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Review article

Isolated inctracranial Whipple's disease—Report of a rare case and review of the literature

Wazim Mohamed [a], Erin Neil [a], William J. Kupsky [b,d], Csaba Juhász [a,d,e], Sandeep Mittal [c,d], Sunitha Santhakumar [a,d,*]

[a] Departments of Neurology, Wayne State University, Detroit Medical Center, Detroit, MI, USA
[b] Department of Pathology, Wayne State University, Detroit Medical Center, Detroit, MI, USA
[c] Department of Neurosurgery, Wayne State University, Detroit Medical Center, Detroit, MI, USA
[d] Karmanos Cancer Institute, Detroit, MI, USA
[e] Children's Hospital of Michigan PET Center, Detroit, MI, USA

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ABSTRACT

Introduction: Whipple's disease (WD) is a rare multisystemic infectious disease that can involve a variety of organs namely the gastrointestinal tract, lymphatic system, heart and nervous system. Myorhythmia is a hallmark of WD. Isolated CNS involvement is very rare.
Case: We present a 50 year-old African-American woman with rapid cognitive decline, visual hallucinations, insomnia, dysarthria, and gait unsteadiness. She subsequently developed pendular nystagmus and gaze paresis. Serial brain MRI scans showed T2 hyperintense lesions in the left striatum and right parahippocampal gyrus. FDG-PET scan showed marked increase of glucose uptake in the left putamen. Serum and CSF PCR for *Tropheryma whipplei* was negative. Stereotactic biopsy of the lesion and tissue PCR was consistent with WD.
Review of literature: A systematic review identified 24 cases of isolated intracranial presentation of WD since 1975. Cases with systemic and extracranial manifestations were excluded.
Discussion: In patients with rapidly progressive cognitive decline with negative workup for common etiologies, there should be a high index of suspicion for WD. Diagnosis of WD remains a challenge as traditional methods commonly fail to culture *T. whipplei*. PET scans can help in identifying areas of inflammation that can be biopsied. Our case proves that a negative serum and CSF PCR should not exclude CNS WD and a brain biopsy of the lesion with PCR assay should be performed when possible.

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* Corresponding author at: Department of Neurology, Wayne State University, University Health Center Suite 8D, 4201 St. Antoine, Detroit, MI 48201. Tel.: +1 313 745 4994; fax: +1 313 745 4216.
E-mail address: ssanthak@med.wayne.edu (S. Santhakumar).

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1. Introduction

Whipple's disease (WD) is a rare multisystem disease of infectious etiology, caused by a gram positive bacillus belonging to the *Actinomyces* family, *Tropheryma whipplei* [1]. It is a soil-borne infection and has been implicated in patients with underlying immunosuppressive conditions. This chronic infection, characterized by predominant intestinal involvement, can also involve a variety of other organs, such as the lymphatic system, the heart, and the central nervous system (CNS) [2]. In patients with intestinal involvement, abdominal pain, diarrhea, weight loss, malabsorption, wasting, low-grade fever, arthralgia, increased skin pigmentation, and peripheral lymphadenopathy have been described [3].

The largest series of patients with systemic *T. whipplei* was reported by Lagier et al. in 2010 [4]. This series includes 142 patients with PCR and histologic analyses confirming systemic WD. Among these, 113 individuals were found to have "classic WD" defined as positive results of periodic acid-Schiff (PAS) staining and/or specific immunohistochemistry of the small bowel biopsy specimens.

Diagnosis of WD remained a challenge as traditional methods failed to isolate *T. whipplei* in culture. In fact, treatment has largely been based on identification of the causative organism by amplification of the bacterial DNA present in the diseased tissue by the polymerase chain reaction (PCR) [5]. In 1991, Wilson et al. detected the etiologic pathogen by PCR amplification of the bacterial 16S ribosomal DNA from a small bowel biopsy specimen from a patient with WD [6]. In 2000, Raoult and colleagues successfully isolated and grew the microbial pathogen by inoculation in a human fibroblast cell line [7].

Myorhythmia (oculomasticatory myorhythmia and oculofacial skeletal myorhythmia) is a hallmark of WD [8–11]. CNS involvement has been described in 10 to 43% of patients diagnosed with WD and can be limited to the cerebrum, spinal cord, or peripheral nervous system [12]. Isolated intracranial WD is particularly rare [13]. A majority of patients with intracranial WD have abnormal cerebrospinal fluid (CSF) findings. A positive CSF PCR assay has previously proven essential in the diagnosis of CNS involvement with WD [12,14,15]. Duodenal biopsies at multiple levels examined under light microscopy, electron microscopy, and by PCR may be positive even in patients with isolated neurological manifestations [16]. When all tests these are negative, stereotactic brain biopsy and PCR assay of the nervous tissue specimen should be performed on patients with a high suspicion for WD [12,16].

We present the challenging case of a 50 year-old African-American woman presenting with isolated cerebral WD.

2. Case presentation

2.1. Clinical history and physical examination

A 50 year-old right-handed African-American woman with history of hypertension and asthma presented with a 5-month history of rapid cognitive decline. The patient's family noticed her having difficulties with paying her bills on time, completing tasks at work, forgetting passwords, which progressed to getting lost in familiar surroundings. Over these few months, she developed visual hallucinations, insomnia, dysarthria, and gait unsteadiness. She was admitted to another hospital with new-onset seizures. Work-up, including a brain biopsy (discussed below) was negative for Creutzfeldt–Jacob disease (CJD), viral and bacterial encephalitis, and cerebral neoplasm. She was transferred to our hospital with worsening cognition and gaze palsy. She was afebrile with normal vital signs. On neurological exam, she was oriented only to self and had difficulty following commands. She could not recall, write a sentence, or copy a figure. She had a 1.35 Hz pendular, horizontal nystagmus that was convergent–divergent (Video 1). Extraocular muscle testing revealed supranuclear vertical gaze palsy. She had preserved lateral gaze with saccadic pursuits. Occulocephalic eye movements were intact. Her speech was dysarthric and she had mild weakness in the right upper extremity with hyperreflexia in all four extremities, along with gait unsteadiness.

2.2. Laboratory investigations

Basic hematological and electrolyte studies were within normal limits except for mild hyponatremia. Serum studies were negative for HIV-1 and HIV-2, CMV PCR, thyroid peroxidase antibody, *T. whipplei* PCR, hepatitis, vitamin B12 and folate deficiency, thyroid disease, and heavy metal toxicity. CSF studies including HSV, IgG index, oligoclonal bands, 14-3-3 protein, *T. whipplei* PCR, *M. tuberculosis* PCR and gram stain, EBV PCR, HHV6 PCR, and cryptococcal antigen were also negative.

2.3. Neuroimaging

Serial brain MRI scans done over the course of the patient's clinical presentation showed lesions with T2 and FLAIR hyperintense signals in left caudate, left putamen, and right hippocampus (Fig. 1A–C). The patient underwent an ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) PET scan which showed markedly increased metabolic activity in the left putamen (140% more uptake of glucose) and left amygdala with global cortical hypometabolism (Fig. 1D).

2.4. Surgical intervention #1 and histopathology

Open biopsy of the cortex and subcortical region in the right frontal lobe was performed at the outside hospital. Histopathologic evaluation showed slight astrogliosis and focal vacuolation but was overall negative for CJD. Immunostaining of the specimen with monoclonal antibody to prion protein (3F4) failed to reveal the granular deposits as seen with prion diseases such as CJD and therefore further molecular testing for abnormal prion protein was not carried out. Because the patient had continued neurological symptoms, she was transferred to our medical center for further evaluation and treatment.

2.5. Surgical intervention #2 and histopathology

Given the patient's progressive cognitive decline, as well as the MRI and PET findings, it was decided to proceed with stereotactic biopsy of the left putamen. Multiple core samples were obtained and examined. Gray and white matter samples showed gliosis, focal lymphocytic and microglial inflammation, and prominent cytoplasmic inclusions in CD68-immunoreactive monocytic cells suspicious for microorganisms (Fig. 2A, B, E, and F). The cytoplasmic inclusions stained strongly with PAS and Grocott methenamine silver (GMS)