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Original Research Article

Clinico-Haematological Study of Malaria in Adults

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Abstract: Haematological abnormalities are very common in malaria and involve one or more cell lines. A variety of haematological alterations like anaemia, leukocytosis or leukopenia, thrombocytopenia have been reported in malaria. All adult febrile patients diagnosed as malaria according to WHO criteria were included. Haematological parameters like haemoglobin %, red cell distribution width (RDW), total leukocyte count and platelet count were studied as index tests. In results Significant haematological dysfunction was noted in malaria amongst the index tests. 44 (88%) of the cases had thrombocytopenia. This observation was statistically extremely significant (p less than 0.0001). Anaemia was detected in 41(82%) of the patients. The RDW was higher in 80 % of the malaria patients with a $p < 0.001$. In concusion significant haematological dysfunction occurs in malaria. The presence of thrombocytopenia, leucopenia, anaemia and high RDW increase the probability of malaria.
Keywords: Malaria, Anaemia, thrombocytopenia, leukocytosis, leucopenia.

INTRODUCTION

Malaria is an acute febrile illness transmitted by mosquitoes, caused by Plasmodium species found all over the world from 40°s to 60°N and is endemic in many tropical countries. 300-500 million cases of malaria occur annually all over the world with an estimated 1.1-2.7 million deaths each year [1]. Malaria is a major health problem in India With the launch of modified plan of operation the incidence has decreased to 2 million annual cases since 1984 [2].

A variety of hematological alterations like progressively increasing anemia, progressively decreasing RBC counts, thrombocytopenia and leukopenia or leukocytosis occur in malaria [3, 4]. These alterations if present would increase the probability of malaria in febrile patients. Such indicators may heighten the suspicion of malaria prompting a more diligent search for the parasite and prompt institution of specific therapy.

AIMS AND OBJECTIVES

To study clinical features and correlate with haemotological parameters in malaria. To assess the role of haematological parameters in the diagnosis of malaria in patients with acute febrile illness

Classical clinical features are rare nowadays due to early treatment. In uncomplicated malaria, few abnormal signs other than fever, splenomegaly and anaemia are seen. Splenic enlargement is very common among otherwise healthy individuals in malaria endemic regions and reflects repeated infection. However in non immune individuals, the spleen takes several days to become palpable. Slight hepatic enlargement is common, especially in children.

Light Microscopy: Thick and thin blood smears

The gold standard for the diagnosis of malaria is the preparation and examination of Giemsa or Field – stained blood smear under the microscope. Both thick and thin smears should be made. The thick smear, which concentrates by a factor of 20-30 layers of RBC on a small surface, provides the sensitivity of the technique and is much better than the thin smear for detection of malarial infection. The thin smear gives the test its specificity, being much better than the thick smear for species identification and evaluation of intensity of parasitaemia.

Disadvantages of peripheral smear examination:

1. It takes upto 60 minutes of preparation time [9]
2. It is labour intensive.
3. Interpretation of results requires considerable expertise particularly at low levels of parasitaemia.
4. Can miss falciparum malaria as the parasites can be sequestered and are not always present

in peripheral blood [10].

5. Does not differentiate between dead and live parasites.

Advantages:

1. Cheap.
2. Can quantify the parasite load (thick smear).
    a. One method is to count the total number of parasites per 200 WBC and multiply this number by 40 to give the number of parasites / ml after assuming that there are always 8000 WBC / ml of blood.
    b. Second method involves making a thick smear with a known small volume of blood (0.3ml) and then counting all the parasites on the smear. The total parasite count is multiplied then by 3.33 to obtain the number of parasites/ ml.

Haematological parameters in Malaria:

Since erythrocytes are the principle targets of the parasites, many changes occur in the infected RBC's. After invading an erythrocyte, the growing malaria parasite progressively consumes and degrades intracellular proteins, principally haemoglobin [5]. Parasitized RBC's also adhere to uninfected RBC's to form rosettes and to other parasitized RBC's (agglutination) [20]. The processes of cyto adherence, rosetting and agglutination are central to the pathogenesis of falciparum malaria. They result in sequestration of RBC's containing mature forms of the parasite in vital organs where they interfere with microcirculatory flow and metabolism. Severe malaria is also associated with reduced deformability of the uninfected erythrocytes [21].

Anaemia results from accelerated RBC destruction and removal by the spleen in conjuction with ineffective erythropoiesis [22, 23]. In severe malaria both infected and uninfected RBCs, show reduced deformability which correlates with prognosis and development of anaemia [24]. In non-immune individuals and in areas with unstable transmission, anaemia can develop rapidly and transfusion is often required [25- 27]. Anemia is a common consequence of antimalarial drug resistance, which results in repeated or continued infection [28].

Slight coagulation abnormalities are common in falciparum malaria and mild thrombocytopenia is usual. However <5% of patients with severe malaria have significant bleeding with evidence of DIC. The term Malarial Hepatopathy attempts to describe the involvement of one or more haematopoietic cell lines and includes the endothelial dysfunction that can cause thrombotic microangiopathy that may evolve in to consumptive coagulopathy

Total leukocyte count is usually normal, however leukocytosis can occur especially when associated with pernicious malaria and superadded bacterial infections [29 ,30, 31]. In Kenyan studies leukocytosis was associated with both severity and mortality in children with falciparum malaria irrespective of bacteraemia. Increase in number of atypical lymphocytes has been reported in acute falciparum infection at times leading to false positive serological tests like widal titres [32, 33].

Increased red cell population dispersions or red cell distribution width has been observed in malaria and has been attributed to the red cell response to malarial parasite and correlated with the degree of microcytosis [34]. RDW is an index of variation in red cell volume within the red cell population.

Red cell population with higher than normal RDW's are termed heterogeneous and those with normal RDW homogenous. Increase in number of reticulocytes causes increased RDW .Normal range is 11.5 to 14.5. An increased RDW indicates anisocytosis. Increased RDW and intra erythrcytic Hb concentration were demonstrated in malaria. The increased RDW correlated with increased % of macrocytes. RDW increases when erythropoiesis is stimulated. Thrombocytopenia is a common feature of acute malaria and occurs in both P. falciparum and P. vivax infections regardless of the severity of infection [35-37].

The mechanism of thrombocytopenia is malaria is uncertain. Immune mediated lysis, sequestration in the spleen and a dyspoietic process in the marrow with diminished platelet production have all been postulated. Abnormalities in platelet structure and function have been described as a consequence of malaria, and in rare instances platelets can be invaded by malarial parasites themselves [38, 39]. Patients with malaria can also have platelet function abnormalities [40].

Thrombopoietin is a key growth factor for platelet production and is elevated in states of platelet depletion. Thrombopoietin serum levels have been shown to be significantly higher in subjects with severe malaria, normalizing within 14-21 days of therapy [41]. Two types of platelet dysfunction are seen in malaria. Initially there is platelet hyperactivity; this is followed by platelet hypo activity. Platelet hyperactivity results from various aggregation agents like immune complexes, surface contact of platelet membrane to malarial red cell and damage to endothelial cells.

The injured platelets undergo lysis intravascularly. The release of platelet contents can activate the coagulation cascade and contributes to DIC.

Transient platelet hypo activity is seen following this phase and returns to normal within 1-2 weeks [39]. Thrombocytopenia also appears to be associated with elevated concentration of pro and anti-inflammatory cytokines, their exact role, still being under investigation.[42]Antiplatelet IgG has also been implicated in thrombocytopenia [43].

Lathia TB and Joshi R studied a total of 184 patients with acute febrile illness from July to December 2003 at Mahatma Gandhi Institute of Medical Sciences, Sevagram, and Maharashtra. Four haematological parameters were studied (Hb%, red cell distribution width, total leukocyte count and platelet count). Thrombocytopenia alone was a predictor of malaria (Sensitivity 60%, Specificity 88%) and in combination with anaemia was the next best predictor (Sensitivity 69%, specificity 74%). RDW and leukocyte count were not predictive. The conclusion of this study was that the presence of thrombocytopenia in a patient with acute febrile illness increases the probability of malarial infection [44].

UM Jadhav, VS Patkar, NN Kadam studied 1565 patients with malaria. They concluded that absence of thrombocytopenia is uncommon in the laboratory diagnosis of malaria. Thrombocytopenia less than 20,000/**ui** can occur in P.vivax malaria although was statistically more common with P. falciparum malaria. Presence of thrombocytopenia is not a distinguishing feature between the two types of malaria [45].

Ekhart LM *et al.;* studied 2149 cases with acute febrile illness. 414 of their patients were infected with P. falciparum and 646 were infected with P. vivax. Patients with malaria tended to have significantly lower WBC counts, RBC counts, and platelet and haemoglobin levels than those who were malaria negative. A parallel trend in thrombocytopenia with parasitaemia was found to be associated with both P. falciparum and P. vivax infection. Persons with platelet counts <1, 50,000/ui, were 12-15 times more likely to have malaria than persons with platelet counts above 1, 50,000/ul Thrombocytopenia was identified as a key indicator of malaria in these febrile patients [46].

MATERIAL AND METHODS

All adult patients of both sexes who were diagnosed as smear positive according to WHO criteria during the study period of September 2012 to January 2016 were included in the study. A complete clinical examination was done with special reference to the presence of fever, jaundice, bleeding spots, and hepatosplenomegaly and to exclude fever with localizing signs such as meningitis, pneumonia, upper respiratory tract infection, skin and subcutaneous tissue infection, etc.

All patients were investigated with complete blood counts, peripheral smear for malaria parasite, chest film, serum biochemistry and urine microscopy. Peripheral smear positivity was taken as the gold standard for diagnosis of malaria. Other investigations like blood culture, serology for typhoid, urine culture were done where indicated. Smear examination was repeated twice in the next 2 days when the patient was febrile before concluding that the illness was non malarious. Malaria was diagnosed when any one of the smears was positive for malaria parasite.

RESULTS

Age distribution in Malaria patients:

The mean Age for Malarial patients is 25.98 yr

Table 1: Age distribution in Malaria patients

Age group (yrs)	Malaria Patients	
	No.	%
< 30	36	72%
30-40	12	24%
41-50	2	4%
>50	0	0%

The table shows age distribution of cases which suggests that malaria is common amongst the younger population who are commonly exposed to mosquitoes by way occupation, travel, etc.

Table 2: Sex distribution in Malaria patients

	Malaria patients
Male	40(80%)
Female	10(20%)
Total	50(100%)

Of the 50 malaria patients 80% were males and 20% were females.

Table 3: Type of fever

Type of fever	Malaria Patients	
	No.	%
Continuous	37	74
Intermittent	13	26
Total	50	100

Intermittent fever was present in 26% the cases.

Table 4: Fever with chills and rigors

Fever with chills and rigors	Malaria Patients
Present	18(36%)
Absent	32(64%)
Total	50(100%)

Chills and rigors during the febrile episode occurred in 36% of the patients.

Table 5: Fever with splenomegaly

Fever	Malaria Patients	
Spleen +	30	60%
Spleen -	20	40%
Total	50	100%

Of the 50 Patients of malaria, 30 had splenomegaly. The p< 0.0001 which was statistically extremely significant?

Table 6: Distribution of Jaundice in malaria cases

	Jaundice	No Jaundice	Total
P. falciparum	4(8%)	5(10%)	9(18%)
P. vivax	6(12%)	35(70%)	41(82%)
	10(20%)	40(80%)	50(100%)

The presence of jaundice was significantly associated with P. falciparum malaria. Of the 9 Patients with falciparum malaria 4 had jaundice but only 6 of the 41 Patients with vivax malaria had jaundice.

Table 7: Hematological dysfunction in malaria

Parameter	Mean ±SD	't' Value	'p' Value	Significance
Hb - g %	7.974±2.1201	21.917	<0.0001	Highly significant
TC - cell / mm^3	5178±3365.51	10.877	<0.0001	Highly significant
RDW %	18.058±4.201	28.298	<0.0001	Highly significant
Platelet count cell / mm^3	73626.8±59531.1	8.745	<0.0001	Highly significant

The table shows that significant haematological dysfunction occurs in malaria. The haematological dysfunction in malaria was studied with the help of single't' test. All 4 index tests revealed statistically highly significant dysfunction. The p value was < 0.0001 for all 4 parameters.

Table 8: Analysis of Hb values

Hb g%	**Malaria Patients**	
< 10	41	82%
> 10	9	18%
Total	50	100%

Anaemia was significantly associated with malaria with p< 0.0001 Mean Hb: Patients : 7.974 g% with a standard deviation of ± 2.1201g%. p < 0.0001 – highly significant.

Table 9: Analysis of total leukocyte count

Total Count cells / mm^3	Malaria Patients	
< 4000	22	44%
4000-11000	25	50%
>11000	3	6%

Mean TC: 5178 WBC / $mm^3$with a standard deviation of ± 3365.5807 cells/mm^3 .The p < 0.001 which was very significant.

Table 10: Analysis of leukopenia

Total count	**Malaria Patients**	
Leukopenia	22	44%
Normal count / leukocytosis	28	56%
Total	50	100%

Table 11 : Analysis of RDW

RDW	**Malaria Patients**
< 15%	40(80%)
> 15%	10(20%)
Total	50(100%)

Mean RDW - Cases 18.058 %; standard deviation ± 4.2% . 80 % of the Patients had a RDW value of more than 15%. The p < 0.001 which was highly significant.

Table 12: Analysis of platelet count

	Cases
With thrombocytopenia	44(88%)
Without thrombocytopenia	6(12%)
Total	50(100%)

Mean platelet count – 73626.8 / mm^3. The standard deviation for cases was ± 59531.05/mm^3. The p value < 0.0001 which was extremely significant.

Summary of statistical analysis

Table 13: Haematological dysfunction in malaria

Parameter	Mean ±SD	't' Value	'p' Value	Significance
Hb - g %	7.974±2.1201	21.917	<0.0001	Highly significant
TC - cell / mm^3	5178±3365.51	10.877	<0.0001	Highly significant
RDW %	18.058±4.201	28.298	<0.0001	Highly significant
Platelet count cell / mm^3	73626.8±59531.1	8.745	<0.0001	Highly significant

DISCUSSION

The present study demonstrates that significant haematological dysfunction occurs in malaria across all cell lines [3, 4]. The study also demonstrates that haematological parameters can be used as predictors of malaria [35, 36, 37, 44, 45, 46].

The presence of Increased RDW34, Anaemia [22, 23] leucopenia and thrombocytopenia [35, 36, 37] emerged as the strongest indicators of malaria. In our study there was significant haematological dysfunction [3,4] in malaria as demonstrated by the highly significant p values (less than 0.0001) as studied by the single 't' test.

Low platelet count emerged as one of the strongest predictors of malaria [35, 36, 37, 38, 39, 40, 46] Of the 50 malaria patients 44(88%) had thrombocytopenia [35, 36, 37].The $p < 0.0001$ which was extremely significant. Anaemia [22, 23, 24] was detected in 82% of the cases. The $p < 0.05$ which was significant? In our study 44% of the patients with malaria had Leukopenia. The $p < 0.001$ which was very significant for Leukopaenia? RDW in our study showed that it was also very significant predictor of malaria with a $p < 0.001$.The presence of splenomegaly was seen to be significantly associated with malaria. Splenomegaly was present in 60% of our cases. The $p < 0.0001$ which was extremely significant?

CONCLUSION

Significant haematological dysfunction occurs in malaria across all cell lines [44, 45, 46]. The presence of thrombocytopenia [35, 36, 37] and leukopenia increases the probability of malaria. The presence of high RDW [34], and anaemia [22, 23, 24] are also significantly associated with malaria. These findings along with a clinical suspicion should prompt a more diligent search for the malaria parasite.

SUMMARY

- The association of splenomegaly with malaria was found to be statistically extremely significant.
- Jaundice was present in 44.44% of falciparum malaria cases and in only 14.63% of the vivax cases. The association of jaundice with falciparum malaria was found to be statistically significant.
- The $p < 0.0001$ was extremely significant for Thrombocytopenia.
- The $p < 0.001$ was very significant for leukopenia.
- Anaemia was detected in 82% of the cases.. The $p < 0.0001$ was very much significant.
- The RDW was higher in 80 % of the malaria patients. It was very significant predictor of malaria with a $p < 0.001$.

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