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A study of atypical presentations and rare complications of malaria

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Abstract
Objective: To analyse and observe various atypical presentations and rare complications of malarial disease
Material and Methods: In this analytical study, 60 patients who are admitted with or diagnosed with malaria (*P. falciparum*/*P. vivax*) in GSL General Hospital, Rajahmundry studied in a period of 2years investigated with complete homograft, peripheral smear, liver function tests, renal function tests, CT chest, ECG, 2D ECHO in relevance to complaints/symptoms/presentation were included after a well-informed consent. Detailed history and findings of clinical examination were noted in a prevalidated proforma.
Results: In this current study the mean age of the participants was observed to be 46.83±17.23 years. 58.3% were the cases which are falciparum positive, 8.3% were positive for vivax and falciparum, 33.3% were positive for vivax. most common presenting complaints were that 40% had pain abdomen 3.3% had anasarca, 23.3% had diarrhoea, 1.7% had jaundice, 5% had pedal edema, 5% had decreased urine, 11.7% had seizures, 1.7% had quadriplegia, 6.7% had add altered sensorium, 1.7% had weakness and tingling toes, 5% had headache.
Conclusion: In the area's endemic to malaria, even with unusual presentation with multisystem involvement one need to consider Malaria as high degree of suspicion or as an alternate diagnosis to prevent further clinical deterioration.

Keywords: Malaria, pain abdomen, complications

Introduction
Despite being one of the most common infectious diseases, malarial disease and its complex and widely varied clinical presentations, complications are not clearly understood. Such atypical presentations and symptomatology often lead to delayed diagnosis leading to serious complications and death also the uncommon complications of malarial disease can lead to quest for detecting any alternative diagnosis, which can lead to delay in treating and diagnosing, and waste of valuable time and resources. Every year, 1.5-2 million people die as a result of this. Malaria is caused by intra erythrocytic Plasmodium protozoa. Plasmodia is spread through the bite of infected female Anopheles mosquitos.
Malaria's common/typical presentation include fever paroxysms with chills and rigors, weakness, malaise, fatigue, nausea. But patients presenting with these symptoms are around 50-70%. Which accounts for around 30-50% patients presenting with uncommon/atypical complaints, symptoms malaria in endemic areas often doesn't present acutely. Many people have smear positivity for years together without any apparent symptoms/complaints.

Material and Methods
Study design: Analytical study in patients who were diagnosed with malaria (*p. falciparum/p. vivax*)
Study period: 2 years
Setting: Department of General Medicine GSL Medical College located in Rajahmundry, Andhra Pradesh.

Selection of the patients

Inclusion Criteria

1. Smear positive *P. vivax* and *P. falciparum*
2. Quantitative buffy coat test positive *P. vivax* and falciparum cases
3. Age more than 13years
4. Patients with *P. vivax* and falciparum combined infection

Exclusion Criteria

1. Patients with malaria and dengue combined infection
2. Patients with superadded or combined bacterial infections
3. Patients for whom the atypical presentations can be explained by pre-existing pathology or disease.

Sample size

- Sample size (n): 60

Methodology

The study was started after approval of the Institutional Ethics Committee was obtained. Data was be collected in a pre-decided proforma.

Using quantitative buffy coat and blood smear for malarial parasite as mode of selection.

The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, Ver 21.0. For statistical significance, p value of less than 0.05 was considered statistically significant.

Results

Table 1: Age distribution

	Frequency	Percentage
15 – 30	11	18.3%
31 – 40	10	16.7%
41 – 50	16	26.7%
51 – 60	9	15%
61 – 70	10	16.7%
71 – 80	3	5%
81 – 90	1	1.7%
Total	60	100%
Mean ± SD	46.83±17.23	

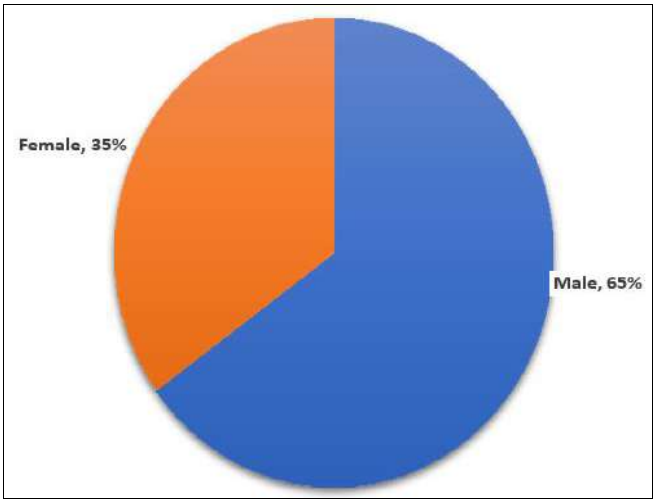

Fig 1: Pie Diagram: Gender distribution

Table 2: Chief complaints

	Frequency	Percentage
Pain abdomen	24	40.0%
Anasarca	2	3.3%
Diarrhoea	14	23.3%
Generalised weakness	1	1.7%
Vomiting	12	20.0%
Bloody stools	4	6.7%
Diarrhoea	13	21.7%
Jaundice	1	1.7%
Pedal oedema	3	5.0%
Decreased urine	3	5.0%
Seizures	7	11.7%
Quadriparesis	1	1.7%
Altered sensorium	4	6.7%
Weakness and tingling toes	1	1.7%
Headache	3	5.0%

Table 3: Smear and Cultur

	Frequency	Percentage
Falciparum positive	35	58.3%
Vivax and Falciparum positive	5	8.3%
Vivax positive	20	33.3%
Total	60	100%

Table 4: Special investigations

	Frequency	Percentage
24hr Urine Protein, Renal Biopsy	2	3.30%
2d Echo	2	3.30%
Absolute Eosinophil Count	1	1.70%
Cpk, Urine Analysis	1	1.70%
Ct Brain	11	18.30%
Ct Brain, Mr Venogram	4	6.70%
Ct Chest	5	8.30%
Ct Chest,2d Echo	1	1.70%
Nerve Conduction Studies	2	3.30%
Stool Analysis	24	40.00%
Ultrasound Abdomen	1	1.70%
Ultrasound Abdomen, Cect Abdomen	1	1.70%
Ultrasound abdomen, Mrcp	2	3.30%
Ultrasound abdomen, Renal Function Test	3	5.00%

Table 5: Final diagnosis

	Frequency	Percentage
Acalculous Cholecystitis	1	1.70%
Acute Gastroenteritis	24	40.00%
Acute Pancreatits	2	3.30%
Acute Renal Failure	3	5.00%
Ards	4	6.70%
Cardiomyopathy	1	1.70%
Cerebellar Ataxia	2	3.30%
Cerebelllar Ataxia	1	1.70%
Cerebral Venous Thrombosis	4	6.70%
Cva Ischemic Stroke	5	8.30%
Guillian Barre Syndrome	1	1.70%
Hyperreactive Malarial Splenomegaly	1	1.70%
Nephrotic Syndrome	2	3.30%
Pericardial Effusion	1	1.70%
Peripheral Neuropathy	1	1.70%
Pneumonia	1	1.70%
Pulmonary Edema	1	1.70%
Rhabdomyolysis	1	1.70%
Sub Arachnoid Hemorrhage	1	1.70%
Subdural Hemorrhage	2	3.30%
Urticaria	1	1.70%
Total	60	100%

Discussion

Malaria is a huge public health problem in developing countries. It has huge impact on the overall productivity by reducing quality of life and increasing DALY (disease adjusted life years). It is more prevalent in tropical and subtropical regions of the world. It is transmitted by female anopheles' mosquito which is a chief vector for the malarial spectrum of diseases. The plasmodium species continue to propagate throughout the centuries and the development of resistance to conventional antimalarial medications like quinine, chloroquine, also poses a bigger challenge in tackling the disease. It is a leading cause of mortality among infectious diseases second only to tuberculosis.

Major causes of mortality related to malaria are attributed to the atypical and delayed presentations and complications leading to misdiagnosis or delayed diagnosis. Falciparum malaria remains the leading cause of mortality among the malarial parasites.

The endemic nature of malaria in India along with seasonal outbreaks and epidemics causes a quantum jump in cases during certain seasons. Natural disasters like floods also causes propagation of mosquitoes in turn leading to spike of malarial cases.

The malathion and DDT resistance leading to emergence and proliferation of mosquitoes and alongside development of resistance to antimalarial agents like chloroquine and quinine by plasmodium lead to re-emergence of resistant forms of falciparum and vivax, which causes a huge challenge epidemiologically.

Hence the proper education and training of both health care providers and the community is essential to detect the atypical presentations of malaria in early phase and treated appropriately to avoid life threatening complications.

The present study was undertaken to study the clinical features, atypical presentations, complications, of malaria in the present study setting, with the aims and objectives being-To diagnose malaria and treat appropriately without diagnostic delay in patients with clinical presentation not so typical for malaria.

To study various effects of malarial parasite on human body and various adverse effect and some rare complications.

QBC report / peripheral smear report

In the present study 58.3% were the cases which are falciparum positive, 8.3% were positive for vivax and falciparum, 33.3% were positive for vivax.

In the study done by Chowta N *et al*., the distribution of the cases of malaria based on the type of parasite was in near concordance with the present study.

In the case study done by Sharma S *et al*., the positive cases were 261 (57.2%), the number of *p. falciparum* cases were 192 (42.1%) and 3 cases were of a mixed infection (vivas + falciparum).

In the study done by Rizvi *et al*., the distribution was also similar to the present study findings.

Socio demographic characteristics

In this current study the mean age of the participants was observed to be 46.83±17.23 years. In the study conducted by Rizvi I *et al*., age of the participants ranged from 18 to 72 years, mean age was 31.11±13.14 years. Thirty-seven (59.7%) out of these 62 patients were males and 25 (40.3%) were females.

In the study conducted by Rajput R *et al*., Mean age of the cases was 29.3 years with a male predominance.

Chief complaints

Plasmodia are mainly transmitted via the bite of female anopheles' mosquito. It can also be transmitted by transfusion of infected blood products. Case of congenital / transplacental transmission of malaria have also been recorded. Majority of the severe and complicated diseases of malaria are primarily caused by *p. falciparum*. While *p. vivax* usually runs a milder course, hence named benign tertiary malaria. But in recent years many numbers of severe diseases and complications of malarial disease are observed in vivax- mono disease

The classical/typical features of malaria consist of bouts/ paroxysms of febrile episodes associated with chills, rigours, followed by sweating. Headaches, weakness, fatigue, malaise, back pain, jaundice. As it is previously described this classical presentation accounts for about 50-70% of the cases. Leaving up to 30-50% of cases of malaria presenting with atypical/ uncommon presentations. In endemic areas this number is even higher.

In the present study the most common presenting complaints were that 40% had pain abdomen, 3.3% had anasarca, 23.3% had diarrhoea, 1.7% had jaundice, 5% had pedal edema, 5% had decreased urine, 11.7% had seizures, 1.7% had quadriplegia, 6.7% had add altered sensorium, 1.7% had weakness and tingling toes, 5% had headache.

Deb t *et al*. Has conducted a study in Jamshedpur in Jharkhand, who has described the atypical presentations of p.falciparum malaria who has convulsions in – 28.55%; pain abdomen in -5.7%; hemiplegia in 2.8%; generalised weakness and palpitations in – 5.5% cases among total sample size of 86 cases.

Dass r *et al*. Has conducted a study on unusual cases and presentations. Among the total cases of 162 – 16 cases i.e., 10% have unusual presentations. 3 patients have hemiplegia; 2 patients have viral hepatitis like presentation. 1case of acute abdomen; 1 case of gastrointestinal bleed; 1 case of generalised oedema; 1 case of hyperglycaemia.1 case of ptosis, 1 case of severe headache; 1 case of subacute intestinal obstruction like presentation. Among these 11 cases have mixed (Vivax + falciparum) parasitaemia; 2 cases of vivas and 2 cases of *p. falciparum*.1 case is diagnosed on clinical criteria

System-wise complications observed in various other studies

Presentation in cerebral malaria

Cerebral malaria is often a life threatening and one of the most documented complication of *p. falciparum* malaria. It is characterised by deep unarousable comatose state. Similar comatose manifestations in *p. vivax* infections are rarely documented, when involved the *p. vivax* ethology in causing the cerebral malaria is least understood. The cytoadherence mechanism is postulated to be the pathophysiological mechanism in *p. falciparum* but its role in *p. vivax* is contested. Some opined the mixed infection of vivax and falciparum could be the cause of what is thought to be vivax complicating cerebral malaria. Microvascular endothelial damage and thrombo-inflammatory response could be the cause in vivax-mono infections.

Most the epileptic or seizures in cerebral malaria seem to be generalised, but EEG (electroencephalogram) has shown

otherwise. EEG recordings have shown focal origin of the seizures with secondary generalisation Although the encephalopathy in malaria is symmetrical.
Neurological findings include-altered mental status/ altered sensorium, convulsions; signs of meningitis such as- resistance to passive neck flexion. Neuro- ophthalmological signs such as divergent gaze, 6th nerve palsy, nystagmus. Focal signs such as absent abdominal reflexes, plantar response being extensors, variable tone in limbs, and deep tendon reflexes being variable.
Generalised hypertonic a with decerebrate rigidity and opisthotonos posturing is observed in very severe cases which suggest involvement of brain stem. Poor prognostic signs include deep coma, decerebrate posturing, absent corneal reflexes, convulsions at presentations.
Subarachnoid haemorrhages are observed in cases of cerebral malaria and as isolated occurrence too.it secondary to occlusion of small vessels with infested RBCs followed by rupture of the occluded vessels. It can occur in the prescience of thrombocytopenia or in conjunction with disseminated intravascular coagulation.
The more sinister atypical/uncommon/rare neurological manifestations of cerebral malaria include central pontine myelinolysis. And subdural empyema. It occurs secondary to is Eric effects via micro vascular occlusion and toxin mediated injury via infected RBCs.
The neuropsychiatric manifestations like acute delirium; schizophrenia; dementia; have been described in acute phase. Personality changes; transient amnesia; agitation and confusion are often observed in chronic cases too in the endemic areas.
The frequently encountered cerebral symptoms among the atypical presentations include- cerebella ataxia; post malarial neurological syndrome; ataxia; hemispheres is; aphasia; GBS; cortical blindness; hemiplegia; pseudobulbar palsy; extrapyramidal symptoms; psychosis.

Ocular manifestations
Kale *et al*. Has observed a case with *p. falciparum* with sudden onset blindness attributed to the acute retrobulbar neuritis. Exact pathophysiology of this manifestation is unknown. The postulated mechanisms were - micro vascular damage with endothelial activation, ischemic injury, cytoadhesion, rosette formation of infested RBCs and clumping and occluding the capillaries. Steroids and antimalarial therapy were recommended to treat the complication.

Musculoskeletal involvement
Miller *et al*. Has observed cases of muscle involvement in malaria such as myosotis; muscle necrosis; rhabdomyolysis and has attributed the etiopathological mechanisms to the TNF- Alfa and inflammatory cytokines; micro vascular damage; endothelial activation, occlusion of capillaries with infested RBCs, electrolyte imbalances like hyperkalaemia can also cause periodic paralysis. Early detection of muscle involvement is necessary to predict and prevent acute kidney injury.
Senanayake *et al* and wimalawansa *et al*. Has described cases with generalised weakness and periodic paralysis during the acute phase with fever paroxysms. It is postulated that the haemolysis and cellular lysis during the acute phase causing sudden surge of potassium from intracellular compartment to extra cellular compartment causing hyperkalaemia leading to periodic paralysis. It coincides with chills and rigors.

Atypical Haematological manifestations
Aouba *et al*. Has observed a case with febrile paroxysms with splenomegaly and pancytopenia. It is attributed to the hyper reactive malarial syndrome and hypersplenism.
Ohnishi *et al* has described a case with prolonged anaemia attributed to IL-18 and TNF- alfa even post malarial cure.

White blood cell count and malaria:
Sharma *et al*. Has observed cases of leukopenia; leucocytosis; leukemoid reaction in cases with severe malaria. Out of 30 cases; 13.3% cases have leukocytes and 6.6%cases have Leukopenia. It is attributed to secondary gram-negative bacteraemia. Hence bacterial therapy should include gram negative coverage Modiano *et al*. Has observed in the cases with leucocytosis in conjunction with hypoglycaemia and anaemia has a reported 3.5 times increased mortality risk. Thus, gram negative coverage and avoidance of hypoglycaemia to prevent neuroglycopenia is key in decreasing mortality.

Thrombocytopenia
Cerebral venous sinus thrombosis is observed in cases of severe *p. falciparum* patients. The pathophysiology of the thrombosis in cerebral venous system is not clearly known. But it postulated to be secondary to multi factorial causes such as micro vascular damage; endothelial activation; occlusion of venues with infested RBCs; up regulation of inflammatory cytokines leading hypercoagulable state.

Hypovolaemia and cardiac dysfunction
Cases of severe malaria often develops severe metabolic acidosis in conjunction with hypovolemia and cardiac dysfunction.
Yacoub *et al*. Has observed the hemodynamic compromise in patients with severe malaria. Cardiac function being assess by 2DECHO, volume status assessed by IVC compressibility.
The overall cardiac function was assessed by stroke volume; ejection fraction; regional wall motion abnormality; global ' LV hypokinesia. These hemodynamic and cardiac parameters are assessed periodically on day-0; day-3 and day-5.
With prompt correction of volume by I.V fluids and bolus of fluids theirs is correction of intravascular volume. It raises stroke volume and has improved IVC compressibility. With correction of volume, acidosis has improved and the overall cardiac function improved. Patients with LV hypokinesia have improved subsequently without any residual failure.

Gastrointestinal and hepatobiliary involvement:
Liver involvement in malaria is often seen. But the extreme ends of the hepatic involvement are not seen regularly in all patients. The fulminant hepatic failure should be differentiated from the hepatitis without coagulopathy, which is assessed by PT, INR, other parameters of liver function tests such as enzymes, serum ammonia, albumin, glycaemic status are also assessed to grasp the level of hepatic involvement. Altered mental status secondary to hepatic encephalopathy should be differentiated from cerebral malaria. Falciparum malaria is often the cause of

severe hepatic involvement, but vivax malaria has also been reported to cause fulminant hepatic failure.

Splenic involvement:
Agarwal *et al*. Has reported and observed cases of malaria with spleen involvement in the form of splenic infarction. The other splenic pathologies described in malaria include hypersplenism; splenic torsion; rupture; hematoma; and the widely reported case of hyper reactive malarial syndrome in chronic cases and endemic areas which leads to pancytopenia.
Contini and Lewis *et al*. Has an observed patients with splenic abscess after recurrent attacks of falciparum. The repeated splenic hepatomas and infarctions lead to secondary bacterial infection. Occurrence of splenic abscess is grave prognostic in malaria as the splenic abscess alone contributes to 15% mortality.

Acute gastroenteritis
Acute gastroenteritis is observed in around 15% of all cases of malaria. As this is such a common occurrence, patients presenting with gastroenteritis in endemic areas should be suspected for malaria and should be treated appropriately when detected. Mahmoud *et al* has reported similar findings in his study.

Other manifestations:
Maitland *et al*, has observed in his study of 436 patients with severe malaria – 96 patients -22% has severe acidaemia with a ph of less than 7.2.
Sowunmi *et al*. has described in 51 patients with severe malaria, 7 patients had hyperkalaemia. Rhabdomyolysis also can cause hyperkalaemia. Acute kidney injury can also result in hyperkalaemia.
Sowunmi *et al*., has also described hyponatremia in patients with severe malaria among 30 patients 16 cases have hyponatremiaie. 53% of severe malaria cases.
It can be due to SIADH like mechanism or renal haemodilution are cerebral salt wasting, or due to gastrointestinal or renal losses
Use of hypotonic fluids may often cause cerebral elements a raised ICT and seizures.

Dermatological manifestations
Skin manifestations have been reported in cases of malaria both *p. falciparum* and *p. vivax*. Maheswari and Gupta *et al*. Has described 9 patients of malaria with urticaria as their initial/ presenting feature. Urticaria has subsided within 2days after instituting antimalarial therapy.
Urticaria is thought to be secondary due to effect of malarial parasite on mast cells causing histamine release. Involvement of complement system and raise of IgG and IgM antibodies is also reported.

Investigations done
In the present study, the investigations done were that in 3.3% of cases 24 hour urine protein, renal biopsy was done, 3.3% of the cases were done 2-D Echo 1.7% were done absolute is no Phil count 18.3% had got CT brain 1.7% were asked to get CPK, urine analysis done 1.7% got CT chest, 2-D Echo, 3.3% had got net of conduction studies done, in 40% stool analysis was done, in 1.7% ultrasound abdomen was done, in 1.7% ultrasound and CECT abdomen was done, 3.3% ultrasound abdomen, MRCP was done, in 5% ultrasound abdomen, renal function tests were done.

Conclusion
Physicians in the areas endemic to malaria have to understand the multi system involvement of malarial parasite and high degree of suspicion with alternate diagnosis with malaria as an etiological factor in cases with unusual presentations. Thus, early diagnosis and treatment leads to decrease in mortality and morbidity of patients presenting with atypical presentations and complications of malaria.

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