Primary Whipple disease of the CNS presenting with chorea and dystonia

A video case report

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Practical Implications

Consider Whipple disease in the differential diagnosis of patients with parkinsonism and chorea-dystonia.

Video

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Whipple disease (WD) is a rare, multisystem infectious disease caused by the Gram-positive bacillus *Tropheryma whippelii*. The classic clinical features comprise diarrhea, weight loss, arthralgia, and abdominal pain.¹ Neurologic signs and symptoms can also be observed.² The diagnosis of CNS involvement is difficult in the setting of systemic WD, and is even more difficult when the disease is confined to the CNS (primary WD of the CNS).

Case report

A 50-year-old right-handed man presented with a 1-year history of gait impairment, speech difficulties, and hoarseness. He denied diarrhea, arthralgia, or abdominal pain. Neurologic examination revealed a mild eye supraversion limitation with saccadic intrusions, dysarthria, and dysphonia. The rest of the cranial nerves were normal. Mini-Mental State Examination score was 29/30. He exhibited oral dyskinesias and choreic movements of his left limbs, particularly of the left hand. Dystonic postures were observed in the left limbs. A mild bradykinesia was detected in both hands, more severe on the left side. Deep tendon reflexes were brisk, with bilateral ankle clonus, and right Babinski sign. His gait was characterized by small, shuffling steps, mainly with the right leg, with no right arm swing (video at Neurology.org/cp). There were no sensory deficits. General physical examination showed no lymphadenopathy or skin hyperpigmentation.

Complete blood count, electrolytes, erythrocyte sedimentation rate, serum and urine copper, ceruloplasmin, and a blood smear were normal. A brain MRI showed nonspecific nonenhancing hyperintense foci in supratentorial white matter (figure, A). Genetic testing for Huntington disease was negative. CSF analysis (cells, proteins, oligoclonal bands, and viral, bacterial, and mycobacterial cultures) was normal. Brain ¹⁸F-fluorodeoxyglucose PET

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Funding information and disclosures are provided at the end of the article. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.

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Figure Neuroimaging and electron microscopy findings

(A) Fluid-attenuated inversion recovery sequences on brain MRI show supratentorial hyperintense foci (arrows) that did not enhance after gadolinium administration; these findings were nonspecific, normal for the patient's age, and probably unrelated to Whipple disease. (B) ^{18}F -fluorodeoxyglucose PET shows bilateral hypometabolism in the basal ganglia, predominantly on the right side (arrows). (C) Electron microscopy of the CSF demonstrates the typical appearance of the rod-shaped bacilli, with a trilaminar cell wall and granular-fibrillar cytoplasm.

(FDG-PET) showed a decreased metabolism of the basal ganglia, predominantly on the right side (figure, B). Electron microscopy of a new CSF sample disclosed bacilli consistent with *T. whipplei* (figure, C). The patient was treated with IV ceftriaxone 4 g/day and streptomycin 1 g/day for 15 days. Then he switched to trimethoprim-sulfamethoxazole (TMP-SMZ) 160/800 mg/day. One month later, symptoms had worsened and the patient had developed diarrhea. He was admitted for an IV course of ceftriaxone 4 g/day for 1 month. *Clostridium difficile* toxin in stool was negative. An upper endoscopy with duodenal and jejunal biopsies disclosed no bacilli and the diarrhea was attributed to the antibiotherapy. A third CSF analysis was negative for *T. whipplei* but CSF PCR analysis was positive. He was discharged with the same TMP-SMZ regimen. Eight months later (11 months after presentation), he described mild gait improvement. Diarrhea had disappeared. A fourth CSF analysis disclosed no bacilli, but PCR remained positive. Ten months later (21 months after presentation), treatment with TMP-SMZ was withdrawn and the patient experienced a relapse in the symptoms with worsening of the gait and dysarthria. Treatment with TMP-SMZ was restarted, and an 18-month course of oral doxycycline 200 mg/day was added, with no improvement. Since then, the patient has been receiving TMP-SMZ indefinitely, with a slowly progressive symptomatic worsening. Chorea and dystonia have not changed; cognitive function remains intact.

DISCUSSION

The differential diagnosis of parkinsonism with chorea and dystonia comprises neuroachantocytosis, neuroferrinopathies, familial parkinsonism, and Huntington disease.³ In our patient, the diagnostic workup excluded most of these possibilities. Oculomasticatory myorhythmia and oculo-facial-skeletal myorhythmia, pathognomonic for CNS-WD, are only present in 20% of patients, and were absent in our case. The detection of the trilaminar wall of the bacilli from a CSF sample in electron microscopy led to the final diagnosis, which was confirmed by subsequent CSF PCR analysis. Remarkably, the MRI did not show masses or multiple enhancing lesions, as most cases of CNS-WD do.^{4,5} The brain FDG-PET showed a decreased basal ganglia metabolism, predominantly on the right side, contralateral to the chorea. This metabolic pattern has not been previously reported in CNS-WD. The presence of chorea-dystonia along with the FDG-PET results suggest that, in our case, WD concerned predominantly the basal ganglia, although the pyramidal tract was also bilaterally impaired, as evidenced by the upper motor neuron signs.

Prognosis and outcome of patients with treated CNS-WD is variable. CNS involvement implies the highest risk for relapse.⁵ Despite long-term antibiotherapy, our patient did not improve, and even worsened, similarly to previously reported series.² Resistance of *T. whipplei* to TMP-SMZ should be considered in patients with no response to the treatment.⁶

This case emphasizes the need to consider WD within the differential diagnosis of patients with parkinsonism, chorea-dystonia, and pyramidal signs, underlies the utility of FDG-PET in patients with movement disorders of unclear origin or with normal brain MRI, and highlights the fact that the disease may persist after several years of treatment.

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ACKNOWLEDGMENT

The authors thank the personnel of the Unidad de Microscopía Electrónica y Confocal del Instituto de Salud Carlos III, Majadahonda, Madrid, Spain, for help with the electron microscopy procedures.

STUDY FUNDING

No targeted funding reported.

DISCLOSURES

The authors report no disclosures. Full disclosure form information provided by the authors is available with the **full text of this article at Neurology.org/cp**.