Rhombencephalitis Secondary to *Toxoplasma gondii* Infection: Case Report and Literature Review

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Abstract

Immunocompetent (IC) individuals with primary toxoplasmosis are usually asymptomatic. However, in some IC, toxoplasmosis can present with brainstem encephalitis. We report an adult female patient with headache associated with worsening coordination. Physical examination showed bilateral, symmetrical, and nontender cervical lymphadenopathy. Toxoplasmosis immunoglobulin G (IgG) and IgM were high, and the IgG antibody avidity pattern was low. The cerebrospinal fluid analysis was requested that revealed a positive polymerase chain reaction results for toxoplasmosis. A brain magnetic resonance imaging (MRI) showed a T1-hypointense left pontine lesion. Pyrimethamine and sulfadiazine were started. After 1 month, the patient had full recovery. Four months after, the individual was admitted due to progressive abnormal eye movements and tremor. Her neurological examinations showed ocular myoclonus and Holmes tremor. A second brain MRI showed hypertrophy of the ipsilateral inferior olivary nucleus. In the follow-up, her symptoms decreased mildly. The tremor was managed with clonazepam and levodopa. Furthermore, immune suppression investigation was negative.

Keywords: Encephalitis, myoclonus, toxoplasmosis, tremor

Introduction

Toxoplasma gondii is an intracellular protozoan parasite that infects almost all warm-blooded animals.[1] In this context, immunocompetent (IC) individuals with a primary *T. gondii* infection are usually asymptomatic.[2] However, in some participants that are IC, toxoplasmosis can present with an acute systemic infection, ocular disease, or in rare situations, with brainstem encephalitis.[2,3]

Few cases of hypertrophic olivary degeneration (HOD) caused by rhombencephalitis associated with *T. gondii* infection have been reported in the literature. More specifically, to the authors' knowledge, there are two case reports of immunosuppressed (IS) individuals with toxoplasmosis who developed HOD.[3,4] Nevertheless, this condition has not been reported in an IC participant until the present moment.

Here, we reported the case of an adult female who presented with headache and poor coordination. Cervical lymphadenopathy was observed. Laboratory results confirmed a *T. gondii* infection, and the patient was treated. A brain magnetic resonance imaging (MRI) revealed a lesion in the left pons. After 4 months, the patient presented with ocular myoclonus and Holmes tremor. A new brain MRI showed the left HOD.

Case Report

A 50-year-old female patient presented to our hospital with a sudden onset of headache associated with worsening coordination within 5 days of onset. The patient was a previously healthy farmer, and her family history was negative for neurological diseases. On neurological examination, she was fully conscious and orientated. A mild action tremor was observed bilaterally. Laboratory tests, including complete blood cell count, sodium, potassium,

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Submitted: 02-Sep-2019 **Accepted:** 02-Oct-2020 **Published:** 15-May-2020

Access this article online

Quick Response Code:

Website: www.actamedicainternational.com

DOI: 10.4103/ami.ami_78_19

How to cite this article: Rissardo JP, Caprara AL, Silveira JO. Rhombencephalitis secondary to *toxoplasma gondii* infection: Case report and literature review. Acta Med Int 2020;7:51-4.

glucose, urea, creatinine, bilirubin, aspartate, and alanine transaminase, were within the normal limits. A cranial computed tomography (CT) scan was normal. Supportive management was conducted.

On the 3rd admission day, the patient stated that before the onset of the first neurological symptoms, she had a mild fever for 3 days associated with myalgia and the appearance of persistent cervical adenopathy.

Physical examination showed the neurological findings mentioned above and revealed bilateral, symmetrical, nontender cervical lymphadenopathy. Laboratory examinations were requested: toxoplasmosis immunoglobulin G (IgG, IgM, and IgG antibody avidity pattern), hepatitis B and C (anti-HbsAg and anti-hepatitis C virus), cytomegalovirus (IgG and IgM), Venereal Disease Research laboratory, anti-HIV (1, 2), Herpes simplex virus (1, 2), Epstein–Barr (IgG and IgM), Chagas (IgG and IgM), Borrelia Burgdorferi (IgG and IgM), rheumatological diseases (anti-ribonucleoprotein, Anti-Sjögren's-syndrome-related antigen A (SSA), Anti-Sjögren's-syndrome-related antigen B (SSB), creatine phosphokinase, antinuclear antibody, and rheumatoid factor), anti-thyroid peroxidase, anti-transglutaminase, and purified protein derivative skin test.

The results were within the normal limits, except for toxoplasmosis IgG and IgM, which were high, and the IgG antibody avidity pattern that was low.

Afterward, the cerebrospinal fluid (CSF) analysis was requested, which revealed a positive polymerase chain reaction result for toxoplasmosis, 26/mm^3 of white blood cells and 50 mg/dL of protein. The CSF culture and Gram stain were negative. A brain MRI showed a T1-weighted hypointense left pontine lesion with extension into the midbrain. Pyrimethamine 100 mg loading dose followed by a maintenance dose of 50 mg a day and sulfadiazine 4 g a day were started. After 1 month, the patient had a full recovery.

Approximately 4 months after, the individual was admitted due to progressive abnormal eye movements and tremors. On the neurological examination, her eye movements were pendular with an equal smooth speed in both directions; a resting and intention tremor with irregular amplitude was observed in the upper extremities, but it was worse in her left side.

Upon further questioning, the individual admitted that she had two other similar episodes, in the last month, of nausea and inability to focus her vision in a point, she thought that were normal due to working hard daily in agriculture. She only sought medical assistance this time because her symptoms remained.

Laboratorial tests and CSF analysis were within the normal limits. A cranial CT scan was normal. A second brain MRI showed hypertrophy of the ipsilateral left inferior olivary nucleus. In the follow-up, her symptoms decreased mildly, but she did not have a full recovery. The tremor was managed with clonazepam and levodopa. Furthermore, immune suppression investigation was negative.

Discussion

Toxoplasmosis is an infection caused by *T. gondii*. In this way, contact with this obligate intracellular protozoan can occur by four pathways in humans: ingestion of contaminated food or water-containing oocysts, ingestion of undercooked meat with tissue cysts, transplacental from mother to fetus, or by organ transplantation.[1] *Felidae* is the only family of animals where *T. gondii* can complete its reproductive cycle, and the domestic cat is an important definitive host for this parasite.[1]

The most common clinical manifestation of toxoplasmosis in an IC is similar to an acute systemic reaction presenting with mild fever, headache, and persistent lymphadenopathy that is found bilateral, symmetrical, nontender, and more frequently localized in the cervical region.[2] The diagnosis in IC can be made with typical presentation and serological results of serum or CSF confirmatory for *T. gondii*.[2,5] However, atypical and severe complications such as rhombencephalitis can occur, although rarely, even in IC patients.[2,3]

The Guillain–Mollaret Triangle, also known as the dentate-rubro-olivary pathway, is composed of three corners: dentate nucleus, inferior olivary nucleus, and red nucleus.[6] In this way, a disruption in any of the three sides (tracts) that connect these corners can result in HOD.[4,7] The clinical symptoms associated with this transsynaptic degeneration include Holmes tremor, ocular myoclonus, and palatal tremor.[6,7] Although HOD is not always symptomatic, clinical manifestations have been reported months later of the inciting lesion in the majority of the cases.[4,6,7]

A presentation of toxoplasmosis with rhombencephalitis followed by HOD was rarely reported in the literature. We identified two case reports in English, and we compared them with the present case [Table 1].[3,4] Nevertheless, the reported participants were IS, and hence, the present case is the first in an IC individual.[3,4] A literature search was performed in Embase, Google Scholar, Lilacs, Medline, Scielo, and ScienceDirect, on a set of terms that included toxoplasmosis, rhombencephalitis, and HOD.

The literature review of Jubelt *et al*. about brainstem encephalitis found that toxoplasmosis only involving the rhombencephalon/brainstem, primarily involving it, or only involving it at the disease onset was very rarely reported.[8] Their study only found one case report.[8] Thus, this presentation is uncommon and the fact that it occurred in an IC individual could probably be explained by the local environmental factors.

Interestingly, on epidemiological research, we found that in the first semester of 2018, there was a substantial increase in

Table 1: Case report of patients with *toxoplasma gondii* infection who developed hypertrophic olivary degeneration

Reference	Kure *et al*.	Sabat *et al*.	Present case
Age (year-old)/sex	-	62/male	50/female
Symptoms at presentation	Ipsilateral ophthalmoparesis and contralateral ataxia	Falling backward, headache, and poor coordination	Headache and poor coordination
Immunocompetent or suppressed	IS, HIV+	IS, HIV+	IC
T. gondii diagnosis	Autopsy?	Previous diagnosis	*T. Gondii* IgG, IgM, IgG antibody avidity pattern; cerebrospinal fluid PCR positive for *T. Gondii*
HOD characteristics			
Method that diagnosed HOD	Autopsy	Brain MRI	Brain MRI
Findings of the method used	Necrotic midbrain lesion due to *T. gondii* and HOD	1st MRI: Ring-enhancing lesions in the left parietal and occipital lobes, right superior thalamus, and left cerebellum. HIV encephalopathy findings in the periventricular white matter and centrum semiovale 2nd MRI: New T2W changes in the right anterior medulla	1st MRI: T1W hypointense left pontine lesion with extension into the midbrain 2nd MRI: Hyperintense lesion on T2W and FLAIR in the left ION
Lesion that probably caused the HOD	-	Left cerebellum	Left pons
HOD site	-	Right ION	Left ION
Time from initial lesion until HOD diagnosis	-	3 months	3 months
HOD-associated symptoms	-	None	Ocular myoclonus and Holmes tremor
Management	-	After the 1st MRI, sulfadiazine, pyrimethamine, and leucovorin were started	Sulfadiazine, pyrimethamine, and leucovorin were started. Clonazepam and dopaminergic agents

FLAIR: Fluid-attenuated inversion recovery; HIV+: Human immunodeficiency virus-positive, HOD: Hypertrophic olivary degeneration, IC: Immunocompetent, ION: Inferior olivary nucleus, IS: Immunosuppressed, MRI: Magnetic resonance imaging, T1W: T1-weighted, T2W: T2-weighted, *T. gondii*: *Toxoplasma gondii*

the number of patients diagnosed with toxoplasmosis in the city of Santa Maria, Brazil, which is the city where the patient lives.[9] A cross-sectional study of Dal Ponte *et al*. using the data published in bulletins by the Municipal Health Department of the city revealed that this outbreak was the largest reported in Brazil and apparently in the world.[9] Therefore, we hypothesized that this presentation only happened because of the occurrence of the toxoplasmosis outbreak in the city of Santa Maria.

The cerebral cortex and basal ganglia are the areas that most commonly affected by *T. gondii*, and only fewer lesions in the cerebellum, brainstem, and spinal cord are found.[5] However, almost all the information available today about the predilection of *T. Gondii* for the central nervous system (CNS) derives from the studies with severely IS individuals.[5] In this context, more research is needed to elucidate the physiopathology of CNS infection by *T. Gondii* in IC participants. The study of Alvarado-Esquivel *et al*. was the first with IC and showed *T. gondii* in the neurons and astrocytes of IC individuals, but the methodology and how this observation was determined are unclearly described in their study.[5,10] Thus, more data from IC individuals are needed to better evaluate risk factors, most common associated comorbidities, areas of CNS predilection, and prognosis of this group of individuals when they are infected with *T. gondii*.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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