Original Article

Unusual Presentations of Malaria in Children: An Experience from a Tertiary Care Centre in North East India

Rashna Dass, Himesh Barman, Saurabh Gohain Duwarah, Nayan Mani Deka, Pankaj Jain and Vivek Choudhury

Department of Pediatric Disciplines, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS), Shillong, Meghalaya, India

ABSTRACT

Objective. To identify cases of malaria with unusual presentations.

Methods. The medical record of all the cases of malaria admitted to PICU and pediatric general ward from Oct 2006 to Sep 2009, were reviewed and cases with unusual presentations were identified. The study design was retrospective descriptive study.

Results. Sixteen (10%) out of 162 malaria cases had unusual presentations - three had hemiplegia, two each with viral hepatitis-like presentation, acute abdomen, gastrointestinal bleed, generalized edema and hyperglycemia and one each with ptosis, severe headache and subacute intestinal obstruction-like presentation. Eleven cases had mixed parasitemia and two each with P. vivax and P. falciparum. One case was diagnosed on clinical grounds.

Conclusions. Malaria is a common disease, but both typical and atypical presentations deserve attention for early diagnosis and management. **[Indian J Pediatr 2010; 77 (6) : 655-660]** *E-mail: rashnadass@rediffmail.com*

***Key words**: Malaria; Unusual presentations; Hyperglycemia*

Malaria, a disease caused by infection by the protozoan parasite of the genus plasmodium, is a disease of global importance. The four Plasmodium species infecting humans are: P. falciparum, P. vivax, P. ovale and P. malariae. Plasmodium falciparum is responsible for the most serious form of the disease and is common in tropics. Rarely, infections with other malarial parasites, such as P. knowlesi, also occur. It is a common disease and its presenting features have been well described. The first symptoms of malaria are nonspecific, and similar to the symptoms of a minor systemic viral illness. At this stage, with no evidence of vital organ dysfunction, the case-fatality rates are low provided prompt and effective treatment is given. But if treatment is delayed in falciparum malarial infection, the parasite burden continue to increase and severe malaria may ensue. A patient may progress from having minor symptoms to having severe disease and then from severe disease to death, within a few hours. If untreated, severe malaria is almost always fatal.

The residents of endemic areas are often familiar with the usual combination of symptoms, leading to frequent self-diagnosis and hence, over-diagnosis of malaria, based on symptoms alone. However, a small proportion of cases that present in an uncommon way and mimic other illnesses, may be missed with consequent catastrophe. W.H.O. recognizes that failure to suspect malaria in a patient with either typical or atypical illness, is a common error in the diagnosis and the management of the disease.

Much of the concerns about falciparum malaria revolve around four complications: cerebral malaria, hepatopathy, hyperparasitaemia and acute respiratory distress syndrome (ARDS). The other manifestations have been highlighted less often. Reports of unusual presentations of malaria are few and are mostly described in studies as smaller part of a bigger picture. Thus, they may fail to catch due attention. We thereby carried out this study with an intention to bring to notice our clinical

Correspondence and Reprint requests : Dr. Rashna Dass, Department of Pediatric Disciplines, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences (NEIGRIHMS), Room no. 218, PO: Mawdiangdiang, Shillong-793018, India.

[DOI-10.1007/s12098-010-0055-8]
[Received January 12, 2010; Accepted February 8, 2010]

experience which, we think, deserves attention for early diagnosis and subsequent management of malaria cases.

MATERIAL AND METHODS

Medical records were reviewed over a period of 3 yr from October 2006 to September 2009 and charts of all patients admitted to Pediatric ICU or pediatric general ward with a diagnosis of malaria, were identified. The history sheet and daily case notes were reviewed to identify cases presenting in an unusual way.

RESULTS

A total of 162 cases of malaria were encountered, out of which 16 cases (10%) presented in an unusual way. Age ranged from one and a half to 17 yr (median age 7 yr).

All, except one of the proven cases showed asexual stage of malarial parasite in the peripheral blood smear (PBS). Eleven cases had mixed parasitemia and two each with P. vivax (Pv) and P. falciparum (Pf). One case was diagnosed on clinical grounds. The case with ptosis had a rapid test positive for Pv. Four cases were afebrile at presentation but all of them had varying grades of fever at some point of their illness. Seven cases had altered sensorium at presentation, eight cases had splenomegaly and six cases had both hepatomegaly and splenomegaly. Five children had hyperparasitemia and two of them were treated with exchange transfusion. All except the two cases with viral hepatitis–like presentation, survived. The clinical and laboratory features are summarized in tables 1 and 2. The cases are briefly described hereunder.

Gastrointestinal presentation

Both the cases of viral hepatitis - like presentation (Case 1 & 2) were siblings, had history of travel to a highly endemic area (West Garo hills) prior to onset of their illness and both presented within 24 hr of each other, with prominent symptoms of altered sensorium and deep jaundice. Notably fever was not a chief complain. Both had a low Glasgow coma scale (GCS) at presentation, with high bilirubin, anemia, thrombocytopenia, prolonged prothrombin time and more than two times elevation of enzymes. Viral markers for Hepatitis A, B and C were negative in both. Case 2 had extensive ecchymosis and upper gastrointestinal bleeding. Both patients were initially managed as hepatic encephalopathy and, quinine was added only after the PBS showed presence of malarial parasite. Both progressed rapidly inspite of antimalarials and supportive therapy. Case 1 died within 48 hr and case 2 died within 3 hr of admission. The two cases with acute abdomen (Case 3 & 4) presented with high grade fever and severe pain abdomen. Examination revealed diffuse abdominal tenderness. Bowel sounds were present and no other sign of hollow viscus perforation was noted. The first case with acute abdomen (Case 3) had only hepatosplenomegaly and case 4 had associated thrombocytopenia. Plain picture abdomen and abdominal ultrasonography in both the cases, were normal. Case 5 and 6 presented with gastrointestinal bleeding. Case 5 presented with hematemasis and melaena and on investigation was detected to have hepatopathy, thrombocytopenia and multiple gastric erosions on endoscopic studies whereas case 6 presented with fever and stools mixed with blood and associated thrombocytopenia. The child with subacute intestinal obstruction–like presentation (case 7), presented with fever, vomiting and abdominal distention. There was no dyselectrolytemia but had thrombocytopenia. Plain picture abdomen and ultrasound study of the abdomen were normal.

Central nervous system presentation

All the three cases with hemiplegia (Case 8, 9 & 10) had fever, headache and altered sensorium at presentation. Case 8 also had one episode of vomiting. On examination, case 8 had decreased power (4/5) in the right upper and lower limbs and case 9 and 10 had decreased power (3/5) in the left upper and lower limbs. Case 10 required entotracheal intubation for 18 hr for airway protection. All of them had bilateral extensor plantar reflex. Cerebrospinal fluid examination and neuroimaging (CT brain in case 8 & 9 and MRI brain in case 10) were normal in all the cases. All the cases responded well to parenteral quinine and had no neurological deficit at discharge. Case 11 presented with ptosis of the right eye for two weeks duration, which was associated with fever and vomiting in the beginning of the illness. There was no history of hypohydrosis of the same side or any difficulty in vision. GCS was 15/15, other cranial nerves and motor system examination was normal. Spleen tip was palpable. A detailed ophthalmic evaluation concluded the presence of isolated 3rd nerve palsy. CSF study and MRI of the brain and orbit was normal. She was started on oral chloroquine and gradually improved. At one week follow up, she showed significant improvement in ptosis and at one month follow up there was no residual ptosis. Case 12 was a 16 year old girl who presented with intense headache for 4 days. There was no history of fever, vomiting or seizures and no history of similar episodes in the past. Low grade fever was documented (up to 101.4°F) during the hospital stay. Central nervous system examination was normal. Abdominal examination revealed presence of splenomegaly. CSF study revealed sugar 58 mg/dl (RBS 84mg/dl), protein 135 mg/dl and 7 cells, all lymphocyte per high power field. Contrast enhanced CT scan of brain showed a solitary calcified granuloma. Malaria was suspected on clinical grounds and oral Quinine was started. Headache disappeared within the next 48 hours.

Table 1. Summary of Clinical Profile of the Cases

Case no	Age in years/Sex	Parasite	Parasite indexPI*	Presenting complains	Unusual features	Complications	Splenomegaly	Hepatomegaly
1.	12/F	Mixed**	Occ.	Fever Altered sensorium, Pain abdomen Jaundice	Viral hepatitis like presentation	Cerebral malaria Severe anemia Deranged renal functions	-ve	+ve
2.	17/M	Mixed	28%	Fever Altered sensorium Pain abdomen Jaundice Spontaneous bleeding	Viral hepatitis like presentation.	Cerebral malaria Spontaneous bleeding Deranged renal functions	+ve	-ve
3.	3/M	Mixed	4.2%	Fever Pain abdomen	Acute abdomen	-	+ve	+ve
4.	4/M	Mixed	3.4%	Fever Pain abdomen	Acute abdomen	-	-ve	-ve
5.	15/M	Pf #		GI bleed	Fever, jaundice	Hepatopathy	+ve	+ve
6.	3/M	Pf	18%	GI bleed	Fever, vomiting	Meningitis Thrombocytopenia hyperparasitemia	-ve	-ve
7	1 ½/F	Pv	-	Fever, vomiting, abdominal pain.	Subacute Intestinal obstruction		-	+ve
+ve								
8	6/F	Mixed	Occ.	Fever Altered sensorium Vomiting	Hemiplegia	Cerebral malaria Hepatopathy Deranged renal functions	-ve	+ve
9	8/F	Mixed	Occ.	Fever Altered sensorium	Hemiplegia	Cerebral malaria	+ve	-ve
10.	1y 7m	Mixed		Fever, cough, altered sensoreium	Hemiplegia	Cerebral malaria	+ve	+ve
11	16/F	Pv#	-	Fever Vomiting Right sided ptosis	Ptosis	-	-ve	-ve
12	16/F	Clinical	-	Headache	Unexplained headache	-	-ve	-ve
13	17/F	Mixed	1.4%	Fever Altered sensorium Convulsion	Hyperglycemia	Cerebral malaria Shock Severe anemia Deranged renal functions	-ve	-ve
14	15/M	Mixed	6%	Fever Jaundice Altered sensorium	Hyperglycemia	Cerebral malaria Hepatopathy Deranged renal functions	-ve	-ve
15	3/F	Mixed	8.2%	Fever Generalized edema Petecchiae	Generalized edema Pleural effusion	Black water fever Thrombocytopenia Hepatopathy	+ve	+ve
16	6/M	Mixed	35%	Fever Generalised edema	Generalized edema Pleural effusion	Pneumonia Thrombocytopenia Hepatopathy	+ve	+ve

**Mixed= Pv + Pf, # Rapid test positive, Occ. = occasional

Table 2. Summary of Laboratory Profile of the Cases

Case no.	Hemoglobin in mg/dl	Total Count	Neurophils (%)	Lymphocytes (%)	Platelet count	Blood Urea (mg/dl)	S. creatinine (mg/dl)	Bilirubin (mg/dl)	ALT (U/L)	AST U/L	PT/TC in seconds	Serum Sodium (meq/L)	Serum Potassium (meq/L)
Case1	5.0	25,800	70	28	80000	90	NR	17.2	116	270	19/13	137	4.0
Case 2	9.5	11,000	29	70	60000	140	NR	9.2	55	220	High*	138	6.0
Case 3	12.2	6000	56	32	250000	27	0.6	0.8	64	107	ND	138	4.5
Case 4	10.8	55000	65	30	60000	46	0.8	0.9	27	76	ND	132	3.2
Case 5	6.7	9800	35	64	40000	121	1.0	16.0	89	126	16/15	132	4.2
Case 6	10.5	10,800	50	47	90000	50	0.6	0.6	65	133	15/14	133	4.1
Case 7	10.2	11,400	62	38	22000	60	0.6	ND	ND	ND	ND	135	4.2
Case 8	6.0	16400	55	44	180000	74	0.4	8.0	65	62	ND	132	3.8
Case 9	7.8	7000	66	26	320000	30	0.4	0.8	32	34	ND	132	4.5
Case 10	8.5	15700	54	44	220000	32	0.6	ND	ND	ND	ND	132	5.0
Case 11	11.4	8,500	65	27	220000	40	0.7	0.8	22	26	ND	143	4.5
Case 12	12.2	10,400	70	30	190000	42	0.9	0.8	35	38	ND	136	3.2
Case 13	3.5	10,000	61	37	150000	85	2.2	1.2	24	91	ND	132	4.5
Case 14	9.0	20,950	62	36	170000	238	1.8	5.4	92	178	ND	130	3.5
Case 15	6.7	10,800	70	28	45000	69	0.6	4.0	68	165	18/13	131	4.1
Case 16	9.5	5,200	59	37	50000	35	0.8	2.0	68	109	ND	128	4.2

ALT- Alanine amino transferase AST- Aspertate amino transferase. NR: not recordable due to high bilirubin. ND: Not done. High*- Blood did not clot.

"HI" on the glucometer. Case 14 had Blood sugar of 131mg/dl on admission but on regular glucose monitoring was detected to have a "HI" value within 26 hours of admission inspite of being on parenteral quinine. Blood sugar measurements were done by Accu-Check sensor (Roche diagnostics, Germany) and a reading of "HI" on this instrument indicated a blood sugar >600mg/dl. The simultaneous laboratory values were also in the same range. Both had glycosuria but no ketonuria. Both were managed successfully with insulin therapy.

Disturbance of Fluid Homeostasis

Two boys (Case 15 & 16) presented with fever and generalized edema. Case 15 had associated petechiae and right sided conjunctival hemorrhage. Both the cases had hepatosplenomegaly. 'Weight for age' in both cases were >80% at admission as well as at discharge. Ultrasound examination revealed presence of minimal ascites and bilateral pleural effusion in both the cases. Both cases had associated thrombocytopenia but normal serum cholesterol and were initially managed with quinine. The course of case 15 was complicated by development of black water fever which was managed by withdrawal of quinine, addition of artesunate and alkaline diuresis. The course of case 16 was complicated by development of pneumonia. Edema disappeared with improvement in general condition.

DISCUSSION

The clinical presentation of malaria depends on the severity and rapidity of infection and the immune response of the host. P. falciparum causes serious illness and children usually present early and undergo a rapid down hill course, if not diagnosed and treated early. The signs and symptoms in children, range from asymptomatic infection to life threatening illness. A classic description would include fever with chills accompanied by constitutional symptoms consisting of headache, body ache, fatigue, dizziness and malaise.[1] The salient differences from adults include, increased incidence of cough and respiratory distress (acidosis), convulsions, pretreatment hypoglycemia and neurological sequelae whereas, jaundice, pulmonary edema, renal failure and bleeding disturbances are less common.[2]

In children, fever and headache may be the sole symptom or gastrointestinal symptoms including nausea or vomiting, abdominal pain or diarrhea may predominate.[1-3] Taskande *et al* found vomiting and abdominal pain to be the usual abdominal features.[4] However, when it becomes a predominant symptom, difficulty arises in diagnosis as in the series by Gordon *et al.* In their series of 24 malaria cases, 18 presented with prominent abdominal feature and of these, 5 were admitted with unrelated diagnoses.[5] Abdominal pain is due to ischemic changes in the intestine secondary to microvascular changes due to sequestrated RBCs. Cases of frank perforation have also been reported.[6,7] So, malaria should be suspected in a febrile child presenting even with a surgical abdomen. In all our three cases, the abdominal symptoms were prominent and the clue to malaria was the presence of fever in a child from a malaria endemic area and confirmation on

a PBS study.

According to WHO, jaundice is not taken as a feature of severe malaria and, serious liver damage seldom occurs.[2,3] However, this has been refuted by many reports from South-east Asia which have assigned falciparum malaria to be a cause of fulminant hepatic failure and encephalopathy, especially in adolescents and adults.[10,11] Kocher *et al* have also shown in their report that many of their patients presented with hepatic encephalopathy.[10] Though WHO reports that bilirubin in patients with malarial jaundice is in the range of 3-10 mg/dl, Indian reports have found it to be >10mg/dl in many such patients and mostly in the conjugated form.[10,12] Various mechanisms such as intra-vascular hemolysis, associated renal failure and hepatocellular damage have been postulated.[10,12,13] Higher levels of bilirubin have been said to be associated with a more severe outcome.[14] Whether severe falciparum malaria with jaundice and encephalopathy is "cerebral malaria" or "falciparum malaria with hepatic encephalopathy", is still an unresolved issue. In endemic areas, it is prudent to rule out malaria in any case admitted with a working diagnosis of hepatic encephalopathy. The two cases reported by us were both adolescents and were initially diagnosed as hepatic encephalopathy, had bilirubin ranging from 9-10 mg/dl with high conjugated fraction, deranged enzymes, coagulopathy and deranged renal functions. Anti-malarials were started only after a PBS report revealed the presence of malarial parasite, thus resulting in a delay of a few hours before start of definitive therapy.

Cerebral malaria is a global encephalopathy. However, various neurological sequelae involving both pyramidal and extra-pyramidal systems as well as cerebellum have been described.[6] Neurological sequelae are more common in pediatric population and hemiplegia is the commonest sequelae.[2,15] However, they pose a diagnostic difficulty when a focal neurological sign develop during the acute phase of illness. Molyneux *et al* and Smutzhard *et al* in their series reported 4 cases each of hemiplegia in pediatric patients.[16,17] Simlar findings in Indian adults have been described by Kochar D *et al*.[18] We report 3 cases presenting with hemiplegia. All the cases had no residual neurological sequelae at discharge. Ptosis, as was the presenting manifestation in one of our cases has not been described in the literature as yet and we postulate that it was because of microvascular changes involving the 3rd nerve secondary to sequestration and this gradually improved with only oral medications. However, a single report of bilateral ptosis following chloroquine therapy has been reported.[19] Other eye findings well described are papilloedema secondary to increased optic nerve head blood flow in patients with malaria.[20] Unexplained severe headache can be the only manifestation as seen in one of our cases and is likely to be missed and go untreated, unless there is a high index of suspicion.

Hyperglycaemia is a well documented entity in critically sick patients in contrast to malaria, where hypoglycaemia is a more common finding and is postulated to be caused both by the disease process and also secondary to quinine therapy. Hyperglycaemia, is therefore rarely thought of or looked for in malaria patients. Tombe M *et al* described one case of severe malaria with hyperglycaemia in their series.[21] Hyperglycaemia in malaria, as seen in our series, could be because of associated sepsis or may be a stress response with increased counter regulatory hormones similar to those in critically sick patients. It is important to note that both our patients were found to have hyperglycaemia on routine blood sugar monitoring to detect hypoglycaemia (protocol for all cases of malaria) and responded well to insulin therapy.

Renal manifestations in malaria include acute renal failure, glomerulonephritis and nephrotic syndrome.[22] We also encountered 2 children with severe disease with hyperparasitaemia, presenting as generalized edema in absence of features of glomerulonephritis or significant proteinuria. This can probably be explained by increased capillary permeability, consequent to systemic inflammatory response.[9,23,24] Subtle renal impairment in salt and water handling may also contribute.[25]

CONCLUSIONS

Our experience shows that malaria may present with atypical manifestations which may mimic other medical and surgical illnesses. A high index of suspicion is therefore needed in managing all cases of fever at some point of their illness, especially in endemic areas so that diagnosis and treatment is not delayed.

Contributions: RD conceived the idea, designed the study, reviewed the manuscript for important intellectual content and approved the final version for publication. HB collected, analysed and interpreted the data, did the literature search and drafted the paper. SGD and NMD helped in data collection and drafting of the paper. PJ and VC gave important intellectual inputs and revised the manuscript. All authors were involved in the patient care. All authors read and approved the final manuscript.

Conflict of Interest: None.

Role of Funding Source: None.

REFERENCES

1. Barnett ED. Malaria. In Feigin Cherry, Demmer and Kaplan eds. *Textbook of Pediatric Infections Diseases*, 5th ed. Elsevier; Saunders; 2714-2720.
2. *World Health Organization: Management of severe malaria: A practical handbook*, 2nd ed. 2000.
3. White NJ. Malaria. In Gordon Cook, Alimuddin Zumla, eds. *Manson's TB of Tropical Medicine*, 21st ed. Saunders, 2003; 1205-1295.

4. Taksande A, Vilhekar K, Jain M, Atkari S. Clinico-haematological profile of cerebral malaria in a rural hospital. *JIACM* 2006; 7: 308-312.
5. Gordon S, Brennessel DJ, Goldstein JA, Rosner F. Malaria: A city hospital experience. *Arch Intern Med* 1998; 148: 1569-1571.
6. Ramana Murty CHV, Prabhakar YVS, Rao VBB, Jonnalangadda SS. Drug resistant falciparum malaria with bowel symptoms. *Am J Gastroenetrol* 2000; 95: 1101.
7. Gopisetty S, Sarveswaran J, Achuthan R, Davies J, Ausobsky JR. Acute surgical abdomen—an atypical presentation of *Plasmodium vivax* malaria. *Gut* 2007; 56: 447-448.
8. Seydel KB, Milner DA, Kamiza SB, Molyneux ME, Taylor TE. The distribution and intensity of parasite sequestration in comatose Malawian children. *J Infect Dis* 2006; 194:208–215.
9. Clark IA, Budd AC, Alleva LM, Cowden WB. Human malarial disease: a consequence of inflammatory cytokine release. *Malaria J* 2006; 5: 85.
10. Kochar DK, Agarwal P, Kochar SK *et al.* Hepatocyte dysfunction and hepatic encephalopathy in plasmodium falciparm malaria. *Q J Med* 2003; 96: 505-512.
11. Mahmood K, Jairamani KL, Abbasi B *et al.* Falciparum malaria : various presentations. *Pak J Med Sci* 2006; 22: 234-237.
12. Chawla LS, Sidhu G, Sabharwal BD, Bhatia KL, Sood A. Jaundice in Plasmodium falciparum malaria. *J Asso Phys India* 1989; 37: 390-392.
13. Anand AC, Ranji C, Narula AS, Singh W. Histopathological changes of liver in malaria: a heterogenous syndrome? *Natl Med J India* 1992; 5: 59-62.
14. Murthy GL, Sahay RK, Sreenivas DV, Sundaram C, Shantaram V. Hepatitis in falciparum malaria. *Trop Gastroenterol* 1998; 19: 152-154.
15. Brewster DR, Kwiatkowski D, White NJ. Neurological sequelae of cerebral malaria in children. *Lancet* 1990; 336: 1039-1043.
16. Molyneux ME, Taylor TE, Wirima JJ, Borgstein A. Clinical features and prognostic indicators in paediatric cerebral malaria: a study of 131 comatose Malawian children. *Q J Med* 1989; 71: 441-459.
17. Schmutzhard E, Gerstenbrand F. Cerebral malaria in Tanzania. Its epidemiology, clinical symptoms and neurological long term sequelae in the light of 66 cases. *Trans R Soc Trop Med Hyg* 1984; 78: 351-353.
18. Kochar DK, Shubhakaran, Kumawat BL *et al*. Cerebral malaria in Indian adults: A prospective study of 441 patients from Bikaner, North West India. *J Asso Phys of India* 2002; 50: 234-241.
19. G Bedu-Addo. Bilateral ptosis induced by chloroquine. *Trans R Soc Trop Med Hyg* 2006; 100: 696-697.
20. Beare NA, Riva CE, Taylor TE *et al*. Changes in optic nerve blood flow in children with cerebral malaria and acute papilloedema. *J Neurol Neurosurg Psychiatry* 2006; 77: 1288-1290.
21. Tombe M, Bhatt KM, Obel AO. Clinical surprises and challenges of severe malaria at Kenyatta National Hospital, Kenya. *East Afr Med J* 1993; 70: 117-119.
22. Rajapurkar MM. Renal involvement in malaria. *J Postgrad Med* 1994; 40: 132.
23. Areekul S, Kasemsuth R, Kanakakorn K.Studies on the transcapillary escape rate of fibrinogen and capillary permeability in patients with Plasmodium falciparum malaria. *Trop Geogr Med* 1984; 36: 151-157.
24. Areekul S. Transcapillary escape rate and capillary permeability to albumin in patients with Plasmodium falciparum. *Ann Trop Med Parasitol* 1988; 82: 135-140.
25. Sowunmi A. Renal function in acute falciparum malaria. *Archives of Disease in Childhood* 1996; 74: 293-298.