Heliyon 9 (2023) e18293

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

A case report of a successful alternative regiment therapy for toxoplasma encephalitis in AIDS patients

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ARTICLE INFO

Keywords:
Toxoplasma encephalitis
HIV
Cotrimoxazole
Clindamycin
Case report

ABSTRACT

Introduction: AIDS patients are more susceptible to opportunistic diseases, such as toxoplasma encephalitis, because of weakened immune systems. Toxoplasma encephalitis manifests as a severe neurological crisis in HIV patients. The standard initial treatments are sulfadiazine and pyrimethamine. This case presents an HIV patient treated with an alternative regimen for toxoplasma encephalitis.

Case description: A young Acehnese man, 32 years old, arrived at the emergency unit after complaining of a general seizure 2 hours before arrival. He has a history of a two-week fever and white patches on his tongue and oral cavity. The result of the HIV test was positive, and after a thorough examination, he was diagnosed with toxoplasma encephalitis. The patient was given cotrimoxazole 960 mg twice daily and clindamycin 600 mg four times daily as an alternative treatment. Clinical improvement was reported after six weeks of therapy.

Conclusion: A case of toxoplasma encephalitis was reported. The first-line treatment for toxoplasma encephalitis is pyrimethamine and sulfadiazine; however, the patient was treated with cotrimoxazole and clindamycin as an alternative treatment. Clinical improvement was used to assess the success of therapy. Cotrimoxazole and clindamycin can be utilized as alternative regiment therapy if the first-line treatment option is unavailable.

1. Introduction

Patients with AIDS have a weakened immune system, making them more vulnerable to opportunistic infections such as toxoplasma encephalitis. Toxoplasmosis is an infectious disease caused by the parasite Toxoplasma gondii (T. gondii), which is commonly asymptomatic in immunocompetent patients. In immunocompromised individuals, such as those with AIDS, however, these parasite infections can reactivate and manifest clinically. Typically, pathogenic infections are caused by consuming inadequately prepared meat, infected vegetables, fruits, air-borne oocysts, or T. gondii bradyzoites. This disease can also be transmitted vertically through the placenta, blood transfusions, and organ transplants [1].

T. gondii is a common obligatory parasite prevalent in regions with hot and humid climates, including Latin America, Africa, and

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https://doi.org/10.1016/j.heliyon.2023.e18293
Received 4 January 2023; Received in revised form 6 July 2023; Accepted 13 July 2023
Available online 14 July 2023

Southeast Asia [1,2]. T. gondii has infected 50% of the world's human population. Approximately 10–45% of AIDS patients develop toxoplasma encephalitis [3]. Southeast Asia has a high incidence of toxoplasmosis, with Malaysia having the greatest prevalence. In Indonesia, T. gondii infection affects roughly 45% of HIV-positive individuals [2].

In HIV patients, toxoplasma encephalitis (TE) is a neurological emergency. About 30–40% of HIV patients with CD4 counts less than 100 cells/mm^3 who do not receive prophylaxis develop toxoplasmosis [1]. The brain is the most frequently infected organ in this condition and the leading cause of focal central nervous system disorder in AIDS patients [4,5].

Toxoplasma encephalitis therapy includes active infection control followed by maintenance therapy to prevent recurrence in individuals with CD4 counts of less than 200 cells/mm^3. Standard treatment consists of sulfadiazine and pyrimethamine or pyrimethamine plus clindamycin. However, due to a shortage of supplies of sulfadiazine and pyrimethamine at our local hospital in Aceh, an alternative regiment was used for an HIV patient who experienced symptomatic TE. This case reports a successful therapy of a TE patient with an alternative regiment.

2. Case description

A 32-year-old Acehnese man was admitted to the hospital after experiencing a seizure prior to his arrival. The seizure caused his entire body to become rigid, and he fell into an unconscious state for 5 min. Afterward, the patient fell asleep and woke up 10 minutes later. He also had intermittent fever and white patches on his tongue and oral cavity for two weeks. During anamnesis, he has trouble articulating words and appears to speak more slowly.

The patient had not been eating much in the past two weeks due to oral candidiasis, and he appeared weak. He did not report any nausea or vomiting. He had lost 10 kg over three months. His bowel and urinary habits were normal. Seven years ago, he had unprotected sexual activities with a partner who had multiple sexual partners. There was no history of injectable drug use. He worked as a driver for intercity bus services.

On physical examination, the patient was in stable condition with a clear sensorium. His blood pressure was 110/60 mmHg, pulse rate was 60 beats per minute with a regular rhythm, respiratory rate was 20 breaths per minute, and temperature was 36.7 °C. His body mass index was 20.9 kg/m2 (57 kg weight, 165 cm height). There was no evidence of lymphadenopathy. He had flaking skin resembling dandruff on his eyebrows and around his beard. Patches of greasy skin with flaky white scales and crust appeared on his cheeks, sides of the nose, ears, and chest.

An oral examination revealed multiple ulcer patches on the border of the patient's tongue. The thorax and abdominal examinations were normal. The neurological test demonstrated weakness in the right limb, with a motor strength of 3, enhanced physiological reflexes (+2), and a positive Babinski reflex on his right leg.

The laboratory finding were as follow: Hemoglobin 14.3 g/dL, hematocrit 42%, leukocytes 4600/mm^3, platelets 269,000/mm^3, a slight increase of erythrocyte sedimentation rate (23mm/hour), alanine aminotransferase (ALT) 28 U/L, aspartate aminotransferase (AST) 25 U/L, urea 18 mg/dL and creatinine 0.97 mg/dL. The HIV rapid test showed a reactive result, CD4 count of 54 cell/μL, HIV

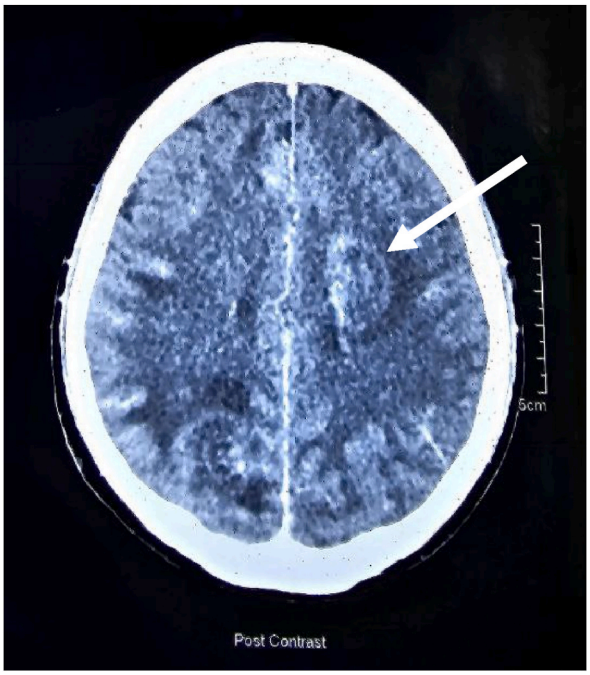

Fig. 1. Head CT scan of the patient show a ring enhancement lesion.

RNA load of 5.1 × 104 copies/mL, and a positive toxoplasma IgG antibody (>1200 IU/mL; reference range: <4 IU/mL). A contrast and non-contrast CT scan of the head revealed a solid lesion measuring 2.1 × 2.8 × 2.3 cm in the left corona radiata to the left basal ganglia, with ring enhancement and perifocal edema surrounding it.(see Fig. 1)

Based on the history, clinical findings and investigations, the patient was diagnosed with AIDS, toxoplasma encephalitis, oral candidiasis, and seborrheic dermatitis. He was prescribed a high-calorie diet of 1700 calories per day, a daily anti-retroviral (ARV) in the form of fixed-dose combination pill (tenofovir 300 mg, lamivudine 150 mg, and efavirenz 600 mg), cotrimoxazole 960 mg twice daily, clindamycin 600 mg four times daily, 3% salicylic acid blended with mometasone (applied to his face), 2% thyamicin blended with lotasbat cream (applied to his feet).

After 14 days of acute phase therapy, patients have a good clinical response. Acute treatment should last at least 3–6 weeks. Following the completion of acute therapy, chronic maintenance dosages were continued. The suggested chronic maintenance dose is half that used during the acute phase of therapy. Maintenance therapy is administered for 6 months after ARV administration until CD4 counts reach 200 cells/L.

3. Discussion

HIV patients have very poor immunity, making it easier for them to become infected with various opportunistic infections which are common in AIDS. It can affect organs such as the lungs, gastrointestinal tracts, and brain. Toxoplasma encephalitis is an opportunistic infection that frequently affects the brain and causes space-occupying lesions in AIDS patients. Infection of Toxoplasma gondii in the nervous system occurs in 30–70% of AIDS patients, and neuropathological abnormalities are detected in 90% of post-mortem tissues [3,6].

This patient was diagnosed with AIDS based on history of unprotected intercourse and loss of body weight, physical examination showing oral candidiasis and seborrheic dermatitis, and a positive HIV result. Oral candidiasis, seborrheic dermatitis, and weight loss of 10 kg are symptoms of an immunocompromised patient.

Toxoplasma gondii enters the body through the consumption of contaminated food or drink. Tachyzoites of T. gondii migrate through the epithelium of the small intestine and enter the bloodstream [7]. Several factors influence the pathogenesis of toxoplasmosis in immunocompromised patients, including decreased $CD4^{+}$, failure to produce IL-12, IL-2, and IFN-γ, and decreased T-lymphocyte cytotoxic activity. HIV-infected cells can inhibit the synthesis of IL-12 and IFN-γ, increasing the susceptibility of AIDS patients to toxoplasmosis infection. Reduced IFN-γ levels in AIDS patients can potentially cause reactivation of chronic toxoplasmosis, leading to symptomatic infection in immunocompromised individuals. Furthermore, this parasite infection can activate the endothelial factors, resulting in the production of adhesion molecules such as ICAM-1 and VCAM-1, which can influence the permeability of the blood-brain barrier, allowing the pathogens to penetrate and induce neurological symptoms [8].

This patient presented with multiple symptoms, including seizure, unconsciousness, oral candidiasis, difficulty articulating words, slow speech, weight loss, seborrheic dermatitis, abnormality physiological reflexes and the presence of pathological reflexes. More than 50% of AIDS patients with toxoplasma encephalitis exhibit intracerebral symptoms and motoric function abnormalities. Headache (38–93%), focal neurologic deficit (22–80%), fever (35–88%), mental confusion (15–52%), seizures (19%–58%), behavioral and psychomotor changes (37%–42%), cranial nerve palsy (12–28%), ataxia (2–30%), and visual disturbances (8–19%) are the most common clinical manifestations in HIV patients with toxoplasma encephalitis [3].

This patient had slow speech and difficulty articulating words, along with abnormal tendon reflexes, which could be caused by a lesion in the brain. A deficit lesion in the basal ganglia was characterized by a reluctance of the patient to communicate, slow and modest movements, and an inability to follow instructions. The basal ganglia is involved in a variety of motor processes, including expression of emotion, integration of sensory and motor impulses, and cognitive functions. It is also responsible for initiating and facilitating voluntary movement while inhibiting involuntary impulses. Pathological reflexes are easier to detect when examining the Babinski reflex [9]. This explanation align with the finding in this patient, which revealed an increased physiological reflexes (+2) and babinski pathological reflex on the right leg.

The diagnostic criteria for TE have been categorized into four terms based on the modalities used to establish the disease: (1) histology-confirmed, (2) laboratory-confirmed, (3) probable TE, and (4) possible TE. Histology-confirmed TE requires a compatible clinical syndrome, brain lesions detected by imaging, and brain biopsy showing evidence of T. gondii. Laboratory-confirmed TE necessitates a compatible clinical syndrome, brain lesions detected by imaging, and evidence of T. gondii DNA in cerebrospinal fluid (CSF) through nucleic acid amplification assays. Probable TE requires a compatible clinical syndrome, brain lesions detected by imaging, and unequivocal radiological response to 10 to 14 days of empiric anti-toxoplasma therapy. Possible TE demands a compatible clinical syndrome, brain lesions detected by imaging, the presence of serum T. gondii immunoglobulin G (IgG) antibodies, and no other alternative diagnosis [10].

Approximately 77.4% of HIV-positive patients with TE have positive anti-IgG toxoplasmosis results, indicating reactivation of a dormant infection [11]. IgG serological results can appear in the first 1–2 weeks after infection, peak in about 1–2 months and may disappear within a few years or persist for life. A positive IgG results indicates that the patient has been chronically infected and is currently experiencing reactivation of T. gondi [12]. The laboratory examinations results in this patient were consistent with the theory, showing a slight increase in the erythrocyte sedimentation rate and a positive IgG result.

Radiologic modalities such as CT scan and/or Magnetic Resonance Imaging (MRI) can be used to assess the presence of TE. Approximately 80% of AIDS patients with positive IgG serology for toxoplasma reveal multiple ring enhancement on head CT scan, which strongly suggest TE. However, some CT scan results in TE cases show a single lesion [5]. According to one study, as many as 41.5% of patients AIDS with TE exhibit a single lesion on the head CT scan [7]. The use of contrast is required to clarify the existence of

TE lesions in the brain because the lesion absorbs the contrast agent and forms a ring image with a thin wall after contrast administration. Some TE lesions may also exhibit perifocal edema. The most common predilection sites are the thalamus, corticomedullary junction and basal ganglia [5]. A head CT scan performed on this patient revealed an encapsulated solid lesion measuring 2.1 × 2.8 × 2.3 cm in the left corona radiata to the left basal ganglia, with perifocal edema around it and contrast enhancement following contrast administration.

Currently, the Food and Drug Administration (FDA) has approved approximately 28 antiretroviral (ARV) drugs from six key classes for the treatment of HIV patients. These classes include nucleoside reverse-transcriptase inhibitors (NRTIs), non-nucleoside reverse-transcriptase inhibitor (NNRTI), protease inhibitor (PI), integrase strand transfer inhibitor (INSTI), fusion inhibitor, chemokine receptor 5 (CCR5) antagonist [13]. Initial antiretroviral therapy typically consist of two NRTIs plus a drug from these classes; NNRTI or PI or INSTI [14]. The World Health Organization (WHO) encourages the use of antiretroviral therapy that has fewer side effects, is more convenient, and comes in a simpler pill form. The choice of ARV should also consider the drugs used for various co-infections and comorbidities commonly found in people living with HIV [15]. Based on availability in our hospital setting, this patient received a fix-dosed combination ARV of 2 NRTIs and 1 NNRTI which contain tenofovir disoproxil fumarate/emtricitabine/efavirenz (TDF/FTC/EFV) as recommended by the national guideline.

The first-line treatment for TE is a combination of pyrimethamine, sulfadiazine, and leucovorin [16]. Pyrimethamine effectively penetrates the brain parenchyma, while leucovorin reduces the risk of hematologic toxicity associated with pyrimethamine treatment. Sulfadiazine inhibits the process required for organisms to synthesize folic acid [16,17].

Various alternative drug regimens are currently used for TE, including pyrimethamine + clindamycin + leucovorin; cotrimoxazole twice daily; pyrimethamine + atovaquone + leucovorin; atovaquone + sulfadiazine; atovaquone twice daily; azithromycin + pyrimethamine + leucovorin; pyrimethamine + clarithromycin + leucovorin; pyrimethamine + dapsone + leucovorin; clindamycin + 5-fluorouracil; doxycycline + either pyrimethamine plus leucovorin, sulfadiazine, or clarithromycin and; clindamycin + azithromycin [18].

Cotrimoxazole (the combination of trimethoprim 5mg/kg – sulfamethoxazole 25 mg/kg), is often considered a first-line treatment option for TE in many countries, particularly when pyrimethamine is unavailable. It is also widely used in hospital with limited resources due to its low cost [18,19]. As an alternative regimen, Cotrimoxazole and Clindamycin might be used [20]. In a randomised investigation of 77 patients, Cotrimoxazole was as efficacious as pyrimethamine-sulfadiazine [21].

Cotrimoxazole acts by inhibiting T. gondii proliferation and eradicating the pathogen by interfering with the folate metabolic pathway. These drugs inhibit the enzymes dihydrofolate reductase and dihydropteroate synthase, thereby inhibiting the synthesis of tetrahydrofolate, which is the precursor for the synthesis of T. gondii DNA. Due to its selective action on dihydrofolate reductase enzyme, cotrimoxazole has less hematological toxicity than pyrimethamine. The mechanism by which clindamycin inhibit T. gondii is not clearly known [18].

In this case, the patient received cotrimoxazole and clindamycin as alternative therapy for toxoplasma encephalitis, in addition to ARV. This alternative regimen was chosen due to unavailability of pyrimethamine and sulfadiazine in our city.

Currently, almost eighty to ninety percent of patients who receive anti-toxoplasma therapy currently exhibit clinical and radiological improvement. This clinical improvement was also reported in patients receiving alternative regimens in comparison to standard regimens [20]. In this case, patients responded well and showed a good clinical response after 14 days of acute phase therapy.

Acute therapy should be continued for at least 3–6 weeks. After the completion of acute therapy, chronic maintenance doses should be administered. The recommended maintenance dose is half of the dose given during the acute phase of therapy. Maintenance therapy should continue until CD4 counts reach more than 200 cells/μL for six consecutive months after ARV administration [22].

After six weeks of alternative therapy in this patient, clinical progress was observed. The patient's right limb regained movement, and the patient could speak coherently and cautiously.

4. Conclusion

Toxoplasma encephalitis is an opportunistic brain infection that is frequent in AIDS patients with low CD4 count. It is a neurological emergency that requires immediate and proper treatment to attain the best therapeutic effects. In this report, a patient was successfully treated using alternative regimen, as shown by clinical improvement. When first-line treatment is not available, Cotrimoxazole plus Clindamycin can produce a significant clinical response for toxoplasma encephalitis.

Author contribution statement

All authors listed have significantly contributed to the investigation, development and writing of this article. </p>

Data availability statement

Data will be made available on request.

Disclosures

Ethic declaration

The authors have obtained approval and a written informed consent from the patient.

Funding

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We appreciate the patient's willingness to submit this case.

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