Neuropsychiatric Considerations of a Rare Chronic Bacterial Infection: Literature Review of Whipple's Disease

Maximilian Fulop, Nita Bhatt MD

OHIO UNIVERSITY Heritage College of Osteopathic Medicine

Introduction

Whipple's Disease (WD) is a very rare, multisystem, chronic bacterial infection with varying presentations. It is caused by the gram positive bacillus *Trophyrema whipplei*, which invades the intestinal mucosa and resides within macrophages. Symptomatic individuals typically present with signs of malabsorption, however dissemination can result in a multitude of symptoms involving various organ systems[1].

WD is relevant to psychiatrists because it can present with neurologic, cognitive, and behavioral symptoms. It is often misdiagnosed and improperly treated as neurocognitive degeneration or mood disorders at the expense of delayed care, financial costs, and exposure to unnecessary interventions. Early detection and treatment can halt progression or reverse CNS symptoms. Therefore, it is important to increase clinical suspicion of WD in a psychiatric patient with classic WD symptoms.

Clinical Presentation

Classic Symptoms[1]:

1. Classic WD presents as a prodromal phase of intermittent, migratory, seronegative, polyarthralgias and recurrent fever. Commonly affected joints include the ankles, knees, and wrists
2. Weight loss, diarrhea/steatorrhea, abdominal pain, and anemia develop months to years after the initial onset of symptoms
3. Signs of multisystem involvement – neurologic, pulmonary, cardiovascular – develop up to a decade after initial presentation

CNS Involvement:

1. CNS involvement is common and neurologic symptoms are present in up to 40% of cases; isolated CNS WD only comprises about 4% of total WD cases[3,4,6]
2. The most common neurologic manifestations include cognitive decline, mood disturbances, and movement disorders[1,2,6]
3. Psychiatric manifestations are variable: depression, apathy, psychosis, hallucinations, and behavioral changes have been reported[1,4,6]
4. Oculomasticatory myorhythmia (OMM) is a rare but pathognomonic finding of CNS WD[1,2]

Diagnosis

A

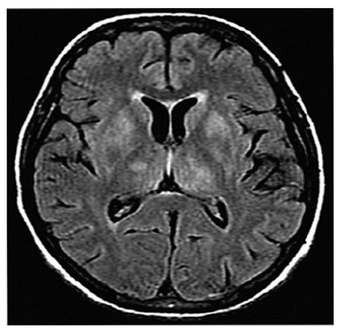

Figure A: FLAIR image demonstrating hyperintense, bilateral, subcortical lesions in a patient with WD[1]

B

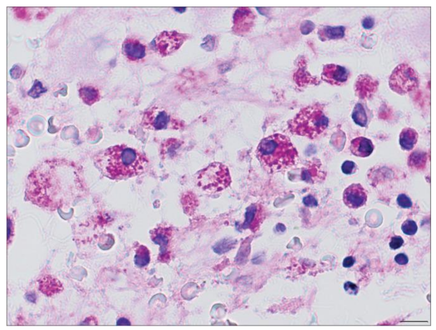

Figure B: PAS-positive staining macrophages from cerebral biopsy in a patient with suspected glioblastoma that was later diagnosed with WD[2]

Diagnostic Criteria[1]: (2/3 required)

1. tissue biopsy showing Periodic Acid Schiff (PAS) staining macrophages
2. PCR detection of *T. whipplei* in the CSF
3. immunohistochemical staining of *T. whipplei* antibodies in tissue samples

Clinical triad of CNS WD[1]: (only present in ~10%)

- Supranuclear gaze palsy
- Rhythmic myoclonus (including OMM)
- Dementia (+/- psychiatric changes)

Imaging findings:

- Brain imaging findings are nonspecific, with prior cases showing generalized cerebral atrophy, multiple nodular lesions in cortical or subcortical grey matter, or solitary focal lesions
- Imaging is recommended in suspected or confirmed CNS WD to characterize structural involvement, monitor progression of disease, or track response to treatment

Treatment

Currently, there is no standard protocol for the treatment of WD. Common practice involves the use of long-term antibiotic therapy with agents that have strong penetrance into the blood-brain barrier. Intravenous ceftriaxone for 2-6 weeks followed by oral sulfamethoxazole-trimethoprim for 12 months or oral doxycycline and hydroxychloroquine for 12 months have been shown to be effective at improving clinical condition without recurrence after 24 months[5].

It is unclear whether psychiatric medications provide any relief of psychiatric manifestations of WD. One case report noted a lack of improvement in a patient diagnosed with WD that was administered zolpidem tartrate for new onset psychiatric symptoms[4].

Discussion

The insidious course, multisystem involvement, and variable presentation of WD make it notoriously difficult to identify. Definitive diagnosis commonly occurs years after initial presentation, by which time patients have undergone numerous unrevealing evaluations. Therefore, is it important to consider WD in a patient with a long history of nonspecific symptoms presenting with new onset neuropsychiatric changes. CNS symptoms typically develop years after the initial presentation, so looking for undefined problems in a patient's history could help psychiatrists suspect WD, initiate proper work up, and begin antimicrobial therapy. Literature has reported improvement and reversal of CNS symptoms following long term antibiotic therapy, suggesting an organic etiology for the neuropsychiatric disturbances. However, it would be interesting to investigate the efficacy of psychiatric medications for these symptoms.

References

1. El-Abassi R, Soliman M, et al. Whipple's disease. *Journal of the Neurological Sciences*, 2017;377:197-206. doi:10.1016/j.jns.2017.01.048.
2. Barbero-Aznarez P, Perez-Tanoira R, et al. Isolated central nervous system Whipple disease. *Surg Neurol Int.* 2022;13:477. doi:10.25259/SNI_591_2022
3. Gerard A, Sarrot-Reynauld F, et al. Neurologic Presentation of Whipple Disease: Report of 12 Cases and Review of the Literature. *Medicine* 81(6):p 443-457.
4. Manzel K, Tranel D, Cooper G. Cognitive and Behavioral Abnormalities in a Case of Central Nervous System Whipple Disease. *Arch Neurol.* 2000;57(3):399–403. doi:10.1001/archneur.57.3.399
5. Moos V, Krüger J, Allers K, et al. Oral treatment of Whipple's disease with doxycycline and hydroxychloroquine versus intravenous therapy with ceftriaxone followed by oral trimethoprim-sulfamethoxazole in Germany: a phase 2/3, prospective, open-label, randomised, controlled, non-inferiority trial. *Lancet Infect Dis.* 2025;25(7):788-800. doi:10.1016/S1473-3099(24)00797-7
6. Pessa, M.E., Baldi, A., Gigli, G.L. *et al.* A case of rapidly progressive dementia: Whipple disease of CNS. *Neurol Sci* 39, 591–592 (2018). doi:10.1007/s10072-017-3147-7