Original Article

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Neuropsychiatric Profile in Malaria: An Overview

Internal Medicine Section

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ABSTRACT

Introduction: Malaria is the most important parasitic disease of humans causes clinical illness over 300-500 million people globally and over one million death every year globally. The involvement of the nervous system in malaria is studied in this paper, to help formulate a strategy for better malaria management.

Aim: To study the Neuropsychiatric manifestation in malaria.

Materials and Methods: This was a prospective observational study in 170 patients with a clinical diagnosis of malaria admitted in various medical wards of medicine department of PBM Hospital, Bikaner during epidemic of malaria. It included both sexes of all age groups except the paediatric range. The diagnosis of malaria was confirmed by examination of thick and thin smear/optimal test/strip test. Only those cases that had asexual form of parasite of malaria in the blood by smear examination or optimal test were included in the study.

Results: Out of total 170 patients 104 (62%) reported *Plasmodium falciparum* (PF), *Plasmodium vivax* (PV) were 57 (33.5%) followed by mixed (PF+PV) 9 (5.3%) cases. The total PBF-MP test positivity was 84.5%. Maximum patients were belonging to the age range of 21-40 year with male predominance. Neuropsychiatric manifestation seen in falciparum malaria (n=111) as follow: altered consciousness 20 (18.01%), headache 17 (15.32%), neck rigidity 5 (4.5%), convulsion 5 (4.55%), extra pyramidal rigidity 2 (1.8%), decorticate rigidity 1 (0.90%), decerebrate rigidity 1 (0.90%), cerebellar ataxia 3 (2.7%), subarachnoid haemorrhage 1 (0.90%), aphasia 2 (1.8%), subconjunctival haemorrhage 1 (0.90%), conjugate deviation of eye 1 (0.90%) and psychosis 6 (5.40%). Twenty one patients presented with cerebral malaria out of 111 patients. Most patients of cerebral malaria presented with altered level of consciousness followed by headache and psychosis. Acute confusional state with clouding of consciousness was the most common presentation of psychosis (50%).

Conclusion: Neuropsychiatric manifestations are not an uncommon presentation of malaria. Most commonly caused by PF malaria. Malaria should be thought as a differential diagnosis in pyrexia with neuropsychiatric manifestation. Observation obtained in the study will be highly useful for the diagnosis and management of patients suffering from malaria.

Keywords: *Plasmodium falciparum, Plasmodium vivax*, Neuropsychiatric manifestation

INTRODUCTION

The name malaria is derived from the Italian word “Mal-aria” meaning “bad air”. There are five plasmodium species causing disease in human. In India, incidence of malaria, since 1982, is about 2 million cases per year. About 35 to 43% population were affected by *Plasmodium falciparum* [1]. According to WHO (2009) malaria caused by the *Plasmodium falciparum* (*P. falciparum*) affects 500 million people causes 2.7 million deaths every year [1]. Cerebral malaria by *P. falciparum* ranging from 0.001% to 37.200% in adult patients [2-4]. Severe complicated malaria is mainly caused by *P. falciparum* in form of cerebral malaria. A total of 110 million cases of malaria have been estimated from worldwide, of which *P. falciparum* causes 1 to 2 million death each year [5]. Cerebral malaria is the most important complication of falciparum malaria and also the leading cause of death in malaria [6,7]. According to World Health Organization cerebral malaria is defined as unrousable coma using the Glasgow coma scale, (non-purposeful response or no response on painful stimuli), exclusion of other encephalopathies, especially bacterial meningitis and if possible, locally prevalent virus encephalitis and the finding of asexual forms of *P. falciparum* in the blood film [8,9]. Unconsciousness should persist for at least 30 minute or longer after a convulsion to differentiate cerebral malaria from transient postictal coma. However, for all practice purpose any person with headache, neck stiffness, drowsiness, delirium, delusion, febrile convulsion, focal neurological sign or even behavioural disturbances should be treated as for cerebral malaria. Cerebral malaria is the most severe neurological complication of infection with *P. falciparum* malaria. A characteristic feature of cerebral malaria is the changeability of neurological disorder, which often makes it difficult to attach them to any particular syndrome. In some patients after an episode of cerebral malaria development of neurological and psychiatric symptoms occur within 2 months after the acute illness, which is known as post malaria neurological syndrome [10]. It is a transient neurological syndrome seen after recovery from severe infection. Acute confusional state or psychosis, one or more generalized convulsions and fine tremors are some of the manifestation of this syndrome [10].

Plasmodium falciparum and *P. vivax* together account for more than 95% cases of malaria in the world. Since 1997, there is a consistently declining trend in annual malaria incidence in the country. During 2003 about 1.65 million cases were reported with 943 deaths. There were 0.7 million cases of *P. falciparum* malaria [11].

Bikaner district is a part of the Thar desert, India having extremes of temperature. This region is endemic for malaria. This is basically arid zone, which had recently experienced changes in ecosystem due to increase rainfall and canal irrigation in the last two decades. The morbidity and mortality have altered to a great extent during past decades [12].

Neurocognitive manifestation has been extensively studied in peadiatrics age group but in adult neuropsychiatric profile is not well documented [13-16].

Therefore the aim of present study was to recognized the neuro-psychiatric manifestations of malaria in adult patients, with improve diagnosis and management.

MATERIALS AND METHODS

We studied conjunctive 170 patients with fever admitted in various medical wards of medicine department of PBM hospital, Bikaner during epidemic of malaria from September to November 2014. It included patients of both sexes belonging to above 14 years of age.

The diagnosis of malaria was confirmed by examination of thick and thin smear /optimal test/ strip test. Only those cases that had asexual form of parasite of malaria in the blood by smear examination or optimal test were included in the study.

Clinical and biochemical examination was done for each patient which included complete blood chemistry, liver function test, renal function test and thick and thin smear/optimal test/strip test; the details were recorded using a questionnaire. In order to reach the correct diagnosis when dealing with malaria patients, we need to do what is known as a clinical assessment. This involves the following steps:

- History taking;
- Physical examination;
- Investigations; and
- Diagnosis.

Included the following questions:

1. Asking for patients's full identification details.
2. Ask the following questions concerning patients's illness:
    - How long has he had the fever and vomiting and the frequency?
    - What is the nature of the fever? Is it persistent, intermittent or remittent? Does it occur during the day or night?
    - Is he vomiting everything he takes? Is he vomiting blood? Is the vomiting associated with diarrhoea? Is he thirsty and eager to drink in spite of the vomiting?
    - Has he had convulsions? If yes, do these convulsions occur at the peak of fever? And for how long do these convulsions take?
    - Has he developed yellow colour in the eyes?
    - Is he passing urine? What is the colour of the urine? How much of it does he pass and how frequently?
    - Has he taken any medication since this illness started? If so, what medication?
    - Has he had a similar illness before? Or any other illness? If yes, is there any medical record on previous medication?
    - Is patient allergic to any drugs? Which ones if any?
    - Is he coughing or getting easily tired? Are his feet swollen?
    - Has the mother noticed any unusual behaviour in Nathan's sleep pattern and level of consciousness?
    - Is patient fully immunized?
    - Has he had normal development since birth?
    - Are there any diseases that run in the family, e.g. sickle cell disease? How many brothers and sisters does patient have? Are they all alive and healthy? What is the family source of income? Do the parents of patient stay together? How is the housing in their home?

All other diseases were appropriately ruled out. Every patient will be screened for causes of pyrexia and ruled out other causes of fever by urine complete with culture and sensitivity, chest X-ray, blood culture, ultrasonography, brucella antibody test. Patients with other health condition, either neurologic or systemic were excluded from the study.

Patients with previous history of neurological, psychiatric, systemic illness, trauma and the presence of deficit in the neurological examination, and patients already on antimalarial drugs excluded from the study.

All the patients included in the study will be undergone complete neurological examination and neuropsychiatric evaluation with MMSE (Mini Mental Status Examination), BPRS (Brief Psychiatric Rating Scale). Psychiatric diagnosis will be given as per ICD-10 after evaluation by consultant psychiatrist. All the patients with malaria admitted in medical ward treated according to WHO guidelines.

RESULTS

A total 170 patients with a diagnosis of malaria who were eligible for the study were approached. The mean age of participants was 31.5 years. The maximum patients belonged to the age group of 21-40 years in all age groups, with male predominance. The patients belonged to rural excess compromising 54% of total. A total of 140 (82%) patients presented with chills followed by 20 (11%) without chills and 10 (5%) with nonspecific respectively. Temperature of majority of patients was in between 101-104 degree Fahrenheit. PBF for MP test positivity for PF were 52% (104), followed by PV 28.5% (57), whereas for mixed malaria 4.5% (9). Total PBF-MP test positivity was 84.5%.

Neuropsychiatric Manifestation of Malaria

Glasgow coma scale and MMSE in patients at the time of admission [Table/Fig-1,2]. Of the total 12.9% (n=22) of patients present with alter level of consciousness, their GCS score <5. M: F ratio was 9:2. A 4% (n=7) patients presented with severe cognitive impairments at the time of admission and their MMSE score below 21, 11.5% (n=23) patients presented with abnormal psychiatric behaviours in which 2.5% (n=5) were females whereas 9% (n=18) were males.

[Table/Fig-3] shows that headache was the most common symptoms in malaria reported by 74% (n=126). [Table/Fig-4] shows neurological manifestation of falciparum malaria in which most patients of falciparum malaria presented with altered level of consciousness (18.02) followed by headache (15.32%) and psychosis (5.40%) respectively.

[Table/Fig-5] shows most of patients of malaria presented with acute confusional state with clouding of consciousness (50%).

DISCUSSION

The present study was carried out to know about neuropsychiatric manifestation of malaria in 170 patients of both sexes admitted in medical ward of PBM Hospital Bikaner during the month of September to November 2014. Bikaner district is a part of the Thar Desert, which has extremes of ambient temperature. This region has always been regarded as hypo endemic area for malaria. This is basically an arid zone, which had recently experienced heavy rain falls in the last few years. The scenario of both disease morbidity and mortality seems to have altered to a great extent during the past few years, which is attributable to ecological and physiographical changes in this part of Thar region due mainly to the construction of Indra Gandhi canal and increased rainfall triggered by the EL Nino Southern Oscillation. As a sequences some areas, especially those in the vicinity of canal irrigation have become marshy and favourable for perennial breeding of certain vector species, including *Anopheles culicifacies*, which has apparently intruded the desert rather recently. *A. stephensi*

GCS score	No. of patients	Percentage
<5	22	13
6-10	32	19
>10	116	68

[Table/Fig-1]: Glasgow Coma Scale at the time of admission.

MMSE score	No. of patients	Percentage
<21	7	4
22-26	14	8
>26	149	88

[Table/Fig-2]: MMSE at the time of admission.

	No. of patients	Percentage
Headache	126	74
Neck rigidity	5	2.9
Convulsion	15	8.8
Irrelevant talk	22	12.9

[Table/Fig-3]: Neurological manifestation of malaria at the time of admission

	No. of patients	Percentage
Altered consciousness	20	18.02
Headache	17	15.32
Convulsion	5	4.50
Neck rigidity	5	4.50
Extrapyramidal rigidity	2	1.80
Decorticate rigity	1	0.90
Decerebrate rigidity	1	0.90
Cerebellar ataxia	3	2.70
Subarachnoid haemorrhage	1	0.90
Aphasia	2	1.80
Subconjunctival haemorrhage	1	0.90
Conjugate deviation of eyes	1	0.90
Psychosis	6	5.40

[Table/Fig-4]: Neurological manifestation of falciparum malaria

Sign and symptoms	No. of patients	Percentage
Acute confusional state with clouding of counsiousness	10	50%
Acute confusion stete with clouding of consciousness with visual hallucination	4	20%
Prolonged confusion state following generalized convulsion	2	10%
Acute confusion state had period of classic catatonia with waxy flexibility	2	10%
Acute psychiatric syndrome without clouding of consciousness	3	15%
Acute manic episodes with visual hallucinations	1	5%

[Table/Fig-5]: Psychiatric manifestation of malaria

which is chronologically the oldest vector in the Thar Desert is best adapted to survive and transmit malaria in the interior areas having a great scarcity of water. The migration of labourers from some of the malaria hyperendemic neighbouring state in the country to the site of the canal provides means of transportation of the *P. falciparum* to the desert region. Also, both *A. stephensis* and *A. culicifacies* have exhibited increasing trend of tolerance against DDT [17].

About 170 patients were admitted in three months of course in which having both complicated (37 patients) or uncomplicated (133 patients) malaria. The patients belong to all age group with a slight male preponderance for all ages. The bulk of admitted patients were from the age range 21-40 (mean age 31.10). Rural and urban distribution of patients in the Bikaner district was almost equal being 54% of 46% respectively.

Neuropsychiatric Manifestation of Malaria

Cerebral malaria is observed in patients infected with P. falciparum with the highest incidence in children. Several neurological abnormalities can persist in adult after an episode of cerebral malaria. Neurocognitive squealae which can harm the individual adult, in their quality of life or schooling of children. Neurocognitive assessment studies in adult patients with sequealae of cerebral malaria have been less studied. The methodology used for the neuropsychological assessment of the patients seems suitable according the recommendations of the WHO.

The incidence of cerebral malaria in our study was 21(9.57%) patients. All patients were unconscious at the time of admission, level of coma as assessed by GCS scale.

Our study observed convulsion in cerebral malaria in 5 (15.32%) patients. In another study [17], they observed convulsion in (21.31%) patients. The incidence of convulsion in adults with cerebral malaria varies in early 1980 studies conducted in Thailand and Vietnam, 50% of adults with cerebral malaria had generalized seizure [18] whereas in these countries in the 1990 the incidence was less than 10%. The reason for this difference is not clear. Possible explanation includes differences in parasite virulence characteristic or possibly the decrease in the use of choloroquine. Status epileptics are unusual in adult, although more than one seizure is common [18]. Among Melanesian adult with severe falciparum malaria in central Province, Papua, New Guinea, only 17% presented with cerebral malaria [19].

Kochar et al., advocated in all cases of cerebral malaria prophylactic phenobarbitone either as low dose (3-5mg/kg) or high dose (10-15mg/kg). He reported that convulsions are usually generalized but persistent focal seizure and status epileptics are also observed. A variety of non specific EEG abnormalities have been described in both uncomplicated and cerebral malaria. Mefloquine is also attributed to cause seizure [20].

Neck stiffness is observed in 5 (4.5%) patients of malaria in our study. Nguyen et al., placed neck rigidity is not a feature but mild stiffness of neck is not uncommon, and hyperextension of the neck may occur in severely in adults but there is no photophobia [21]. In cerebral malaria, meningial irritation can occur with headache, vomiting, neck stiffness and positive kerning sign [22]. Other author observed neck rigidity in (19%) of cerebral malaria. Similar result was also found in other studies.

Kochar et al., (2002) observed conjugated deviation of eyes in (2.26%) patients. Similar observation were found in our study which is 1(0.90%), similar result also observed previous study of Bajiya et al., (1996) [17,23].

We do not found papilloedema in our study, Kochar et al., observed papilloedema in 5.5% cases. Papilloedema is very unusual in the adults. The papillary reaction is usually normal and the range of eyes movement full although gaze is disconjugate. Six nerve palsy rarely occur in cerebral malaria [24].

We found subarachnoid haemorrhage in 1 (0.90%) patient. Mathur et al., reported a case of subarachnoid haemorrhage due to disseminated intravascular coagulation (DIC) [25]. Other author reported similar results [26]. Kochar et al., (2002) observed cerebellar dysfunction in 4.72% patients, similar observation also seen in (2.70%) our study [12,17]. We found aphasia in 2 (1.80%) patients. Similar observation found in other studies [17,23]. Kochar et al., (2002) observed extra pyramidal rigidity (2.25%) and trimus (1.31%) [17]. We also find similar result extra pyramidal rigidity in 2 (1.80%) patients.

Similar study observed previously by Kocher et al., (1996) [23] Kocher et al., (2002) observed decorticate rigidity in (1.13%) [23]. Similar observation in our study decorticates rigidity in 1(0.90%). Upper motor neuron type haemiplegia and paraplegia have been reported by various workers in (WHO bulletin) severe complicated malaria [27].

We found in 6 (5.40%) of cases of psychosis in falciparum malaria. Other author observed psychosis (5.21%) in form of confusion, delirium, hallucination, depression, paranoid and manic syndrome [17]. Varney et al., (1977) also reported psychosis in Vietnam veteran showed depression, personality changes and irritability, virulence and partial seizure like syndrome [28].

Other author also reported acute psychiatric manifestation of malaria may be classified as follows:

1. Neuropsychiatric syndrome with marked weakness. It occurs either intermittently or in association with fever.
2. Clouding of consciousness up to coma.
3. Malarian psychosis [29].

Psychiatric manifestations may be the presenting features in patients with acute malaria, especially if there is high fever [30]. Other feature implicated in malaria psychosis include alcohol, stress associate with life or military services in tropical countries, and exacerbation of pre-existing functional psychosis [31]. In our study, psychosis was observed in 20 patients (12%) and these patients not received any psychotic drug, prior to hospitalization and no family history of psychosis and were neurologically or mentally normal before the acute disease, same result was observed by Bijiya and Kochar [23].

We observed 20 cases of post malarial neuropsychiatric manifestation in which acute confusion episode was found in 70% cases in whom 10 patients were in acute confusion stage with clouding of consciousness, 4 patients acute confusion state with clouding of consciousness with visual hallucination and 2 patients developed a prolonged confusional state following generalized convulsion,2 patients with acute confusional state had period of classic catatonia with waxy flexibility and 3 patients developed acute psychiatric symptoms with and clouding of consciousness. Of these, one has acute manic episodes with visual hallucination. Nguyen et al., while describing 22 cases of post malarial neurological syndrome had observed psychosis or acute confusional episodes in 15 (68%) patients [21]. The aggregated and sequestrated parasitized erythrocytes in cerebral capillaries and vanules interfere with micro circulatory flow and metabolism in the brain resulting in local hypoxia and ischemia. This is could be a probable cause of neurological deficit in these cases. The sequestration is caused by adherence of parasite derived protein on the surface of infected erythrocytes to endothelial cells. The endothelial molecules which help in adherence are intracellular adhesion molecules (ICAMA-1), CD36 and through spandin high level of tumour necrosis [32].

We observed cerebellar ataxia in 3.1%. cerebellar sign in acute falciparum malaria as a part of global encephalopathy. Selective impairement of cerebellar function in patients who are fully conscious many other authors also reported similar result [23]. Senanayake and Desilva this neurological syndrome is due to a instant strain of falciparum mediated via an immune mechanism [33]. Pathogenesis of cerebral malaria by producing endothelial damage and alteration of vascular permeability and done via induction of Nitric Oxide (NO) synthesis which inhibiting N-methyl-D as part (NMDA) channel in past synaptic cell [34]. Several other pathological processes combine to cause neurological deficit in cerebral malaria [35].

LIMITATION

This was a prospective observational study without comparing control group, was the main limitation of this study. Neuropsychiatric assessment was carried out by MMSE Score and BPRS which also limit the importance of this study.

CONCLUSION

The study carried out by the author in adults patient would add and promote wider study of malaria that can contribute to the prevention, control and treatment of malaria. Bikaner area is endemic for malaria, regarded as epidemic zone during raining season. There is a demand of research on malaria in this zone. We studied the neuropsychiatric manifestation in malaria. We should always think as a differential diagnosis of malaria in a patient who presented with fever with neuropsychiatric manifestation. So that, we can diagnose early and manage properly and reduce mortality by malaria.

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