, heavy metals), normal liver functions tests, negative hepatitis and human immunodeficiency virus panels, and a mildly elevated erythrocyte sedimentation rate of 30. Analysis of the cerebrospinal fluid (CSF) revealed a mild pleocytosis, with negative results of the Venereal Disease Research Laboratory test and cryptococcus, toxoplasmosis, coccidiomycosis, India ink, fungal, and bacterial cultures. An electroencephalogram revealed only mild diffuse slowing, without focal ictal activity.

Magnetic resonance imaging (MRI) of the brain demonstrated abnormal hyperintense signal in the columns of the fornix and hypothalamic region, without mass effect on the T2-weighted images. Postcontrast T1-weighted magnetization transfer images demonstrated abnormal enhancement of the right putamen and right column of the fornix and an enhancing mass within the hypothalamic region (Fig. 1-3). A postcontrast computed tomographic (CT) scan of the brain demonstrated similar results. A contrast-enhanced computed tomography-guided stereotactic biopsy of the lesion in the right putamen was performed with the patient under local anesthesia (Fig. 4). The patient tolerated the procedure well, without any new neurological deficits.

At stereotactic biopsy, two pieces of tissue were obtained. One-half of the first piece was used for smear preparation and showed reactive gliosis with macrophage and lymphocytic infiltration. Because of a pathological suspicion of Whipple's disease, the remaining half of the first piece was submitted in glutaraldehyde for electron microscopy and the second piece was submitted for

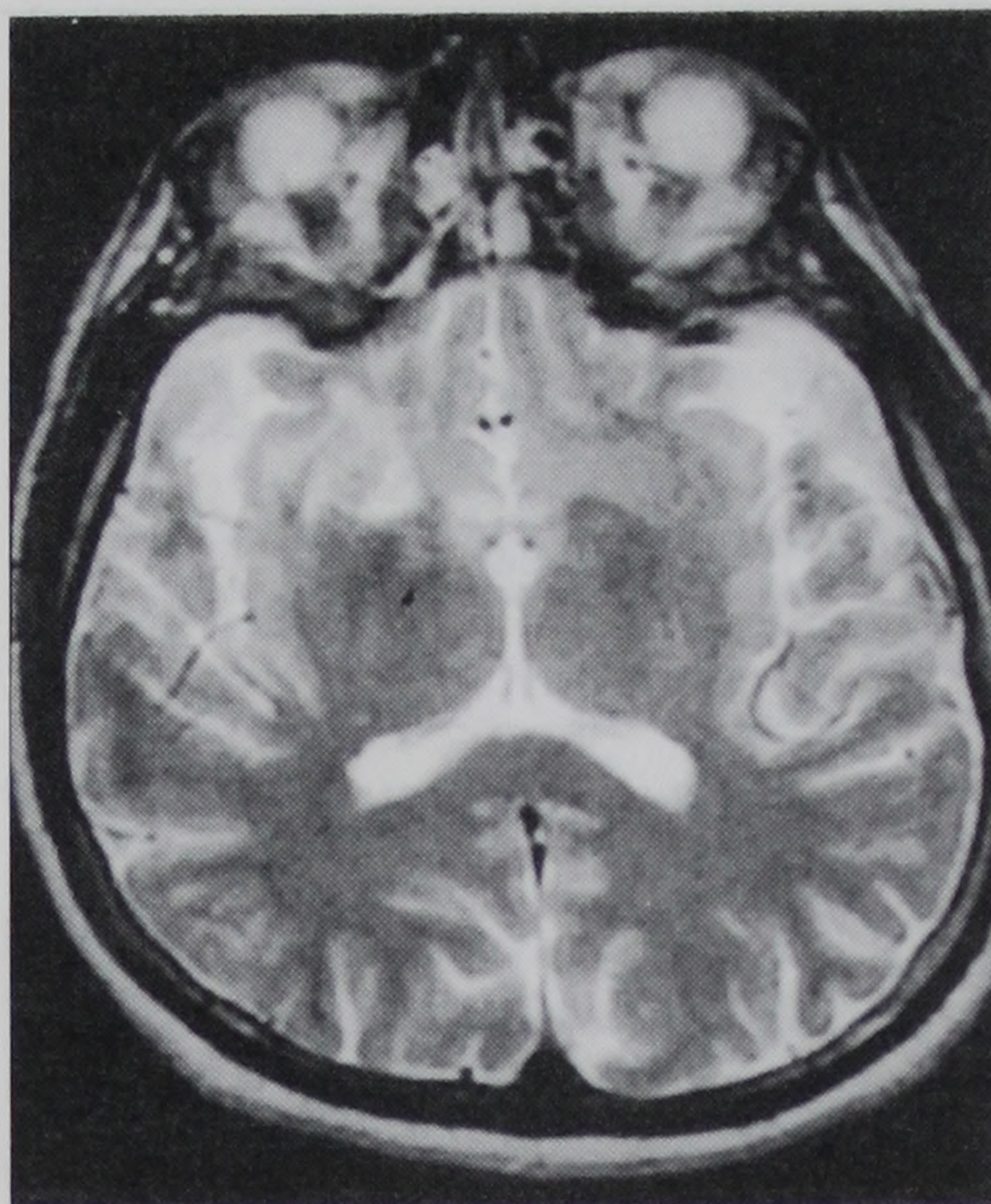


FIGURE 1. T2-weighted axial image, obtained at the level of the anterior commissure, demonstrating abnormal hyperintense signal within the columns of the fornix and hypothalamus without mass effect.

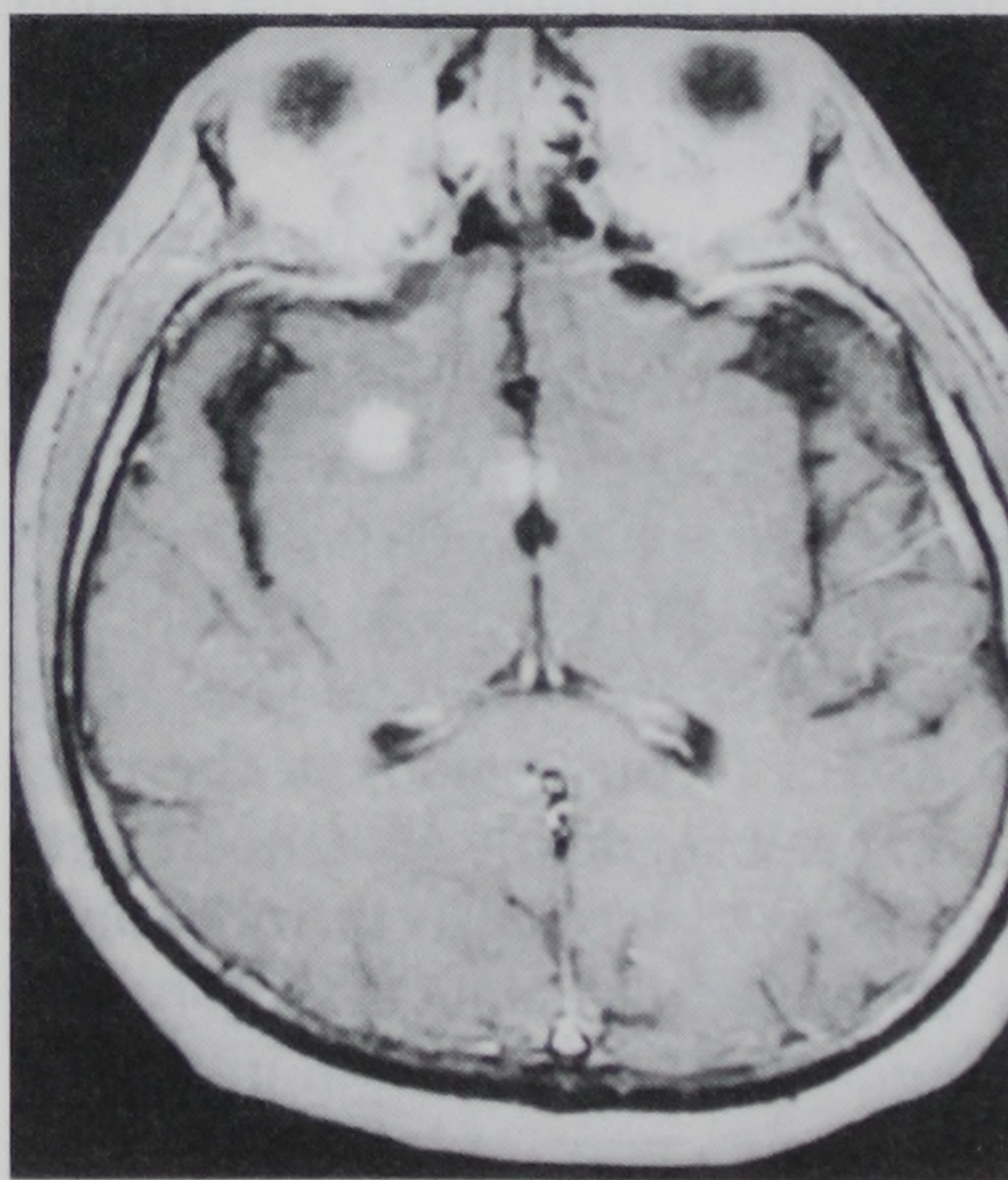


FIGURE 2. Postcontrast T1-weighted axial magnetization transfer image demonstrating abnormal enhancement within the right putamen, hypothalamic region without mass effect.

routine processing after formalin fixation. The permanent sections revealed reactive glial tissue widely infiltrated by macrophages and perivascular lymphocytes (Fig. 5A). There was no evidence of a neoplastic process. Periodic acid-Schiff (PAS) stain revealed that the macrophages were intensely positive and contained irregular PAS-positive/diastase-resistant cytoplasmic material. After

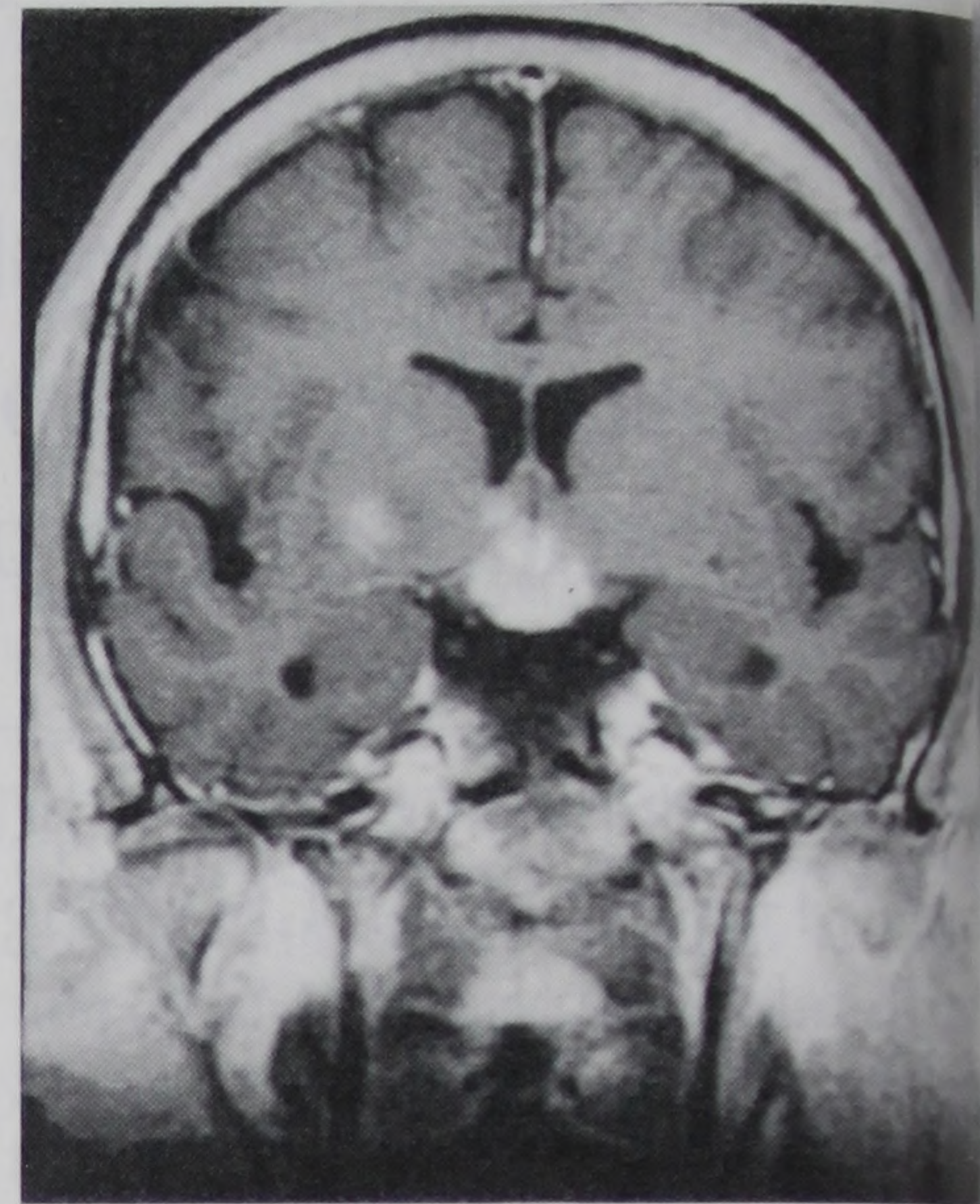


FIGURE 3. Postcontrast T1-weighted coronal magnetization transfer image demonstrating abnormal enhancement of the right putamen, right column of the fornix, and an enhancing mass within the hypothalamic region.

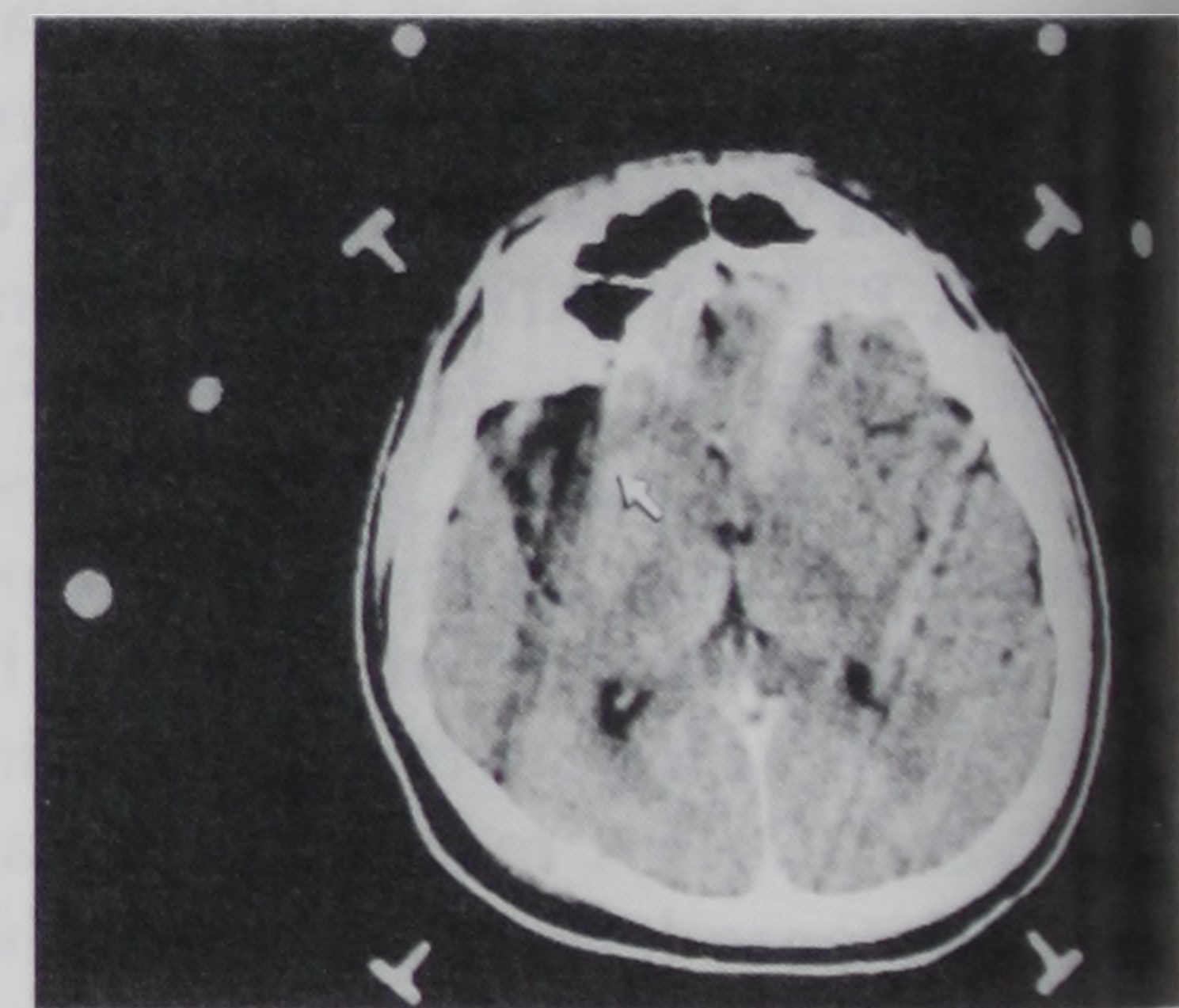


FIGURE 4. Postcontrast CT scan demonstrating abnormal enhancement within the right putamen. This was taken as the target point for stereotactic biopsy (arrow).

PAS staining, the large number of PAS-positive macrophages infiltrating the tissue became apparent, especially in the perivascular regions (Fig. 5B). Special stains for acid-fast bacilli and fungi were negative. Electron microscopy revealed that the macrophages contained numerous rod-shaped bacilli measuring 1.5 to 2.0 \times 0.2 μ m (Fig. 6A). Many of the bacilli showed a well-defined trilaminar membrane inclusion as well (Fig. 6B). The diagnosis of intracerebral Whipple's disease was thereby rendered.

After histopathological confirmation, a regimen of high-dose parenteral pen-

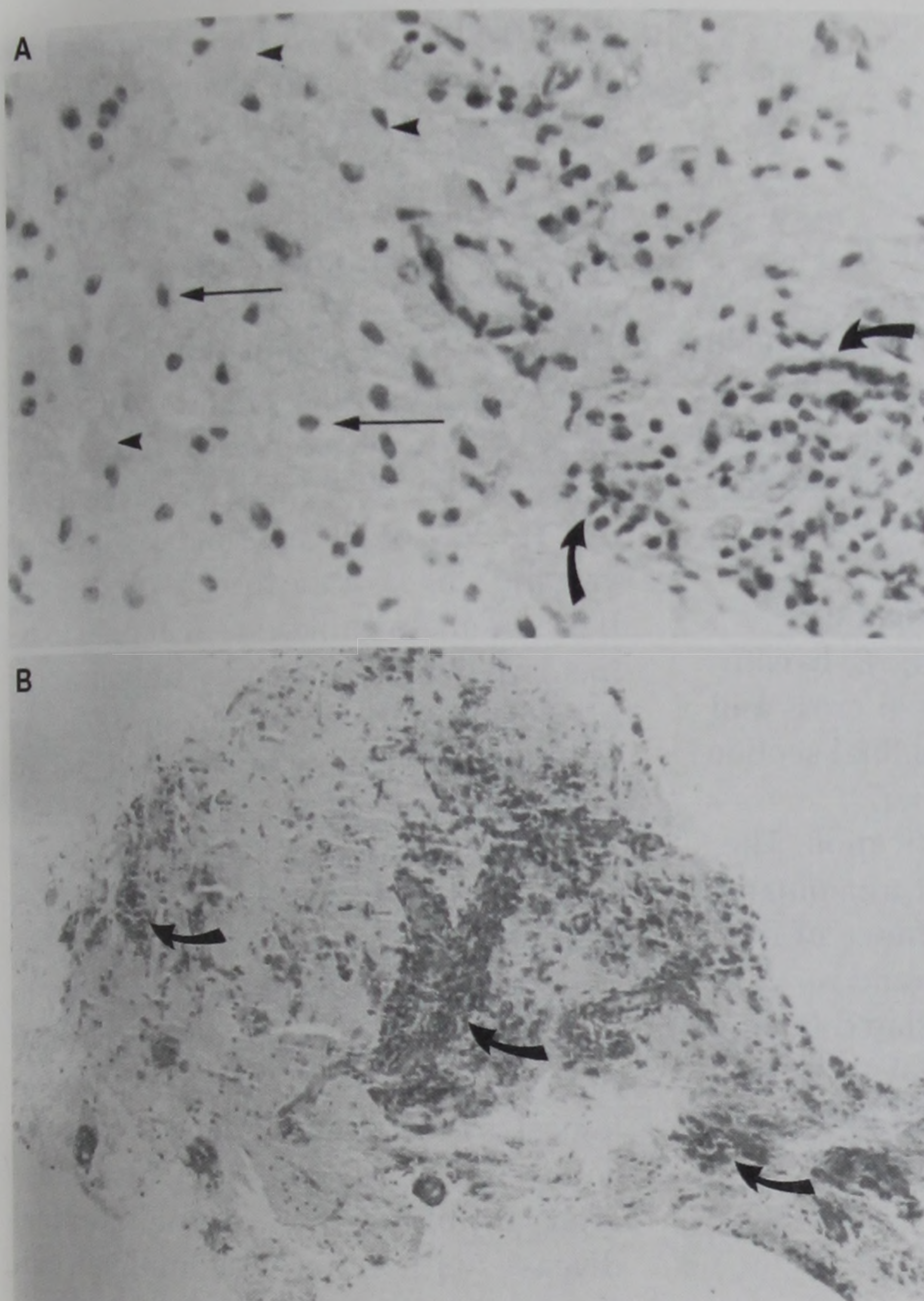


FIGURE 5.
A, hematoxylin and eosin-stained section showing reactive gemistocytic glial tissue (arrowheads) infiltrated by macrophages (straight arrows) and perivascular lymphocytes (curved arrows) (original magnification, $\times 440$).
B, PAS stain of a complete section of one of the stereotactic biopsies, showing the heavy infiltration of PAS-positive macrophages, particularly in a perivascular location (arrows) (original magnification, $\times 110$).

icillin, streptomycin, and oral trimethoprim-sulfamethoxazole (TMP-SMZ) was begun and was continued for a 2-week period. The patient became less lethargic and experienced a decremental number of hypersomnic periods. His affect and behavior remained unchanged. Hormonal assays obtained before discharge were similarly unimproved. The patient was discharged and was to receive a prolonged course of oral TMP-SMZ in the hope that it would arrest intracerebral disease progression and prevent future relapses.

DISCUSSION

Pathological findings

In 1907, George H. Whipple eloquently described an unusual case of a 36-year-old medical missionary who presented to the Johns Hopkins Hospital with a 5-year history of intermittent arthritic pain and fever, weight loss, abdominal distention, steatorrhea, and productive cough (29). An examination revealed anemia, erythema nodosum, dyspnea, peripheral edema, ascites, and

severe cachexia. A postmortem examination revealed the salient finding of neutral fats and fatty acids that were widely distributed in the body, particularly in the small intestine and lymph nodes. A histological analysis demonstrated vacuolation and giant foamy mononuclear cells. From these observations, Whipple postulated an inherent deficiency of fat metabolism and thus termed the entity "intestinal lipodystrophy."

PAS staining was subsequently used by Black-Schaffer in 1949 and led to the observation that the foamy macrophages were filled with mucopolysaccharide or glycoprotein and not lipid as Whipple had thought (8). Most commonly, the diagnosis of systemic Whipple's disease is obtained via histological examination of small bowel biopsy specimens. Findings include macrophages containing PAS granules (resistant to diastase) in the lamina propria, free rod-shaped bacilli in the lamina propria, distortion of the villous architecture, and dilated lymphatic channels (7). Granulomatous infiltrations filled with PAS-staining macro-

phages have since been identified in a diverse number of tissues: small bowel, lymph nodes, CSF, brain, pericardium, endocardium, lung, liver, synovial membranes, spleen, pancreas, esophagus, stomach, colon, muscle, brain, and adrenal glands (8). Accordingly, Whipple's disease is often referred to by the descriptive title of multisystem chronic granulomatous disease (3). Recent work suggests that granuloma formation is a direct and specific reaction to the *T. whippelii* bacillus, with delayed hypersensitivity as the underlying mechanism (30). Although no consistent immunological deficit has been described in Whipple's patients, an association with HLA B27 and abnormalities of T lymphocyte function has been reported (11, 31).

In 1961, the classic electron microscopic findings of Whipple's disease were simultaneously reported by two separate investigators (4, 32). Rod-shaped bacillary bodies measuring 1.5 to 2.5 μm long and 0.25 μm wide with a homogenous cell wall and a bacterial trilaminar plasma membrane are typically seen within the PAS-positive granules of macrophages. A 6.08-nm cytoplasmic membrane is surrounded by a 20-nm cell wall. The core of the bacteria contains a pale, amorphous nucleoid and delicate tubular structures. The PAS-granules have since been defined as lysosomes containing bacilliform bodies in varying stages of degeneration (28). Through molecular techniques, these "Whipple's bacilli" were phylogenetically determined to be in the bacterial subdivision of the order of Actinomycetales and were named *Tropheryma whippelii* (23). Some researchers have theorized that the continued inability to culture the bacillus is because of the outer membrane external to the cell wall of *T. whippelii* (9).

In 1959, Sieracki et al. (27) described pathological changes in the brains of two patients who had succumbed to the disease but had not demonstrated any neurological symptoms. Lampert et al. (18) went on to provide the first postmortem diagnosis of intracerebral Whipple's disease in the case of a patient with neurological deterioration in 1962. Since that time, PAS-positive inclusions of characteristic histiocytes have been a well-described postmortem

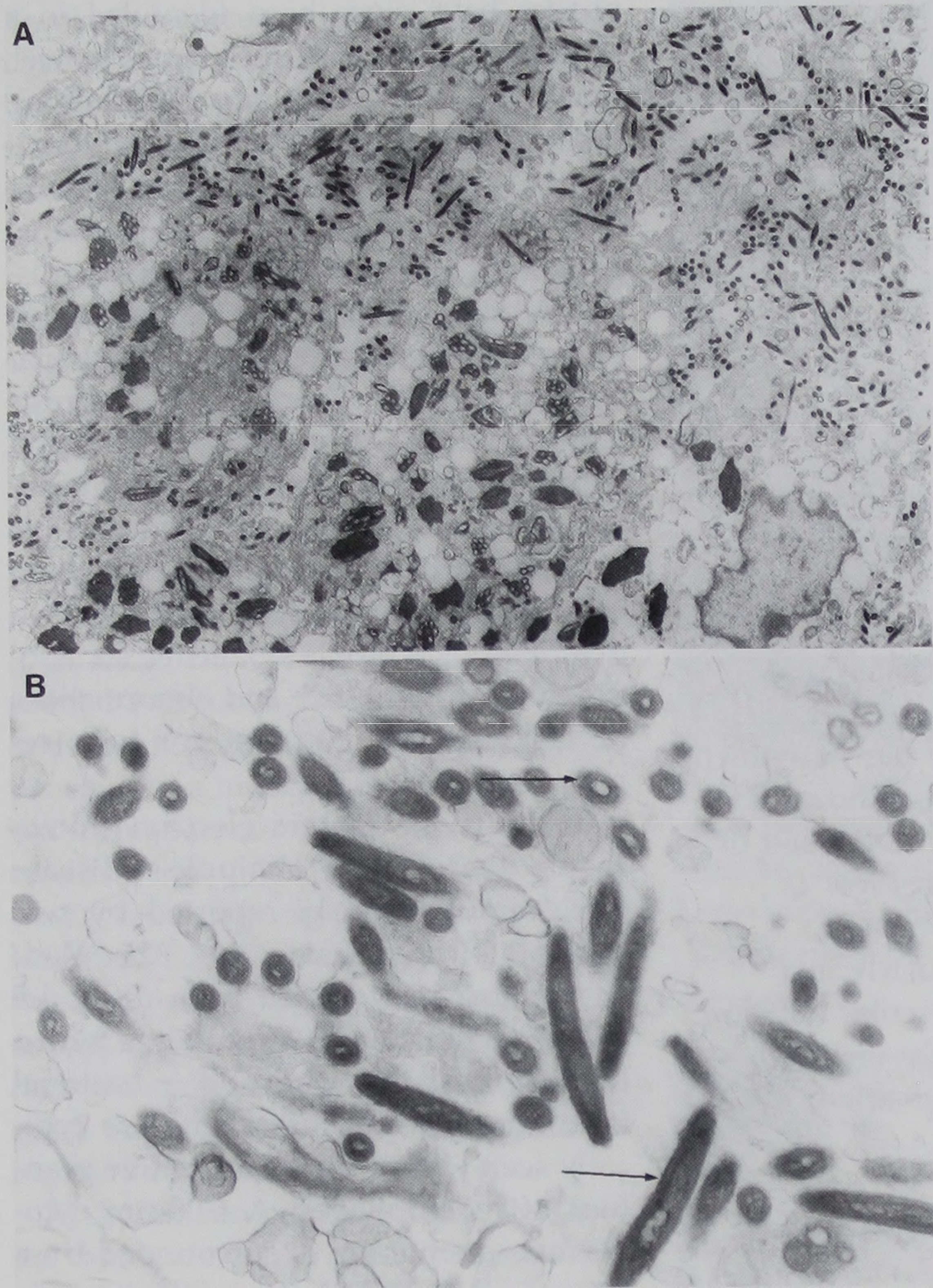


FIGURE 6. *A*, electron micrograph revealing a macrophage containing numerous bacilli measuring 1.5 to $2.0 \times 0.2 \mu\text{m}$ (original magnification, $\times 5500$). *B*, bacilli shown in cross and longitudinal section at higher magnification. The typical trilaminar appearance of the membrane is appreciated (arrows) (original magnification, $\times 26,950$).

finding in patients with Whipple's disease. Lesions consist of a gliovascular inflammatory reaction that replaces cortical and white matter tissue. Investigators have noted a predilection for the hypothalamus, cingulate gyrus, basal ganglia, insular cortex, and cerebellum (1). Large numbers of swollen gemistocytic astrocytes and smaller collections of the classic foamy macrophages are found. Perivascular cuffs of mononuclear cells and lymphocytes are frequently encountered as well (31). Lampert noted that stuffed microglia frequently surround nerve cells causing a definite loss of neurons (18). Free bacilli have been observed infiltrating glial tissue around macrophages and within neural perikarya, with bacillary wall material noted in pericytes and astrocytes. PAS-containing neutrophils and macrophages have also been inconsistently reported to be noted within the CSF of patients (15). The exact mechanism for Whipple's dementia remains unclear.

Clinical findings

Fleming et al. (13) characterized the clinical profile of 29 patients with Whipple's disease. There was a 6:1 male predominance, with the peak age of diagnosis at 50 to 55 years. The chief complaints were usually diarrhea, weight loss, fever, or arthritis. Personality changes and abdominal swelling were encountered less frequently. The most common symptoms reported in the patients' histories were weight loss (89%), arthralgias (82%), diarrhea (75%), fever (54%), CNS disturbance (headache, diplopia, depression, confusion, personality change) (43%), easy bruising (11%), and hematochezia (11%). Migratory nondeforming arthritis affecting the large joints often preceded intestinal symptoms by 10 to 20 years (28). Physical examination findings are nonspecific and include lymphadenopathy, hypotension, hyperpigmentation, hepatomegaly, splenomegaly, ascites, edema, cardiac murmur, pericarditis, pneumonia, and, less commonly, ophthalmoplegia (4%). Laboratory

abnormalities seen include (in order) low serum carotene, hypoalbuminemia, steatorrhea, low serum iron, anemia, elevated erythrocyte sedimentation rate, low protein, proteinuria, pyuria, hematuria, elevated prothrombin time, abnormal chest radiograph, low cholesterol, elevated liver function indices, hypokalemia, electrocardiographic abnormalities, low folate, and hypocalcemia.

Involvement of the CNS is observed in 10 to 20% of all cases and can occur at varying stages of the disease process (8). It may remain clinically silent only to be incidentally diagnosed by radiographic or postmortem examination (27). As with our patient, symptomatic CNS involvement can occur as an isolated finding without any peripheral hallmarks of systemic disease. Instances of Whipple's disease confined to the CNS are rare, with fewer than 10 patients reported to date and comprising less than 5% of all cases (1, 3, 14, 17, 22, 24, 28, 31). Neurological manifestations may also be encountered as a late form of relapse after antibiotic therapy for intestinal disease with otherwise minimal evidence of systemic relapse. The incidence of such isolated CNS relapses characteristically peaks 1 to 4 years after initial treatment and most commonly occurs in patients treated with antibiotics that do not cross the blood-brain barrier (16).

The neurological hallmarks of intracerebral Whipple's disease are protean in nature but may include a slowly progressive dementia, headache, memory and cognitive deterioration, hypothalamic dysfunction, seizures, meningitis, supranuclear ophthalmoplegia, myoclonus, ataxia, nystagmus, uveitis, papilledema, hemiparesis, peripheral neuropathy, myopathy, hyperactive reflexes, and gaze palsies (1, 5, 11, 12, 14, 16, 20, 22). An unusual involuntary movement disorder characterized by a slow (1 Hz) convergent-divergent pendular nystagmus that is associated with a synchronous opening and closing of the mastication muscles, mouth, and other body parts has been observed in some patients. Several clinicians consider this oculomasticatory myorhythmia to be virtually pathognomonic for CNS Whipple's disease (2, 26). The triad of progressive dementia, myoclonus, and

external ophthalmoplegia (with pupillary sparing) is similarly thought to be highly suggestive of the diagnosis (8).

Halperin et al. (14) reported the first antemortem case of isolated CNS Whipple's disease diagnosed via temporal lobe biopsy. Like his patient, our gentleman also presented with a history of behavioral changes, dementia, and impotence. In both cases, endocrinological evaluation revealed a picture of hypogonadotrophic hypogonadism. Such hypothalamopituitary involvement is common among patients with systemic Whipple's disease and includes symptoms of insomnia/hypersomnia, hyperphagia, weight gain, and polydipsia (3, 8). As with most cases, our patient demonstrated a mild pleocytosis in his CSF analysis. Pleocytosis, an elevated protein level, and PAS-staining cells (Sieracki cells) are commonly described CSF findings (13).

Imaging and intervention

CT and MRI findings are not specific for Whipple's disease. Cranial CT scans are often normal or demonstrate only cortical atrophy (31). When present, classic CT abnormalities include nodular abnormalities in the cortical and subcortical gray and white matter (especially in the hypothalamus, cingulate gyrus, basal ganglia, insular cortex, and cerebellum), hydrocephalus, and white matter alterations (14, 19, 22, 31). A review of the literature demonstrates eight previously described case reports of Whipple's disease for which magnetic resonance images were obtained (Table 1) (1-3, 6, 10, 25, 28, 31). The lesions were all hyperintense on T2-weighted images, with predominantly homogeneous enhancement after the administration of gadolinium (2, 9, 25, 28). However, one case demonstrated ring-like enhance-

ment on the postcontrast scan (31). The locations of these lesions on the magnetic resonance images paralleled those seen on the CT scans and correlated with previously described histopathological findings at autopsy (24).

Of the cases presented in Table 1, the diagnosis of Whipple's disease was made by lymph node biopsy in two cases (2, 25), at autopsy in one case (1), by duodenal or jejunal biopsy in two cases (2, 10), by open laparotomy and sampling of mesenteric lymph nodes in one case (6), and by open craniotomy with brain biopsy in three cases (3, 28, 31). Brain biopsy has been recommended for patients in whom the CNS lesion is easily accessible and there is a high degree of suspicion (3, 15). However, the frequent inaccessibility of deep gray matter lesions and the focal nature of the disease has led to a moderately

TABLE 1. Case Reports of Central Nervous System Whipple's Disease^a

Study	Diagnostic Method	MRI Findings
Adams et al., 1987 (1)	Jejunal biopsy; intracranial lesions empirically treated for Whipple's disease	T2-weighted image with low signal in the hypothalamus, uncus, medial temporal lobes, with gadolinium enhancement
Adler and Galetta, 1990 (2)	Retroperitoneal lymph node biopsy	T2-weighted image with increased signal in the medial temporal lobes bilaterally, with enhancement
Brown et al., 1990 (3)	Open right temporal and leptomeningeal biopsy	T2-weighted image showing diffuse cerebral atrophy, increased signal in pons, brachium pontis; later increased signal in right temporal lobe and ventriculomegaly
Davion et al., 1990 (6)	Hepatic and mesenteric lymph node biopsy	T2-weighted image with increased signal intensity in left frontal lobe and caudate nucleus
Erdem et al., 1993 (10)	Duodenal biopsy	T2-weighted image with increased signal in both frontal, left temporal, and occipital lobes, with enhancement
Schnider et al., 1995 (25)	Inguinal lymph node biopsy	T2-weighted image with increased signal showing mediobasal temporal lobes, hypothalamus, amygdala, hippocampal gyrus, mammillary bodies, and optic tracts, with enhancement
Tan et al., 1995 (28)	Open brain biopsy	T2-weighted image with increased signal in subthalamic and anterior thalamic regions and pons; also showed nodular abnormalities in cortical and subcortical gray matter and cerebellum
Wroe et al., 1991 (31)	Open excision of right frontal lesion	T2-weighted image showing multiple high-signal lesions with mass effect throughout gray and white matter of varying sizes; gadolinium-enhanced study showed areas of peripheral enhancement

^a MRI, magnetic resonance imaging.

high rate of inconclusive open biopsies in the past (1). To our knowledge, this is the first case in which the diagnosis of the intracranial lesions was made by stereotactic brain biopsy instead of either by open brain biopsy or empirically from a systemic diagnosis of Whipple's disease. Stereotaxy provides a relatively safe, minimally invasive means of obtaining tissue from deep-seated targets that are otherwise inaccessible to open methods. Because patients with Whipple's disease are often elderly or medically tenuous, stereotaxy-guided biopsy is additionally attractive in its rapidity and ability to be performed with the patient under local anesthesia. Recent work suggests that contrast-enhanced MRI may be particularly useful in identifying lesions in cases in which there is an active breakdown of the blood-brain barrier for optimal brain biopsy. High T2-signal intensity lesions that fail to enhance are thought to be chronic in nature and may lead to indeterminate tissue diagnosis (10, 28).

Treatment and outcome

Historically, cases of untreated CNS Whipple's disease invariably carried a poor prognosis with certain eventual fatality. In 1952, Paulley (21) first reported the successful use of antibiotics in a patient with systemic Whipple's disease. Because the optimal type and duration of antibiotic regimen remain undefined, therapy has primarily been empiric (13). Treatment of systemic Whipple's has included combinations of chloramphenicol, penicillin, streptomycin, tetracycline, ampicillin, sulfonamides, TMP-SMZ, isoniazid, and para-aminosalicylic acid for variable durations (5, 7, 8, 13, 16, 22). For cases of CNS Whipple's disease, the mainstay of treatment is the use of antibiotics that effectively cross the blood-brain barrier (i.e., penicillin, TMP-SMZ, chloramphenicol). The typical regimen for intracerebral disease consists of 1.2 million units of parenteral penicillin G and 1 g of streptomycin for 2 weeks for the intestinal disease, combined with one double-strength tablet of TMP-SMZ for 1 year (8, 28). Patients allergic to sulfonamides may be treated with oral penicillin (250 mg administered four times/d for 1 yr) in place of TMP-SMZ. Oral chloramphenicol administered

for 6 to 12 months may be used for adjunct therapy in unresponsive cases (28). Assessment of therapy is difficult, because symptoms may fluctuate in severity with bland manifestations that do not represent the extent of the disease. Gaze palsies, nystagmus, and focal deficits have been reported to be the signs most responsive to treatment (1, 22). Personality and affect changes are typically much slower to improve after therapy (31). Although our patient's lethargy and hypersomnia responded early on to medication, his apathy and personality changes may thereby require prolonged therapy before improvement is seen.

Despite antimicrobial therapy, relapse of Whipple's disease is well recognized and should be cautiously anticipated in all cases (8, 13). Keinath et al. (16) reviewed 88 treated patients and found symptomatic relapse in 31 (35%) at a mean of 4.2 years after diagnosis. Of these 31 patients, 21 had been treated with tetracycline or penicillin alone and 10 had received combined penicillin, streptomycin, tetracycline, or TMP-SMZ. The CNS is considered the most common and serious site for recurrence. Recurrence occurs in approximately 13% of patients 2 years after treatment. Such symptomatic relapse with neurological manifestations usually indicates a poor prognosis; most patients respond poorly to additional therapy and die within months or a few years (1, 14, 24, 31).

CONCLUSION

Intracerebral involvement is a common finding in patients with known systemic Whipple's disease. Difficulties arise when neurological findings are the initial manifestation of the disease because the symptoms are often vague and nonspecific. For patients presenting with dementia, cognitive decline, hypothalamopituitary dysfunction, and ophthalmological disorders, the diagnosis of CNS Whipple's disease should be considered early on. Appropriate MRI of the brain is then essential to visualize the characteristic deep-seated nodular gray and white matter lesions. Brain biopsy under stereotaxy allows for a relatively safe, minimally invasive, and rapid confirmation of the tissue diagnosis so that appropriate antibiotic therapy can be instituted in a timely fashion

to prevent further neurological deterioration. The possibility that early diagnosis, rapid intervention, new antimicrobial agents, and novel routes of drug delivery may improve the natural course of CNS Whipple's disease requires continued investigation.

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COMMENTS

Whipple's disease is a rare disease, with fewer than 10 cases reported in the world's literature every year. The most common manifestation is a malabsorption syndrome and arthralgias, although cardiac and central nervous system involvement is also common (1). The article describes a case report involving a patient presenting with neurological symptoms who was found, by brain biopsy, to have macrophages that stained positive for the periodic acid-Schiff (PAS) stain. Evaluation by electron microscopy revealed the characteristic gram-positive intracellular *Tropheryma whippelii*. Strongly PAS-positive intestinal biopsies are very suggestive of Whipple's disease if *Mycobacterium avium* is excluded with an acid-fast staining. In other tissues, PAS-positive staining can occur with a variety of diseases and electron microscopy is required to demonstrate the characteristic bacilli. PAS staining can be negative, but the bacilli can still be present and be detectable only by electron microscopy. Newly developed polymerase chain reaction testing involving the amplification of the bacterial 16 S ribosomal ribonucleic acid has recently been developed and promises to be a more sensitive and convenient test (2). Although Whipple's disease is rare, it should be considered in patients with hypothalamic symptoms and ophthalmoplegia because it is a potentially treatable disease.

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The authors present a case in which the precise diagnosis of Whipple's disease was made using standard stereotactic biopsy. The key to reaching this critical conclusion was the careful and thoughtful handling of the biopsy material. A significant suspicion based on the frozen section led to the preparation of material for electromicroscopic evaluation.

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This is a case report of clinically unsuspected central nervous system Whipple's disease that was diagnosed by electron microscopy of the material obtained by performing stereotactic biopsy. This report emphasizes what has been repeatedly demonstrated in recent years as experience with stereotactic biopsy specimens has increased exponentially, i.e., that exact diagnoses can sometimes be made on very small specimens. It is still essential that the pathologist make the correct inferences on the basis of the light microscopic picture and then perform the proper special stains or additional procedures. In this instance, the suspicion was aroused with the initial routine stains that led to the performance of PAS stains and electron microscopy, identifying the peculiar bacteria that cause this still enigmatic condition.

With this said, it needs to be emphasized that this is not always so and that greater care is still needed to recognize when we do not know the diagnosis and must persist in our diagnostic efforts. Further, it must be remembered that sampling error remains a major problem, amplified by the small size of available specimens; this is particularly true for brain tumors, in which so much histological variability can be present. Good fortune should be accepted and appreciated but not expected.

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