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# A Rare Case of Acute Disseminated Encephalomyelitis (ADEM) after Plasmodium Falciparum Infection

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## 1. Abstract

Malaria infections have a wide array of both acute and chronic neurologic presentations that can create unclear clinical pictures, especially when presenting in a region with low malaria prevalence.1 Neurological complications for the pediatric population can be devastating if not correctly identified and promptly treated.2 We describe a case of a 5-year-old male with acute disseminated encephalomyelitis (ADEM) secondary to a previous malarial infection who presented with painful leg extensor spasms and urinary retention; he was determined to have positive Plasmodium falciparum hematological smears, brain magnetic resonance imaging (MRI) findings were consistent with disseminated central nervous system (CNS) demyelination, and he subsequently improved before antimalarial or other specific therapy initiation. This case describes a unique presentation of the neurologic manifestations of malaria and demonstrates the importance of early clinical suspicion and diagnosis.

## 2. Patient Presentation

A 5-year-old Caucasian male presented with a one-day history of gait difficulty, painful extensor spasms of the lower extremity muscles, and urinary retention. His past medical history was significant for multiple malaria infections that reportedly had been appropriately treated, including mefloquine 62 mg weekly for malaria prophylaxis for the past year and a half. He was born full-term in the United States, without complications, and with normal development. He had not received his polio (fourth), measles, mumps, and rubella (MMR) (second), varicella (second), and hepatitis A (second) immunizations. Family history was non-contributory. His social history was significant for living in rural Uganda (50 miles north of Kampala) for the past four years, during which he had multiple exposures to malaria and various exotic animals (lizards, geckos, chameleons, and bats).

His symptoms began one day before his presentation after flying to the United States from Uganda. At the airport, he had nausea and multiple falls. That night, he could not move his legs and was unable to sit upright or walk due to stiffness and extensor spasms in his legs and hips. He had not voided or had a bowel movement for over a day before his presentation to the emergency department. He was afebrile and vital signs were stable. He was awake and alert. Physical examination was significant for extensor posturing and hypertonicity of bilateral lower extremities from hips to toes, that was accompanied by occasional painful spasms that prevented him from ambulating. Bilateral patellar hyperreflexia was observed. He did not have cranial nerve deficits, sensorium was normal, and meningismus was not present. He had tenderness to palpation of the anterior aspect of both thighs and midline tenderness at the C6-T1 spinal levels.

Laboratory tests were significant for aspartate aminotransferase (AST) of 46 units/L (0-37 units/L), lactic acid of 2.8 mmol/L (0.5-2.2 mmol/L), creatine kinase (CK) of 718 units/L (12-191 units/L), erythrocyte sedimentation rate (ESR) of 15 mm/hr (0-15 mm/hr), and C-reactive protein (CRP) of 3.1 mg/L (≤2.9 mg/L). Upon admission, cerebrospinal fluid (CSF) studies showed pleocytosis with an elevated nucleated cell count of 81 cells/mm3 (28% neutrophils, 61% lymphocytes, 11% monocytes), and an opening pressure of 21 mmHg (13-20 mmHg). CSF glucose, protein, clarity, gram stain, and cultures were unremarkable. Blood cultures were negative, and the first two malaria hematological smears were negative. Initial MRI of the brain showed patchy supratentorial and brainstem hyperintense signal abnormalities on T2-weighted Fluid Attenuated Inversion Recovery (FLAIR) without enhancement (Figure 1A-D), and MRI of the full spine showed T2 hyperintense signal abnormalities at the cervicomedullary junction and prominent signal changes at the conus medullaris (Figure 2A-D). Furthermore, MRI of the lumbar spine with short-tau inversion recovery (STIR) protocol showed diffuse, symmetric, bilateral hyperintensity and edema of the psoas muscles, without volume loss, suggestive of inflammation or overuse due to his spasms (Figure 3). The initial routine electroencephalogram (EEG) was normal.

During his hospital course, he continued to have leg spasms and contractions. His serum CK increased to 4000 units/L (12-191 units/L) before showing a decrease on hospital day three. Associated with the decrease in serum CK, his spasms improved, and he regained bladder and bowel control. He underwent an extensive infectious evaluation that ultimately resulted in negative findings for any viral, bacterial, or fungal etiologies. On hospital day seven, his third and fourth blood smears were positive for malaria at a low titer and identified as P. falciparum. Antimalarial therapy with artemether-lumefantrine was started, and his symptoms continued to improve. Repeat MRI brain showed resolving supratentorial and brainstem T2 FLAIR hyperintense signals (Figure 4A-D), and MRI spine showed resolving T2 changes at the conus medullaris (Figure 5A-D).

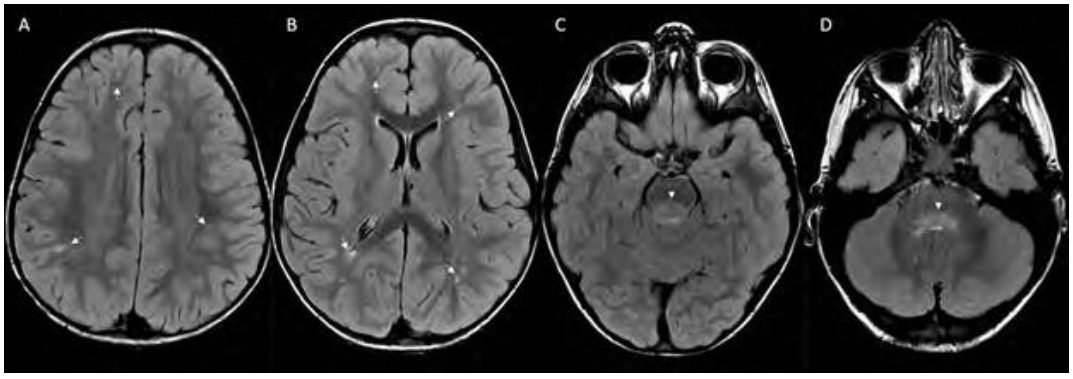


**Figure 1:** Brain MR imaging on the first day of hospitalization. Axial T2-weighted FLAIR image at the level of the centrum semiovale shows abnormal bilateral punctate subcortical white matter hyperintense signals (white arrows) in frontal and parietal regions (A). Axial T2-weighted FLAIR image at the level of basal ganglia shows abnormal bilateral punctate subcortical white matter hyperintense signals (white arrows) in the frontal and parieto-occipital regions (B). Axial T2-weighted FLAIR image at the level of rostral pons shows a subtle abnormal hyperintense signal (arrowhead) in dorsal pons (C). Axial T2-weighted FLAIR image at the level of caudal pons shows an abnormal hyperintense signal (arrowhead) in dorsal pons (D). All abnormal hyperintense signals were not associated with pathologic contrast enhancement.

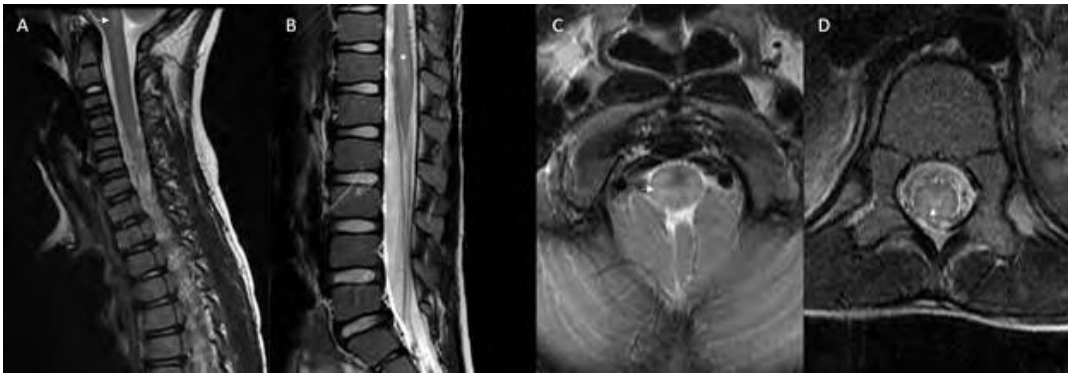


**Figure 2:** Full spine MR imaging on the first day of hospitalization. Sagittal T2-weighted image at the cervical spine level shows a subtle abnormal hyperintense signal (white arrow) at the cervicomedullary junction that continues in the medulla and the dorsal pons (A). Sagittal T2-weighted image at the level of conus medullaris shows central hyperintense signal abnormality (asterisk) (B). Axial T2-weighted image at the level of the medulla oblongata shows subtle abnormal hyperintense signals (white arrow) that are circumferential and dorsal in distribution (C). Axial T2-weighted image at the level of the conus medullaris shows central hyperintense signal abnormality (white arrow)(D). All abnormal hyperintense signals were not associated with pathologic contrast enhancement.

**Figure 3:** Sagittal STIR image of lumbosacral spine on day one of hospitalization showing diffuse hyperintensity and edema of the psoas muscle (triple white arrows), without evidence of volume loss, suggesting psoas muscle myositis.

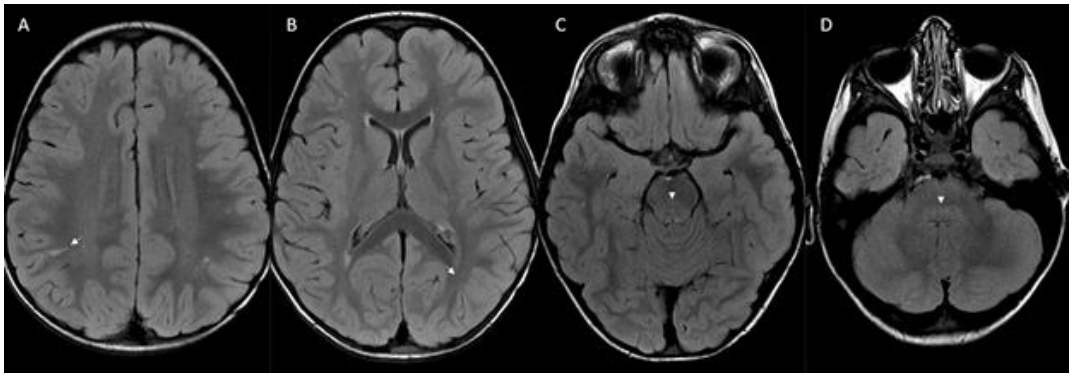


**Figure 4:** Brain MR imaging on day seven of hospitalization. Axial T2-weighted FLAIR image at the level of the centrum semiovale shows resolving bilateral punctate subcortical white matter hyperintense signals with persistence (white arrow) of signal changes in the right parietal region (A). Axial T2-weighted FLAIR image at the level of basal ganglia shows resolving abnormal bilateral punctate subcortical white matter hyperintense signals, most notably at the left parieto-occipital region (white arrow) (B). Axial T2-weighted FLAIR image at the level of rostral pons shows resolving subtle abnormal hyperintense signal (arrowhead) in dorsal pons (C). Axial T2-weighted FLAIR image at the level of caudal pons shows resolving abnormal hyperintense signal (arrowhead) in dorsal pons (D).

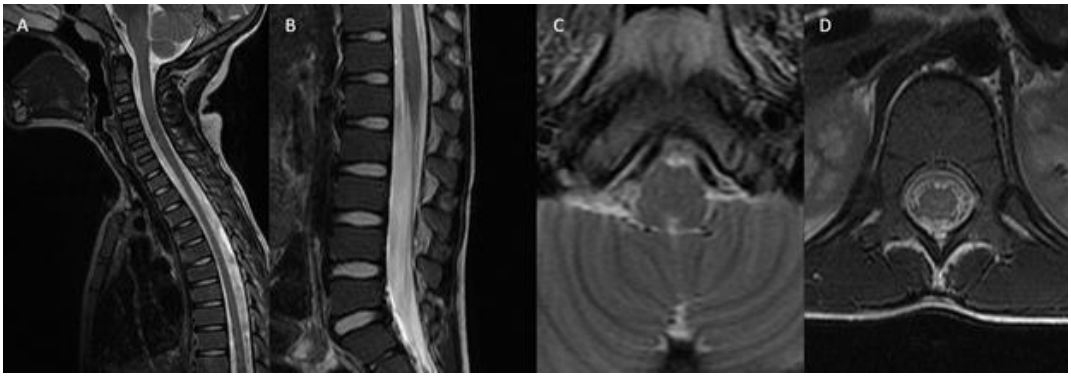


**Figure 5:** Full spine MR imaging on day seven of hospitalization. Sagittal T2-weighted image at the level of the cervical spine shows resolution of the subtle abnormal hyperintense signal previously noted at the cervicomedullary junction that continued in the medulla and the dorsal pons (A). Sagittal T2-weighted image at the level of conus medullaris shows resolution of the previously noted central hyperintense signal abnormality (B). Axial T2-weighted image at the level of medulla oblongata shows resolution of the subtle hyperintense signal abnormality previously noted (C). Axial T2-weighted image at the level of the conus medullaris shows resolution of central hyperintense signal abnormality previously noted (D).

## 3. Discussion

Malaria has various neurologic manifestations, ranging from agitation to coma; the most severe acute manifestation is cerebral malaria [2]. In children, cerebral malaria is characterized by diminished consciousness with a Blantyre Coma Score of less than three [1]. The majority of cases with neurological complications are caused by the Plasmodium falciparum species, and patients with impaired consciousness should be treated for cerebral malaria with antimalarial therapy [2]. High suspicion is necessary for patients traveling from malaria-endemic areas, and three negative blood smears are recommended to exclude P. falciparum malaria [2]. The pathogenesis of malaria has been described as a vasculomyelinopathy. P. falciparum induces erythrocytes to bind to the vascular endothelium in capillaries and postcapillary venules and thus reduces blood flow and causes hypoxia in various organs, including the brain [1]. Involvement of the CNS can cause encephalopathy, seizures, upper motor neuron dysfunction with myoclonic jerks and increased tone, psychosis, impaired consciousness, and coma [2]. Most patients recover with appropriate antimalarial therapy, however, long-term neurologic deficits may be more severe in children than adults [2].

In addition to acute neurological manifestations of malaria, delayed complications can occur after appropriate treatment [3]. These four neurological complications are delayed cerebellar ataxia (DCA), acute inflammatory demyelinating polyneuropathy (AIDP), post-malaria neurological syndrome (PMNS), and acute disseminated encephalomyelitis (ADEM); all are usually associated with a previous infection with P. falciparum [3]. DCA presents with midline cerebellar ataxia, while AIDP presents with ascending paralysis following infection [3]. PMNS presents with acute onset of multiple neurological or neuropsychiatric symptoms, such as psychosis, seizures, and tremor, and is associated with the use of mefloquine [3] as used in our patient. ADEM is a multifocal, usually monophasic, demyelinating disease with temporal association to recent infection or vaccination in which patients present with neurological signs and symptoms resulting from autoimmune demyelination of the CNS [3]. It is difficult to differentiate between PMNS and ADEM since both present with multifocal neurologic deficits following recovery from malaria infection; however, MRI in PMNS patients may be normal or have less prominent lesions than ADEM [3]. Most patients recover fully from these neurological complications, and steroids may aid in treatment [3]. ADEM is a rare complication following various infections and vaccines. The incidence of ADEM worldwide is estimated to be 1 in 125,000-250,000 each year [4]. The majority of individuals affected by ADEM are children less than age 10, while the remainder generally falls below the age of 20.4 Malaria infection as an etiology of ADEM is still largely unknown as there is a paucity of information described in the literature; however, it is suspected to be extremely rare.

Neurological manifestations of malaria can have a wide array of presenting symptoms. Prominent symptoms present in our patient were uncontrolled extensor muscle spasms of the lower extremities, urinary, and bowel retention, and these symptoms were consistent with his MRI spine findings. A prominent neurological system that was likely affected was the reticulospinal system, which is responsible for gross motor movement [5]. Disruption of this tract will result in postural abnormalities, such as the inability to walk or sit up, as seen in our patient. The medial reticulospinal tract, located in the pons, acts spontaneously to control the extensor muscles, whereas the lateral reticulospinal tract, located in the medulla, controls the flexor muscles while also inhibiting the medial reticulospinal tract [5]. In our patient, the T2 signal changes at the cervicomedullary junction correlate with a presumed loss of inhibition of the medial reticulospinal tract and subsequent unopposed extensor leg muscle contractions. The signal changes and enhancement in the psoas muscles on the STIR sequence suggest an increase in tissue water concentration as a result of fluid exchange between muscle and vasculature secondary to persistent muscle contractions [6]. Another system likely affected was the micturition pathway. The pontine micturition center is responsible for detrusor muscle contraction and urethral sphincter relaxation [7]. The Onuf nucleus, located in the sacral spinal cord, controls the striated muscle of the rectum and external urethral sphincter [8]. Damage to the Onuf nucleus or anywhere along the micturition pathways can cause urinary and stool retention. In our patient, the initial MRI showed T2 signal changes at both the cervicomedullary junction and the conus medullaris, including swelling of the conus medullaris. Lesions in either of these areas can progress to urinary and stool retention as they fall along the micturition pathway.

Our patient likely had ADEM secondary to a previous malaria infection, given his acute onset of symptoms, neuroimaging findings, and low malaria titers. His positive third and fourth blood smears for P. falciparum may indicate he had an acute on chronic (flare) malaria infection. However, his low malaria titers and resolving symptoms before antimalarial therapy, both clinically and on neuroimaging, and with decreasing serum CK, cannot exclude a possible late neurologic sequela from previous infections. This case describes the importance of high suspicion for malaria in patients presenting after traveling from endemic areas, such as Sub-Saharan Africa, India, Indonesia, and Northern South America. With international travel becoming increasingly common, it is important to understand the various presentations of malaria, including rare neurological complications.

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