CASE REPORTS/CLINICAL VIGNETTES

Whipple's Disease: Neurological Relapse Presenting as Headache for Two Years

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Whipple's disease is a rare, chronic, multi-systemic infectious disorder caused by the bacterium, *Tropheryma whippelii*. Relapses are commonly associated with neurological symptoms. We report a case of a 55-year-old man who presented with symptoms of progressive headache, 13 years after apparent complete recovery from intestinal Whipple's disease. Studies showed hydrocephalus with obstruction of the aqueduct and cerebrospinal fluid findings consistent with chronic meningitis. Diagnosis of central nervous system Whipple's disease was confirmed by analysis of the cerebrospinal fluid using polymerase chain reaction. After one year of antibiotic therapy, symptoms resolved and cerebrospinal fluid pleocytosis had improved. This case illustrates that Whipple's disease should be included in the differential diagnosis of central nervous system disorders as it is a potentially treatable cause of chronic meningitis. Failure to recognize this presentation can lead to misdiagnosis or a significant delay in diagnosis and treatment.

KEY WORDS: *Tropheryma whippelii*; headache; cerebrospinal fluid; polymerase chain reaction.

J Gen Intern Med 23(12):2131-3

DOI: 10.1007/s11606-008-0776-9

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INTRODUCTION

Whipple's disease, initially described as an intestinal lipodystrophy, is a rare, chronic, multisystemic infectious disorder caused by *Tropheryma whippelii*. Whipple's disease can present with protean manifestations involving any organ system of the body¹. Neurological involvement may occur either on a background of gastrointestinal symptoms in a patient with known Whipple's disease, as a relapse or may present de novo without gastrointestinal involvement². Central nervous system (CNS) Whipple's disease can present in broad and diverse symptoms, extensive or localized. The most common CNS manifestations include dementia, disturbances of ocular movement, involuntary movements and hypothalamic dysfunction. Seizures, focal cerebral signs, ataxia, myelopathy and meningitis features may also be present².

We report a patient with central nervous system Whipple's disease. He presented with neurological symptoms 13 years after apparent successful antibiotic therapy for biopsy confirmed enteric Whipple's disease. In this patient, headaches for several years led to diagnosis of a relapse of Whipple's disease. The diagnosis was based on pleocytosis of the cerebrospinal fluid and confirmed by positive polymerase chain reaction (PCR) for *T. whippelii*. Whipple's disease should be considered as a potential differential diagnosis in a wide range of CNS disorders.

CASE REPORT

A 55-year-old Caucasian male was hospitalized for evaluation of headache of approximately one and a half years' duration. Fifteen months prior to the current admission, he was hospitalized after a fall following an episode of heavy alcohol consumption. A magnetic resonance image (MRI) of the brain at that time revealed hydrocephalus presumed to be from aqueductal stenosis, and he underwent an endoscopic third ventriculostomy. He had marked improvement of headaches. However, a recurrence of headaches after one year compelled the patient to seek outpatient medical advice. A repeat MRI of the brain revealed mild ventriculomegaly. In the interim, the patient was lost to follow up. Mild difficulty with balance and persistent headaches prompted the patient to return for evaluation and treatment. An outpatient radionuclide cisternogram for evaluation of normal pressure hydrocephalus revealed a scintigraphic pattern consistent with the reversal of cerebrospinal fluid dynamics and normal pressure hydrocephalus, and he was referred for inpatient admission.

The patient came to our attention during the resulting hospital admission. He complained of daily increasingly severe headaches and gradual generalized loss of energy and strength over the previous 18 months. These symptoms progressed to the point where he was no longer able to work installing swimming pools. There were no symptoms of lateralizing weakness; rather, he described a general loss of strength and energy. He also experienced a loss of balance and some unsteadiness, but was able to continue walking with minor difficulty. These symptoms had been present for approximately one year. He had no weight loss, no gastrointestinal symptoms and had not traveled recently.

His past medical history was remarkable for Whipple's disease 13 years prior to admission, diagnosed after extensive evaluation for anemia, 50-pound weight loss, and diarrhea. A duodenal biopsy revealed macrophages containing a large

Received February 13, 2008

Revised August 4, 2008

Accepted August 14, 2008

Published online September 11, 2008

amount of diastase-resistant periodic acid Schiff positive material within the cytoplasm. The patient was treated, completing a one-year course of oral double-strength trimethoprim-sulfamethoxazole, which resulted in a resolution of the symptoms.

Physical examination at the time of the current admission showed a well-developed tired-looking man. Vitals signs were normal. General physical examination was unremarkable. The neck was supple with no meningismus. He was awake and alert, oriented to time, place and person, able to follow commands, and displayed logical and abstract thinking. Cranial nerve examination was intact. His motor power, sensation, and reflexes were all normal. He demonstrated a positive Romberg sign and some ataxia, with difficulty performing tandem gait.

Laboratory tests revealed hemoglobin of 12.3 g/dl [MCV: 91 fl], with normal leukocyte and platelet counts. A chest radiograph showed bullous emphysema and a tuberculin skin test was negative. Sputum smears for acid fast bacilli were negative. Serum human immunodeficiency virus serology, serum histoplasma antigen, serum cryptococcal antigen, rapid plasma reagin (RPR), antinuclear antibodies, rheumatoid factor, blood cultures, and serology for hepatitis B and C were all negative. Serum thyroid stimulating hormone was normal. Computed tomography and MRI of the brain revealed mild ventriculomegaly. A lumbar puncture was performed. Cerebrospinal fluid (CSF) opening pressure was not recorded. CSF studies demonstrated the following: 88 white blood cells / cubic mm (28% polymorphonuclear leukocytes, 54% lymphocytes, 1% eosinophils); 2 red blood cells/cubic mm; glucose concentration was low at 24 mg/dl; protein concentration was elevated at 282 mg/dl. CSF gram stain, India ink smear, Lyme antibody, cryptococcal antigen, and smear for fungal elements were also negative. History of prior Whipple's disease prompted analysis of cerebrospinal fluid by PCR for *T. whipplei*. It was positive.

Based on the positive PCR for *T. whipplei*, chronic meningitis and neurological symptoms were determined to be due to Whipple's disease. The treatment recommendation was to administer intravenous ceftriaxone for one month followed by one to two years of oral trimethoprim-sulfamethoxazole. However, the patient refused parenteral antibiotic therapy, and twice daily oral double-strength trimethoprim-sulfamethoxazole was prescribed.

The patient reported improvement in his headaches during the initial few months of antibiotic treatment. After one year of antibiotic therapy, the patient reported complete resolution of his headaches and marked improvement in gait. He had also returned to his baseline functioning status, allowing him to start working limited hours in a janitorial job. Results of CSF analysis revealed improved glucose and protein concentration at 44 mg/dl, and 88 mg/dl, respectively; two RBCs and 17 WBCs/cubic mm. Repeat CSF PCR tested again positive for *T. whipplei*. Based on the positive cerebrospinal fluid PCR for *T. whipplei* and improved CSF pleocytosis, the patient has continued oral antibiotic therapy.

DISCUSSION

In 1907, George Hoyt Whipple published a case report of a 36-year-old physician who presented with severe malabsorp-

tion associated with mesenteric lymph node enlargement, arthritis, and skin pigmentation. At necropsy, Whipple observed the presence of foamy macrophages and large numbers of argyrophilic rod-shaped structures in the lymph nodes³. These foamy macrophages were later shown to stain strongly with the periodic acid Schiff reagent, and this soon became accepted as the diagnostic hallmark of Whipple's disease. First described as an intestinal lipodystrophy with manifestations related principally to intestinal malabsorption, it was thought to be due to either an intrinsic mucosal disorder of fat metabolism or to enteric lymphatic obstruction⁴. The infective etiology of this disorder was first proposed in 1952, when a patient with Whipple's disease responded to antibiotic treatment⁵. *T. whipplei* was subsequently identified as the causative agent.

Whipple's disease is a rare, chronic, multi-systemic infectious disease caused by *T. whipplei*, a weakly gram positive bacillus. Only about 1,000 cases have been reported to date, though there is no valid estimate of its actual prevalence⁶. The organism appears to be present in the general environment, though neither its source nor its transmission is well established⁶. It has been suggested that *T. whipplei* might be acquired through fecal-oral transmission⁴. The disease is associated with a probable underlying immunosuppressant component and occurs predominantly in middle-aged men. Of 664 patients reviewed by Dobbins, men accounted for 86% of cases, with a mean age of 49 years⁷. The possibility that patients with Whipple's disease have a primary defect in host defence mechanisms, which renders them susceptible to this disorder has recently been rekindled by evidence of defective in vitro IL-12 and interferon gamma production by peripheral blood mononuclear cells⁵. Whipple's disease may involve any organ system.

The clinical manifestations of *T. whipplei* are protean. Gastrointestinal involvement occurs in 70% of cases, which classically include symptoms of weight loss, diarrhea, and abdominal pain. These were the initial manifestations in our patient when he was diagnosed with Whipple's disease 13 years previously. Intestinal symptoms are often preceded by arthralgias for several years. Extraintestinal disease often involves a variety of other organs, especially the lymphatic system, CNS [21-43%], and heart^{5,7,8}. Skin discoloration, lymphadenopathy, intermittent low-grade fever and migratory arthralgia involving the large and small joints, also are common manifestations.

Neurological manifestations present in three ways: in classic Whipple's disease, neurologic involvement accompanying the typical intestinal symptoms; isolated neurological symptoms due to *T. whipplei* but without histological evidence of intestinal involvement; and most commonly, as a neurological relapse of previously treated Whipple's disease can occur during or years after antibiotic treatment^{1,2,5,6,9}. The latter was the pattern of CNS relapse in our patient. Because of the rarity of Whipple's disease, it is difficult to know just how often the CNS is affected.

The neurological manifestations of CNS Whipple's disease are diverse and can resemble those of almost any neurological condition. The most common clinical presentations include dementia, disturbances of ocular movement, involuntary movements and hypothalamic dysfunction. Seizures, focal cerebral signs, ataxia, myelopathy and meningitis features may also be present². CSF may either be normal or display

mildly elevated protein and/or a modest pleocytosis, consistent with our case⁷. Headache was the presenting symptom in our patient over ten years after his initial diagnosis. The myriad, non-specific CNS symptoms that can occur in Whipple's disease make for a broad differential diagnosis and because the progression of the disease is usually slow and insidious, there is often a significant delay in making the diagnosis. Our patient had an 18-month interval delay between onset of signs and symptoms of CNS relapse and confirmation of diagnosis. Sylvius aqueduct stenosis and ventricular dilatation can be either a late complication as in our patient or, more rarely, presenting manifestation of Whipple's disease^{1,10}. Our patient had aqueduct stenosis, and the possibility of a diagnosis of Whipple's disease could have been considered at that point.

Typically, the diagnosis of gastrointestinal Whipple's disease is based upon the demonstration of diastase resistant, PAS positive macrophages on small-bowel-biopsy specimens coupled with PCR evidence of infection with *T. whipplei*^{5,6}. The recent development of PCR-based assays to establish a diagnosis of Whipple's disease has fuelled advances in the investigation, diagnosis, and management of this disease⁵. PCR of the CSF is now recognized to be the diagnostic method of choice in cases of CNS Whipple's disease¹¹. Although PCR analysis for *Tropheryma whippelii* DNA is thought to have a high sensitivity for detecting the disease, its specificity has been called into question, and large cohorts with isolated CNS disease have not been studied^{12,13}.

The main objectives of treatment of Whipple's disease are to eradicate primary (usually intestinal) disease and to prevent relapse^{1,5,7,8}. Considering the tropism of *T. whipplei* for the CNS and the threat posed by relapses in the CNS, early use of drugs with good penetration of the blood-brain barrier is considered to be important in preventing relapse^{8,9}. There are still no randomized, controlled trials of different antibiotic regimens upon which to base recommendations for the treatment of Whipple's disease^{5,8}. On the basis of the combined observations from case reports, patient series and retrospective analyses, the therapy most commonly noted to be associated with clinical success is initial intravenous treatment with penicillin G and streptomycin, or a third-generation cephalosporin, followed by administration of trimethoprim-sulfamethoxazole (double strength tablet) given twice daily for at least one year. This regimen was associated with clinical success in our patient who reported complete resolution of headaches after one year of antibiotic treatment with oral trimethoprim-sulfamethoxazole.

Even with a specific antibiotic regimen, clinical relapse occurs in 2% to 33% of cases after an average of 5 years. Relapse is usually characterized by neurologic involvement. The clinical arthralgia, and gastrointestinal relapses are evenly distributed between early relapses [occurring <2 years after diagnosis] and late relapses [occurring >2 years after diagnosis]. All reported cardiac and central nervous system relapses occurred late^{2,6,14}. Little information is available on the role of CSF PCR in monitoring therapy. In one study, two patients with neurological symptoms were continued on intensified regimens on the basis of positive PCR findings despite prolonged treatment. Thereafter, the PCR results of both

patients converted to negative, suggesting that the testing of CSF by PCR may be a useful method to monitor the effect of treatment. However, because the correlation between CSF results and clinical outcome is not yet established, the prognostic value of CSF testing remains to be determined¹⁵.

Clinicians should remain alert to Whipple's disease as a potential differential diagnosis in a wide range of CNS disorders, including encephalopathies, chronic meningitides, cerebral vasculitides, granulomas, dementias and a broad range of focal cerebral disturbances. Analysis of CSF for *T. whipplei* by PCR should be included in the diagnostic work up in the setting of a wide range of CNS disorders.

Acknowledgments: No financial support for the authors related to this case.

Conflict of Interest Statement: None disclosed.

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