Human African Trypanosomiasis Encephalitis in the United States: Serial Magnetic Resonance Imaging

The Neurohospitalist
2016, Vol. 6(4) 170-173
© The Author(s) 2016
Reprints and permission:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/1941874416637403
nhos.sagepub.com

Mary Carter Denny, MD, MPH^{1,2,3}, Leon L. Lai, MD⁴,
and Robert Laurenco, MD^{1,2}

Abstract

It is important to recognize the signs and symptoms of human African trypanosomiasis (HAT) in order to facilitate early diagnosis and treatment. A 36-year-old man developed encephalitis caused by HAT. This encephalitis can appear many years after well-tolerated systemic infection. The neurologic manifestations developed 7 years after he had emigrated from Cameroon to the United States. We demonstrate the magnetic resonance imaging before, during, and after his treatment with intravenous eflornithine. Clinical signs and symptoms of HAT can be nonspecific and precede abnormalities on magnetic resonance imaging. Human African trypanosomiasis should be considered in the differential diagnosis of patients who have lived in sub-Saharan Africa and have a clinical presentation of subacute encephalitis.

Keywords

trypanosomiasis, encephalitis, cerebrospinal fluid, magnetic resonance imaging

Introduction

Human African trypanosomiasis (HAT) or African sleeping sickness is a lethal protozoan infection caused by *Trypanosoma brucei gambiense* in Central and West Africa and by *Trypanosoma brucei rhodesiense* in East and Southern Africa. Both forms of HAT are transmitted to humans by the tsetse fly.^{1,2} Stage 1, the hemolymphatic stage, begins 1 to 3 weeks after the tsetse fly bite and is characterized by fever and generalized lymphadenopathy. Stage 2, the encephalitic stage, can occur months to years later. It is characterized by myriad neurologic symptoms including sleep disturbances, various involuntary movements, allodynia, and personality changes.^{3,4}

Human African trypanosomiasis is endemic to 36 countries in sub-Saharan Africa, with *Trypanosoma brucei gambiense* accounting for 98% of all cases. There has been a steady decline in the reported cases from 25 865 in 2000 to 6 978 in 2010.⁵ From 2000 to 2010, only 94 of the reported cases worldwide were from nonendemic countries. The nonendemic cases of *Trypanosoma brucei gambiense* occurred in expatriates who had lived in endemic countries for prolonged periods and in sub-Saharan Africans who had immigrated to nonendemic countries. Initial misdiagnoses of nonendemic HAT cases can lead to unnecessary invasive testing.⁶ It is important to raise physicians' awareness of the signs and symptoms of

HAT, in nonendemic countries, in order to facilitate early diagnosis and treatment and thereby decrease fatalities.

Methods

A waiver of informed consent for this study was granted by the institutional review board of Medstar Research Institute at Medstar Washington Hospital Center (protocol #2015-149) dated August 13, 2015. The patient discussed in this article was shown the final version of the manuscript and consented to its publication.

¹ Department of Neurology, Medstar Washington Hospital Center, Washington, DC, USA

² Department of Neurology, Georgetown University School of Medicine, Washington, DC, USA

³ Department of Neurology, University of Texas Health Science Center at Houston, Houston, TX, USA

⁴ Section of Infectious Diseases, Department of Internal Medicine, Medstar Washington Hospital Center, Washington, DC, USA

Corresponding Author:

Mary Carter Denny, Department of Neurology, University of Texas Health Science Center at Houston, 6431 Fannin Street, MSB 7.119, Houston, TX 77030, USA.

Email: mary.c.denny@uth.tmc.edu

Figure 1. A and B, Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance images (MRIs) at the levels of the basal ganglia and pons from April 1, 2010, when the patient first presented with alexia, agraphia, and a left homonymous hemianopsia.

Case Description

A 36-year-old man came to clinic with a new complaint of inability to read or write, which prevented him from completing his citizenship exam. He had a history of hypertension, 2 hypertensive intracerebral hemorrhages, stage 2 chronic kidney disease, and chronic anemia. Since emigrating from Cameroon to the Washington, DC area 7 years earlier, he had not left the United States. He had worked in an animal research laboratory since immigration. He was married and monogamous. He denied any illicit drug use. Blood pressure was 144/81, and his general physical examination was normal. Neurologic examination was notable for a left homonymous hemianopsia, inability to repeat, agraphia, and alexia. Stroke was suspected, but magnetic resonance imaging (MRI) showed only evidence of his prior intracerebral hemorrhages. There was no correlate for his new neurologic symptoms (Figure 1A and B).

One month later at the emergency department (ED), he reported 2 weeks of intermittent horizontal diplopia and blurred vision, as a result of which he had driven into another car. For 9 months, his family had observed somnolence, decreased concentration, and worsening gait, all of which had worsened over the past week. Blood pressure was 128/79. New neurologic examination findings included disorientation to date, poor attention and recall, right eye abduction palsy, right lower facial weakness, left upper extremity weakness, wide-based gait, and inability to walk in tandem. White blood cell (WBC) count was 6.7 K/UL, hemoglobin 9.5 g/dL, hematocrit 28.3%, platelet count 135 K/UL, blood urea nitrogen 46 mg/dL, creatinine 2.34 mg/dL, and erythrocyte sedimentation rate of 122, highly positive anticardiolipin immunoglobulin (Ig) M, positive serum Lyme enzyme-linked immunosorbent assay, and highly positive serum Lyme IgG and IgM. HIV antibody testing and rapid plasma reagin were nonreactive. Thyroid-stimulating hormone, ammonia, B12, and folate levels were within normal limits. Cerebrospinal fluid (CSF) showed 600 WBCs (94% lymphocytes), 0 red blood cells (RBCs), protein 107 mg/dL, and glucose 42 mg/dL.

Figure 2. A and B, Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) images at the levels of the basal ganglia and pons from May 4, 2010, when the patient had horizontal diplopia, somnolence, poor concentration, and impaired gait.

Cerebrospinal fluid bacterial, fungal, and viral cultures and Lyme antibodies were negative. Electroencephalogram was moderately abnormal due to focal slowing suggestive of a left temporal disorder. Brain MRI showed diffuse abnormal T2 hyperintensity in the white matter of the bilateral frontal, left parietal, brain stem, and bilateral cerebellar areas that had not been present 1 month earlier (Figure 2A and B). A brain biopsy was deferred. He was given intravenous (IV) ceftriaxone for presumed neuroborreliosis, despite negative Lyme antibodies in the CSF. The patient had improvement in his mental status. Repeat CSF studies showed 156 WBCs (89% lymphocytes), 75 RBCs, protein 80 mg/dL, and glucose 44 mg/dL. After an 18-day hospitalization, he was discharged to home. There he completed 4 weeks of IV ceftriaxone.

One month after discharge, the patient presented to the ED with 1 week of lethargy and decreased responsiveness with a blood pressure of 128/69. He had a generalized tonic-clonic seizure in the ED and was given IV phenytoin. Review of his past medical records showed splenomegaly, presumed viral pericarditis, nephrotic syndrome, and mild, chronic thrombocytopenia. Hepatitis C testing and bone marrow biopsy done 3 years earlier for evaluation of pancytopenia were negative. On neurologic examination, he did not open his eyes to loud speech or sternal rub. Brain stem reflexes were intact and he moved all 4 extremities spontaneously. Electroencephalogram on admission was normal. Cerebrospinal fluid showed 571 WBCs (90% lymphocytes), 43 RBCs, protein 77 mg/dL, and glucose 45 mg/dL. JC virus and malaria smear of the CSF were negative. Human African trypanosomiasis was considered. Blood smears and CSF wet preparations revealed no trypanosomes. A repeat lumbar puncture was performed. By utilizing concentration columns obtained from the Centers for Disease Control (CDC), one mobile trypanosome was found on a wet mount at our institution, Medstar Washington Hospital Center. Blood samples and uncentrifuged CSF were sent to the Prince Leopold Institute of Tropical Medicine in Antwerp, Belgium, where the *Trypanosoma brucei* ss *gambiense* card agglutination test, immunofluorescent

Figure 3. A and B, Axial fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) images at the levels of the basal ganglia and pons from July 4, 2010, at the time stage 2 human African trypanosomiasis (HAT) was diagnosed and intravenous (IV) eflornithine was started.

antibody test (IFAT), and polymerase chain reaction (PCR) were all positive. In the CSF, *Trypanosoma brucei ss gambiense* IFAT and general trypanosoma PCR were positive, but the *Trypanosoma brucei ss gambiense* PCR was negative.

A repeat brain MRI showed increased T2 hyperintensity throughout the white matter of both the cerebral hemispheres and the brain stem (Figure 3A and B). In the areas of edema, there was decreased signal on T1-weighted images without gadolinium enhancement; there was no abnormal signal on susceptibility-weighted imaging or diffusion-weighted imaging.

The patient was diagnosed with stage 2 HAT. Eflornithine 100 mg/kg IV every 6 hours was given for 2 weeks per the recommendation of our CDC consultant. The treatment was held for 24 hours on day 3 when the patient had fever, nausea, vomiting, and 3 generalized seizures. Electroencephalogram showed occasional left temporal sharp waves. By day 10 of eflornithine therapy, he was awake enough to converse. The patient was discharged with home nursing services after a 2-month hospitalization.

At clinic 6 weeks after eflornithine treatment, he was alert. Abducens palsy and gait ataxia had resolved completely. He had significant residual alexia and agraphia, which made it very difficult for him to hold a job. A repeat brain MRI 4 months after his HAT treatment showed resolution of the previously seen abnormal T2 signal in the white matter of the cerebral hemispheres, brain stem, and cerebellum (Figure 4A and B). Repeat CSF studies 6 months after the treatment were within normal limits with no evidence of residual trypanosomes.

Discussion

Human African trypanosomiasis is a parasitic infection whose neurologic manifestations may not be apparent until years after the initial infection. Our patient last lived in Fontem, Cameroon, an endemic area for HAT at least 19 years prior

Figure 4. A and B, Axial fluid-attenuated inversion recovery (FLAIR) images at the level of the basal ganglia and pons from November 10, 2010, 4 months after treatment with eflornithine for human African trypanosomiasis. There had been marked clinical improvement.

to his presentation. He had not resided in any other high endemicity areas. This case, in which he had not returned to Cameroon for 7 years at the time he developed encephalitis, demonstrates a very long latency period. His 2 prior intracerebral hemorrhages, likely secondary to uncontrolled hypertension, initially complicated the neurologic analysis. Human African trypanosomiasis can be associated with splenomegaly, pancytopenia, nephrotic syndrome, and pericarditis, all of which this patient had 3 years prior to neurologic presentation. Despite these clues, HAT was not suspected until the patient had florid encephalitis.

This case also illustrates that Lyme antibody detection is highly prone to cross-reactivity. Against the advice of the neurology consultant, this patient was treated with IV ceftriaxone for presumed neuroborreliosis, which delayed the correct diagnosis and treatment. Physicians should be cautioned against making a diagnosis of neuroborreliosis based on the presence of serum Lyme antibodies in a patient whose clinical presentation and imaging are not consistent with this diagnosis.

The patient's disease progressed clinically, as is to be expected, with this indolent form of encephalitis and, as one might expect, the imaging abnormalities worsened as his neurological condition declined. There is 1 prior case, of which we are aware, that documents the brain parenchymal changes seen on MRI in HAT.¹ The present case is the first to demonstrate that symptoms of HAT can appear before there are any abnormal imaging findings (Figure 1A and B). Human African trypanosomiasis should be considered in the differential diagnosis of patients who have lived in sub-Saharan Africa and have a clinical presentation consistent with encephalitis. The diagnosis is often delayed for several reasons. First, American physicians are not familiar with HAT. Second, they are not familiar with the long latency, that the neurologic manifestation may be delayed for years, and that the preceding systemic disease may cause no prominent symptoms.

The present case demonstrates the importance of accurately diagnosing this often lethal infection. Human African

trypanosomiasis is a treatable disease. Although IV eflornithine is not commercially available as an antitrypanosomal medicine, it can be obtained from the CDC on an as-needed basis for serum and CSF-proven cases of HAT.

Authors' Note

The patient discussed in this article or their surrogate was shown the final version of the manuscript and consented to its publication. Drs Lai and Laureno had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to study concept and design, acquisition of data, analysis and interpretation of data, and critical revision of the manuscript for important intellectual content. Dr Denny contributed to the drafting of the manuscript.

Acknowledgment

The authors thank Dr Lee H. Monsein for his assistance with the MRI images presented here.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

References

1. Kager PA, Schipper HG, Stam J, Majoie CB. Case report: magnetic resonance imaging findings in human African trypanosomiasis: a four-year follow-up study in a patient and review of the literature. *Am J Trop Med Hyg*. 2009;80(6):947-952.
2. Kennedy PG. Human African trypanosomiasis of the CNS: current issues and challenges. *J Clin Invest*. 2004;113(4):496-504.
3. Lejon V, Buscher P. Review article: cerebrospinal fluid in human African trypanosomiasis: a key to diagnosis, therapeutic decision and post-treatment follow-up. *Trop Med Int Health*. 2005;10(5):395-403.
4. Blum J, Schmid C, Burri C. Clinical aspects of 2541 patient with second stage human African trypanosomiasis. *Acta Trop*. 2006;97(1):55-64.
5. World Health Organization. Human African Trypanosomiasis Fact Sheet Number 259. Web site. <http://www.who.int/mediacentre/factsheets/fs259/en/>. Accessed February 2016.
6. Simarro PP, Ranco JR, Cecchi G, et al. Human African trypanosomiasis in non-endemic countries. *J Travel Med*. 2012;19(1):44-53.