Delayed cerebellar ataxia induced by Plasmodium falciparum malaria: A rare complication

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Abstract:

Here, we report the clinical manifestation, investigations, and outcomes of a patient developed delayed cerebellar ataxia following a malaria infection; which is considered an unusual complication. This report highlights the diagnostic challenges associated with identifying cerebellar ataxia and the underlying infection in a country endemic with several infectious diseases.

Keywords: Neurology; infectious diseases; Critical care medicine

Introduction:

Cerebellar ataxia (CA) is a neurological condition involving a loss of coordination caused by a dysfunction in the cerebellum of the brain [1]. It can be caused by a variety of conditions such as stroke, tumours, toxins, and infections with different diseases such as arboviral diseases and malaria [2]. Sudan is endemic with several infectious diseases that are involved in the development of CA including COVID-19 [3,4], arboviruses such as Chikungunya [5,6], Crimean-Congo Hemorrhagic Fever (CCHF) [7], dengue [8,9,10], Rift Valley fever [11,12,13], West Nile virus [14, 15], Zika [15, 16], and Yellow fever [15, 17] as well as emerging infectious diseases like schistosomiasis, TB, and different fungal infection [18,19]. Furthermore, malaria is hyper endemic in Sudan [20] and in addition to it is major role in the development of CA, it involves in several other neurological disorders [21].

Delayed cerebellar ataxia following malaria was first described by Senanayake et al in Sri Lanka in 1984 and is an acute, transient condition that occurs following the resolution of the pyrexial phase of malaria or as a side effect of anti-malarial drugs [22]. In this report, we discuss delayed cerebellar ataxia as a complication of a*P. falciparum* malarial infection and highlight the importance of considering it in the differential diagnosis, especially in malaria-endemic regions.

Case presentation:

A 49- year-old female presented to a hospital in Khartoum state, central Sudan with slurred speech, tremors affecting her upper limbs, and a sense of imbalance and dizziness while walking which lasted for five days. Twelve days prior, she reported a 3-day history of fever with chills for which she took paracetamol tabs 500 mg four time per day. The patient had no history of a rash, common cold, nor headache as well as no neck pain, sensory or motor deficit. Also, she has no history of bulbar symptoms, vomiting, recent vaccination, or alcohol abuse as well as no smoking, joint pains, or fluctuation in body weight. Before admission, she was not diagnosed with malaria, nor did she receive any antimalarial therapy.

On the clinical examination, the patient was conscious and oriented to time, place and person. She had a normal pulse rate (76/min), respiratory rate (17/min), blood pressure (90/50), and temperature (39°C). Neurological examination showed no evidence of meningism. However, the patient had an ataxic gait, dysarthria, tremor of the upper limbs, dysdiadochokinesia, and hypotonia, but no bradykinesia, rigidity and nystagmus. Furthermore, she had normal sensation. Magnetic resonance imaging (MRI) of the brain was done in order to rule out the possibility of post-infectious cerebellitis and it showed normal brain structures; ventricular system; no evidence of haemorrhage or infarct and no midline shift. An electroencephalogram was done and was normal.

A blood sample was collected from the patient and sent to the laboratory for routine investigations. Further investigations revealed microcytic hypochromic anaemia and confirmed the presence of *Plasmodium falciparum* gametocytes in the peripheral blood smear. Viral screening for Epstein-Barr virus (EBV), Cytomegalovirus (CMV), major endemic arboviruses, human immunodeficiency (HIV) and Hepatitis viruses were negative. Liver function test revealed a serum bilirubin 0.7 mg/dl, total protein 7.6 g/dl, serum albumin 5.8 g/dl, alkaline phosphatase 79 U/l, aspartate aminotransferase (AST) 21 U/L, and alanine aminotransferase

(ALT) 26 U/l. Renal functional test showed a normal value of urea in blood (27 mg/dL) and serum creatinine (0.71 mg/dL). Complete blood count examination showed leucocytosis (12.3 x10^3), haemoglobin 11.0 g/dl and platelets count 149x10^3. A sputum sample was collected and was negative for acid-fast bacilli.

The patient received artemether/lumefantrine four tablets (20 mg artemether; 120 mg lumefantrine per tablet) orally (PO) as an initial dose, followed by four tablets P.O. 8 hours later, then four tablets P.O. twice daily (morning and evening) for two days for a total course of 24 tablets. She responded well after three days. The patient was discharged 21 days after admission. She has recovered and regained a normal health status.

Discussion:

In this communication, we reported a case of delayed cerebellar ataxia due to *P. falciparum* infection with the onset of slurred speech, bilateral tremors affecting both upper limbs, and an unsteady gait during walking. Cerebellar involvement in *P. falciparum* malaria can occur during the acute stage of fever, as a consequence of cerebral malaria, as a delayed cerebellar ataxia (DCA), or as a side effect of anti-malarial therapy [23 – 28]. This case of DCA that is induced by malaria infection has occurred in a hyper endemic area in central Sudan, Khartoum state. The development of DCA in this case could be mainly attributed to the lack of detecting the malaria infection during the initial presentation of the patient at outpatient clinic. This delay in reaching a final accurate diagnosis is of high risk particularly in settings like Sudan that are endemic with several life-threatening infection like hemorrhagic fevers. Such delay commonly lead to the development of disease severe sequelae and complication such as neurological syndromes including Guillain-Barre syndrome (GBS) [29] and CA.

Cerebellar ataxia can be caused by many conditions including alcohol misuse, stroke, brain degeneration, multiple sclerosis, drugs, genetic and autoimmune diseases as well as several infectious diseases [23]. Malaria is one of the leading causes for the development of CA [24 - 28]. Malaria in humans is commonly caused by one of five species of plasmodium, and *P. falciparum* is the species most associated with the development of neurological complications [30].

Acute cerebellar ataxia can be caused by a wide range of infections including viral, bacterial, fungal, and parasitic infections. Interestingly, in our reported patient, there was no clinical or molecular evidence of any infection other than *P. falciparum* . Co-infection with main viral infections of public health importance in the country with potential involvement in the development of CA were excluded by screening the blood sample serologically and molecularly [31 - 40]. Additionally, in our reported case, hyperpyrexia is unlikely to cause cerebellar ataxia as our patient developed DCA after an afebrile period. Therefore, the development of DCA can be directly attributed to *P. falciparum* infection. The pathogenesis of DCA due to malaria infection is attributable to an immune mechanisms that include elevated levels of certain cytokines such as Interleukin (IL)-2, IL-6, and tumour necrosis factor alpha (TNF-α), as these cytokines were found in the cerebrospinal fluid of patients with DCA [41].

Therefore, in countries like Sudan that are endemic with malaria and other infectious diseases that are involved in the development of CA, it is very important to investigate patients with cerebellar ataxia for these infections. Early diagnosis and effective case management of patients with infectious diseases is the main strategy to reduce the development and prevalence of CA in the country. Therefore, physicians work in such settings should be vigilant and improve the differential diagnosis of cerebellar ataxia by taking a comprehensive medical and travel histories combined with a complete clinical examination and recommendations for the corresponding laboratory investigation to improve the diagnosis. Furthermore, in countries endemic with several infectious diseases with overlapped clinical manifestation, more investment should be made on improving the diagnostic capacity.

Although malaria is hyper endemic in Sudan with *P. falciparum* , as the predominant species, yet development of neurological syndromes that are associated with malaria infection including CA are understudied. Therefore, more investment is needed to further study sequelae and severe complications that are associated with endemic diseases. Particularly that, such studies are warrant to generate evidence to inform and guide

policymaking and strategic intervention to reduce the health and socioeconomic burden of such preventable health condition.

Key clinical message:

In endemic areas, malaria induced cerebellar ataxia should be suspected in patients presenting with slurred speech, tremors, and a sense of imbalance and dizziness while walking. Healthcare providers should be aware to properly investigate and early detect the causation of cerebellar ataxia to improve the case management and clinical outcome cost-effectively.

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