

Case Report

Chronic Atypical Cerebral Malaria: A Case Study

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Abstract

Malaria, often presents in atypical forms in malaria endemic zones. Repeated mosquito bites as well as infrequent or incomplete antimalarial measures, complicate the clinical picture of patients. Patients often develop tolerance, attributable to development of naturally acquired immunity against the parasite. The present case is an example of atypical cerebral malaria of very long duration (six years), having episodic headache as chief presenting symptom. Intermittent mild fever along with sore throat also was accompanied to the chief symptom. Additionally, CT scan failed to show any detectable abnormality. The CT scan shows that, brain parenchyma, all cortical sulci, all ventricles, basal cistern are normal. There is no mid line shift. Cerebellum and brain stem also appear normal. On the basis of clinical findings as well as chronic history of the patient, a presumptive diagnosis of malaria came in my mind, based on the fact that, malarial parasites are often detected in peripheral blood when patient has fever (with the rise of body temperature, plasmodium migrate to peripheral blood and become detectable). In the present case, patient was experiencing 'evening rise' (8:00 PM onwards) of temperature, hence her blood smear (taken during daytime) failed to detect any malarial parasite. Furthermore, the history of patient includes anti-malarial measures. Moreover, such chronic cases often fail to reveal malarial parasite due to previous partially-effective or under-treatment with antimalarials.

Keywords: Artemether; Cerebral Malaria; Episodic headache

Background and History

A medical student of 1st year, aged 20 years, presented herself having symptoms of chronic episodic headache and intermittent low grade fever in the evening, for the last six years. She has gone through almost all clinically indicated hematological tests as well as radiographic imaging studies. Her blood sample was negative for malarial parasites on three occasions. Her CT scan failed to detect any abnormalities. On clinical examination, she was found to have icterus, tender jugulo-diaphragmatic lymph nodes and liver tenderness. Moreover, she is native of Jharkhand state, which is one of the highly malaria endemic states of India. In the year 2011, there were 1.31 million reported cases of malaria in the country with high endemicity in Odisha, Northeastern states, Jharkhand, Chhattisgarh and Madhya Pradesh [1].

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The test for malarial retinopathy is usually found positive in severe cases of malaria, often those which eventually lead to coma. Such cases are not very difficult to diagnose as their peripheral blood smear are usually positive for the parasite. Additionally, MR can detect retinal hemorrhages or white patches etc, suggestive of malaria. In the present case, the patient has normal fundus. There are no residua suggestive of previous retinal involvement. She has 6/6 vision on right eye and 6/9 on the left. These finding actually explain the anonymity of atypical malaria. Hence, absence of MR does not rule out malaria.

The presumptive diagnosis as 'malaria' for the present case has been done on the basis of

- Residence of patient, in a malaria endemic zone
- Long standing headache with normal CT scan (Figures 1-3) and normal hematological report
- Icterus, suggestive of hemolysis and hyperbilirubinemia
- Intermittent mild fever (suggestive of possible acquired immunity against malaria)
- Ineffective routine analgesics
- History of incomplete antimalarial measures
- Cessation of fever with oral Chloroquine only (without adding an antipyretic)

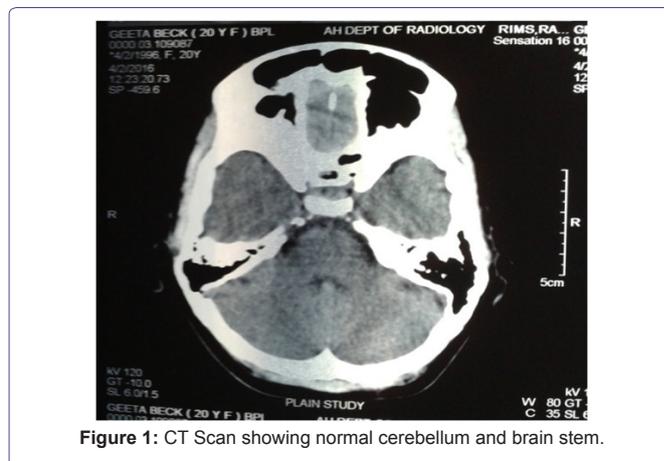


Figure 1: CT Scan showing normal cerebellum and brain stem.

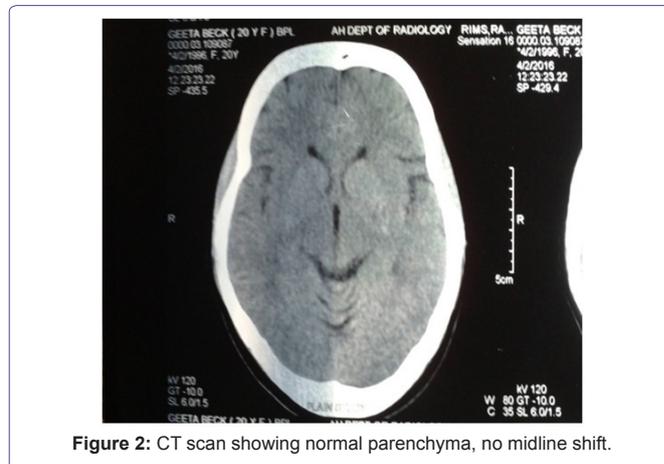


Figure 2: CT scan showing normal parenchyma, no midline shift.

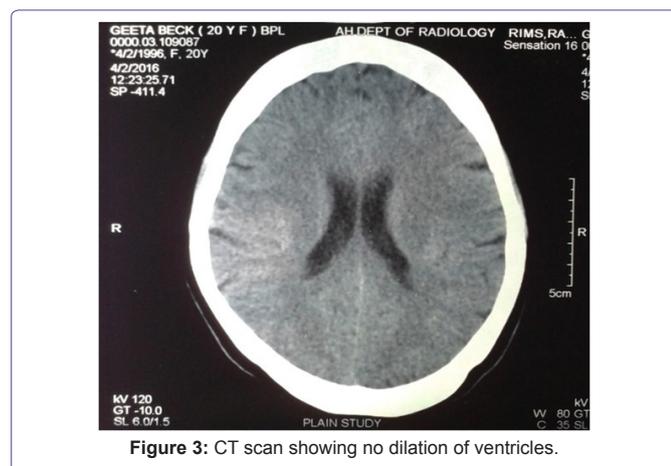


Figure 3: CT scan showing no dilation of ventricles.

Cessation of fever on 2nd day of starting Chloroquine only (without adding an antipyretic) strongly suggests malaria. In India, the guidelines for the treatment of malaria suggests that, every case presenting with headache and fever, should be given a complete dose of Chloroquine, if the patient belong to a malaria endemic zone (blood should be collected for investigation but no prior test for a malarial parasite is required).

Furthermore, in the present case, rapid antigen for malaria, revealed negative result. The reason of a negative rapid antigen test is still obscure, but, it may suggest a mutant strain of plasmodia being possibly involved. In this context, moreover, the atypical features of malaria are often observed in *Falciparum* malaria, early stages of infection, patients at extremes of age, immune-compromised patients, Patients undergoing treatment for malaria, recurrent attacks of malaria specially in endemic zones, pregnancy etc.

The atypical symptoms of Malaria can be seen as:

Atypical fever

Malaria often present with atypical fever pattern in an endemic area. Conversely, some the patient may present with other symptoms, instead of fever [2]. The noted pattern of fever may include spectrum of both extremes, for example it may be either of low grade or of high grade. Moreover, either, it may exhibit chills or paradoxically, chills may be totally absent. Fever pattern also may vary from intermittent to continuous. Early during the illness, quotidian type of fever pattern usually is observed, having multiple spikes each day. These spikes are due to the development of multiple broods of the parasite. Furthermore, at later stages, the fever becomes more uniform. Moreover, as an exception, the multiple spikes may continue in the cases of *P. falciparum* malaria and in mixed infections.

Headache

Headache may be a presenting feature of malaria, which may or may not accompany fever. It can be unilateral or bilateral. Unilateral headache often mimics a case of idiopathic migraine.

Jaundice

Patients may present with icterus and bilirubinuria. Upto 20-40% of the cases of malaria present with mild jaundice. Interestingly, the serum bilirubin may rise above 3 mg/dL in cases of severe *P. falciparum* malaria. Additionally, there may be anemia, hyperparasitemia and hepatitis. The serum enzymes are raised as an indication of hepatic damage [3]. In conclusion, malaria must be considered as a

differential diagnosis for all cases of jaundice, in areas where malaria is endemic [4]. Presumptive diagnosis: Based on the clinical findings and considering the above-mentioned facts, I arrive at the presumptive diagnosis as, 'malaria'. She was given full course of antimalarials. She responded very well to Chloroquine (test dose) and Artemether (definitive dose).

Treatment Regime

The treatment regime comprised of Primary, Secondary and the Final phase of treatment.

Primary phase of treatment

A test dose of Chloroquine was given first, in a dose of

- 1 gram stat (i.e., 4 tablets of 250 mg base)
- 500 mg (2 tablets) after 6 hours
- 500 mg (2 tablets) after 24 hours of 1st dose
- 500 mg (2 tablets) after 48 hours of 1st dose

Fever disappeared on second day of starting Chloroquine. Episodic headache was persisting along with sore throat.

Secondary phase of treatment

Artemether along with Ibuprofen 400 mg SOS, was started after completion of Chloroquine regime. She was given 1 tablet of Artemether (80 mg), 12 hour for three days. On third day of starting Artemether, she reported that her left half of head has become free of pain. Artemether was stopped after the completion of six doses.

Final phase of treatment

Artemether 80 mg+Lumefantrine 480 mg 1 tablet 12 hour for 3 days. She was advised to cope with the pain with Ibuprofen 400 mg SOS (maximum 2 tablets/24 hours), for the next one week. Episode of headache became less frequent by third day. Furthermore, by the end of week, she was feeling well, but was not completely free of headache.

Definitive phase of treatment

On the completion of a week, she was given 2 tablets of Artemether one hour apart as last and final dose. Within next three days of the final dose, the patient informed me that she did not have any episode of headache during the last 24 hours. She was prescribed with Iron+Folic acid supplements along with a multivitamin. She was closely monitored for the next one month. No episode of headache or fever had been complained.

Discussion

Owing to the 'Naturally acquired immunity' to *falciparum* malaria, millions of people routinely exposed to *Plasmodium falciparum* infection, remain protected from severe disease and death. There is no clear-cut concept about how this protection works. Each year malaria infects about one-half billion people, killing 1 million to 2 million and severely dampening economic development [5-10]. Headache may be sole presenting feature of malaria. It may not be always accompanied with fever. The presentation of headache may be unilateral or bilateral. Severe headache may cause confusion in diagnosis, by mimicking either intra-cranial infection or intra-cranial tumor. The pattern and distribution of headache can also resemble to migraine, sinusitis etc. Presence of some important clinical signs like, projectile vomiting, papilloedema, neck stiffness and focal neurological signs help to rule

out malaria [4]. Importantly, virtually all patients with malaria present with headache [11]. The Immunity against malaria can be classified into 'natural' or 'innate' immunity and 'acquired' or 'adaptive' immunity [12].

The innate immunity is naturally present in the host and it does not require any previous exposure to a malarial parasite. The malarial parasite passes through a complex life cycle involving liver and red blood cells of the host [13]. Here, it is worth to note that, the parasite causes expression a great variety of proteins at different stages. Furthermore, more importantly, these proteins also keep changing often. As a result, it is infact only 'partial' or 'short-lived' immunity that the host acquires by a natural infection. Furthermore, development of such immunity will not be able to protect the individual against a new infection [14]. It seems very difficult or even impossible to develop an effective vaccine against malaria since, there is complex interplay between parasitic proteins and the immune system of the host [15-17]. Natural or innate immunity to malaria usually protects an individual by either exhibiting an inherent refractoriness for establishment of the infection or by exerting an immediate inhibitory response against the parasite [18-22]. Additionally, protection against malaria or against its severe manifestations can also be due to alterations in the structure of hemoglobin or some enzymes involved in the pathogenesis of malaria. People residing in high endemic zone of malaria often exhibit these traits [23-24]. Moreover, for example, duffy negativity, in red cells, being widely prevalent in Africa, protects against "*P. vivax*" infection, and may be responsible for the virtual elimination of this parasite from the continent. Certain thalassemias reduce the chances of infection by 50%. Similarly, homozygote hemoglobin C, can prevent upto 90% cases of malaria. Additionally, hemoglobin E, and ovalocytosis carrier status have also been reported to confer protection against "*P. falciparum*" or "*P. vivax*". Last but not the least, Glucose 6-phosphate dehydrogenase deficiency (50% protection) and sickle cell hemoglobin (90% protection) confer protection against severe malaria and related mortality [25-26].

At present the patient is in good health and there is no episode of headache since last six months (till date). Referring to such outcome of the patient, it can be suggested that for a patient belonging to a malaria endemic zone if presents with fever, should be given oral Chloroquine (without any anti-pyretics) first, (instead of going through a battery of tests) to observe its effect on fever. Any change in the pattern of fever or its cessation is suggestive of malaria. Chloroquine is a safe drug and also in use for prophylaxis against malaria for travelers visiting to malaria endemic zones. Mefloquine is another alternative for the same. The antimalarial used 'Artemether' has long elimination half-life, hence should be given under close monitoring. Appropriate dose modification is required for the cases of renal as well as hepatic failure. Artemether should not be used in the first trimester of pregnancy in situations where other suitable and effective antimalarials are available. Drug interaction should be kept in mind while combining Artemether with other anti-malarials, and appropriate data should be referred for the same [27].

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