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Nijerya'da Uyo, Akwa Ibom Eyaleti'nde Bir Üçüncü Basamak Hastanede Trombosit sayısı Üzerine Falsiparum Sıtmasının Etkisi

[The Effect of Falciparum Malaria Infection on The Platelet Count of Children in a Tertiary Hospital in Uyo, Akwa Ibom State of Nigeria]

ÖZET

AMAÇ: Sıtma Nijerya'da çocuklar arasında hastalık ve ölüm nedenleri arasında önemli bir yer tutmaktadır. Ttrombositopenik paternler hakkında yerel topluluklardaki bu çalışmanın amacı çocukluk çağı sıtmasının bu önemli komplikasyonu hakkında farkındalığı arttırmaktır.

YÖNTEM: Yaşları altı ay ile 15 yaş arasındaki p. falciparum sıtması olan 180 çocuğun trombosit sayıları ile sıtma olmayan 180 sağlıklı çocuğun trombosit sayıları yaş ve cinsiyet açısından eşleştirilerek karşılaştırıldı. Trombosit sayıların otomatik analizör (Sysmex KX-21N) kullanılarak tespit edildi.

BULGULAR: Ortalama trombosit sayıları deney ve kontrol grupları için sırasıyla 297,40±128,03 ve 338,27±103,89 x10^9/L idi. Aradaki fark istatistiksel olarak anlamlıydı ($p<0.001$). Hastalıkd urumu ciddi olanlarda sıtma parazit yoğunluğu ile trombosit sayı arasdında ters ilişki olacak şekilde ortalama trombosit sayısı daha düşüktü ($r=-0.21$; $p<0.001$).

SONUÇ: Çalışma daha ağır trombositopeninin daha ciddi p. falciparum sıtması ile birlikte olduğunu gösterdi. Bu yüzden trombosit sayısını monitörize etmek ciddi p. falciparum sıtması olan öocuklarda önemlidir.

SUMMARY

AIM: Malaria is a major cause of illness and deaths in children in Nygeria. The aim of this research on thrombocytopenic patterns in local communities is to improve awareness of this important complication of childhood malaria.

METHOD: The effect of p. falciparum malaria infection on the platelet count of one hundred and eighty children aged six months to fifteen years were compared with 180 healthy controls without malaria matched for age and gender. The platelet counts were evaluated using the automated analyser (Sysmex KX-21N).

RESULTS: The mean platelet count (x10^9/L) for subjects and controls were 297.40±128.03 and 338.27±103.89 respectively. The difference was statistically significant ($p < 0.001$). There was a lower mean platelet count in those with severe malaria, with an inverse relationship between the malaria parasite density and platelet count ($r=-0.21$; $p<0.001$).

CONCLUSION: The study demonstrated a higher level of thrombocytopenia in children presenting with severe manifestations of falciparum malaria in this setting. It is therefore important to monitor the platelet counts of children presenting with severe falciparum malaria.

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Anahtar Kelimeler:
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INTRODUCTION

Malaria remains a major cause of illness and deaths in African children, and those less than five years of age are at greatest risk. The lethality of the *Plasmodium falciparum* specie results from complications estimated to occur in about one percent of episodes (1,2). The effects of the malaria parasite on red and white blood cells in men have been extensively reported, in contrast to the paucity of reports of its effects on platelets. A major aetiologic cause for acquired thrombocytopenia of childhood is increased platelet destruction associated with several clinical conditions including protozoal infections such as malaria especially in the tropical regions (2). In a report, thrombocytopenia was the most common laboratory abnormality seen in severe malaria (60% of cases).3 The association of thrombocytopenia with malaria infection is well recognized, but its pattern of occurrence varies with levels of malarial endemicity

and immunity, age, malarial specie and malarial severity (3,4).

Most studies done in the United Kingdom (5), Sweden (6), United Arab Emirates (7), Saudi Arabia (8), India (9), Gabon (10), Senegal (11) and Ibadan (12,13) in Nigeria noted higher occurences of thrombocytopenia especially in cases of severe malaria, while in holoendemic settings, this may be low (14). The effects of thrombocytopenia with *falciparum* parasitaemia has been mostly documented in adult populations of semi-immune and non-immune individuals, but there have been few documentation for children in the tropical region of Africa, more so in Nigeria, where malaria is endemic. The research on thrombocytopenic patterns in local communities is important to improve awareness of this important complication of childhood malaria, more-so in those who have bleeding tendencies. It will improve the general index of suspicion in clinicians caring for children; improve standard management procedures, clinical treatment and outcome. This study therefore sought to establish the impact of *plasmodium falciparum* malaria infection on the platelet count of children and its relationship with severity of disease as seen in a malaria endemic locality in Nigeria.

METHODS AND MATERIALS

The study was conducted in the Children Out-patient (CHOP) clinic, Children Emergency Unit (CHEU) and the Paediatric ward of the University of Uyo Teaching Hospital (UUTH), Uyo in Akwa-Ibom State. The Teaching Hospital is the only Tertiary Health Institution in the state, and is located on the outskirts of Uyo, six kilometres from the centre of the city. Uyo, the capital city of Akwa-Ibom State is located in the South-eastern region of Nigeria and lies between latitudes 4'33 and 5'33 north, longitudes 7'35 and 8'35 east. This falls within the tropical zone where the anopheline mosquito habitat exists.

Approval for the study was obtained from the Hospital's Ethics committee. Infants and children between the ages of six months and fifteen years were enrolled into the study after an informed consent was obtained from the child, twelve years of age and above or from the parents/guardian(s) for the younger children. A clinical history was obtained from the care-giver and/or the patient and included the onset and duration of fever (temperature$\geq$37.5°C) (1-4) and associated symptoms. Uncomplicated malaria was established by microscopically confirmed malaria parasitaemia with no symptoms of severity. Children with repeated convulsions, hyperpyrexia (axillary temperature$\geq$39.5^{o}celsius), respiratory distress, oliguria (urinary output<1ml/kg/hr), cardiovascular shock, jaundice, severe prostration, haemoglobinuria, severe anaemia (Haemoglobin<5g/dl), hypoglycaemia (serum glucose<2.2mmol/l), acidosis (bicarbonate<15mmol/l) as well as those with hyperparasitaemia (involving>5% of erythrocytes) were classified as having severe malaria (1-4). In children presenting with one or more convulsive episodes, cerebro-spinal fluid was obtained to exclude bacterial or viral meningitis.

Excluded were those who had received any cytotoxic drugs and other drugs that interfere with platelet counts e.g non-steroidal anti-inflammatory drugs (NSAIDS) such as acetylsalicylic acid (Aspirin) within ten days of presentation, and those who had received any antimalarial drug within two weeks of presentation. Also excluded were children with an obvious focus of infection, including a positive blood culture examination. Controls were afebrile, apparently healthy children, matched for age and gender who showed no signs of any systemic disease and had no parasitologic evidence of malaria. They were selected from children attending child welfare clinic for growth monitoring and those presenting for immunization. Also children presenting to the out-patient clinic for school entry medical examination were recruited.

Thick and thin blood films for malaria parasite were prepared directly from capillary blood using the Giemsa staining technique. Each blood film was examined microscopically using the 100X objectives and the 7X eyepieces as these give a brighter and clearer image. The parasite count was estimated using the method by Greenwood and Armstrong (15). The fully automated blood cell analyser (Sysmex KX-21N) was used to determine the platelet count. Thrombocytopenia was defined as a platelet count<100,000x10^{9}/L. Severe thrombocytopenia was defined as a platelet count<50,000x10^{9}/L (2). Aerobic and anaerobic blood cultures were obtained from every subject.

Statistical analysis was performed using the SPSS (Statistical Package for Social Sciences) 17.0 software. Data was summarized into frequency tables and graphs as appropriate. Qualitative variables were expressed as number and percentage while quantitative variables were expressed as mean (X) and standard deviation (S). The arithmetic mean as a measure of central tendency and the standard deviation (S) as a measure of dispersion were applied. The student t-test was used to compare the mean

values of the quantitative variables between the subjects and the controls. For non-normally distributed quantitative variables, the Wilcoxon rank sum test was employed. The Chi-square test was used in finding a difference in the qualitative variables. Univariate and multivariate logistic regression models were built. The multivariate logistic regression model helped in adjusting for possible confounders in the relationship between malarial infection and thrombocytopenia. A p-value of less than 0.05 ($p<0.05$) was considered statistically significant.

RESULTS

Three hundred and ninety six children were initially evaluated. Thirty-six (9.1%) of these were excluded. Those excluded were sixteen (4.04%) of the controls who had malaria parasitaemia in blood film (asymptomatic parasitaemia), twelve (3.0%) subjects who had no malaria parasitaemia in blood film, four (1.0%) subjects with viral exanthema and four subjects (1.0%) who had a positive blood culture examination. Thus, a total of three hundred and sixty (360) children aged six months to fifteen years were ultimately studied. These included one hundred and eighty (180) subjects, and one hundred and eighty (180) controls. The age distribution of the study population is as shown in Table 1. The group of children under five years of age were the most, constituting 73.3% of the study poulation.

Of the one hundred and eighty subjects studied, one hundred and fifty-six (86.67%) presented with uncomplicated malaria, while twenty-four (13.33%) had clinical symptoms and/or signs of severe malaria. Fever was the most common symptom in 117 (65%) of subjects, with 20 (11.1%) presenting with hyperpyrexia. Altered sensorium was present in 3 (1.7%) of the subjects, jaundice in 2 (1.1%), and haemoglobinuria was least, present in only one subject (0.6%).(Table 2)

Of those that had severe malaria, twenty (11.1%) had hyperpyrexia, twenty had prostration (11.1%), severe anaemia in seven (3.9%), hypoglycaemia in five (2.8%), altered sensorium in three (1.7%), jaundice in two (1.1%) and haemoglobinuria in one (0.6%). Most patients had one or more signs of severe malaria at presentation. The mean malaria parasite count in subjects was 25,650.28 ± 88,312.04, with a range of 500 to 725,500 parasites/µl. *P. falciparum* was the only specie found in all the subjects. The control children had no parasitaemia.

Table 1. Age distribution of study population (in years)

Age group (years)	Subject (%)	Control (%)	Total
< I	54 (30.00)	54 (30.00)	108
1 - < 5	78 (43.00)	78 (43.00)	156
5 - <10	19 (10.56)	19 (10.56)	38
10 - <15	21 (11.67)	21 (11.67)	42
15 - <20	16 (4.44)	16 (4.44)	32
TOTAL	180 (100.00)	180 (100.00)	360

Table 2. Characteristics of the six subjects presenting with severe malaria and thrombocytopenia

Subject	Gender	Age (years)	Malaria parasite count (/uL)	Platelet count x 10^9/L	Clinical/Laboratory characteristics
1	Female	1.1	135,000	44	Severe anaemia* Hyperpyrexia** Hypoglycemia Prostration
2	Male	1.3	275,000	65	Severe anaemia Hyperparasitaemia
3	Male	4.0	315,000	83	Hyperparasitaemia Hypoglycemia Hyperpyrexia
4	Male	10.0	10,500	95	Hyperpyrexia Prostration
5	Male	5.0	37,500	70	Hyperpyrexia Prostration
6	Female	3.0	65,500	82	Severe anaemia Hyperpyrexia Prostration

*****Severe anaemia- Packed cell volume<15%; **Hyperpyrexia- Axillary temperature≥39.5°Celsius

The study showed a negative correlation between the malaria parasite count (r=-0.21; p<0.001) and platelet count in the subjects. Thus the higher the malaria parasite count, the lower the platelet value (Figure 1,2). Subjects with severe malaria had lower mean platelet counts compared to subjects with uncomplicated malaria (Table 3). Three of the subjects who presented with uncomplicated malaria also had thrombocytopenia(Table 4,5). No clinical variable was found to be a significant independent predictor of the occurrence of thrombocytopenia (Table 6). Multivariate logistic regression showed a 93% reduction in the risk of developing thrombocytopenia in subjects with uncomplicated malaria compared to those with severe malaria, after adjusting for age, gender, weight and malaria parasite count [OR=0.07, 95% CI=0.013-0.38].

Platelet count in the control group ranged between 113-598x10^9/L (338.27±103.89) and was significally higher than that of the subjects being 44-596x10^9/L (297.40±128.03); (p=0.0008). No significant gender difference in platelet count values was observed in the study population (p=0.84; p=0.66 respectively). Only nine (5.0%) of the 180 subjects in this study had thrombocytopenia, defined as platelet count<100,000x10^9/L while one (0.6%) had severe thrombocytopenia (defined by a platelet count<50,000 x 10^9/L. There was no individual with thrombocytopenia among the controls

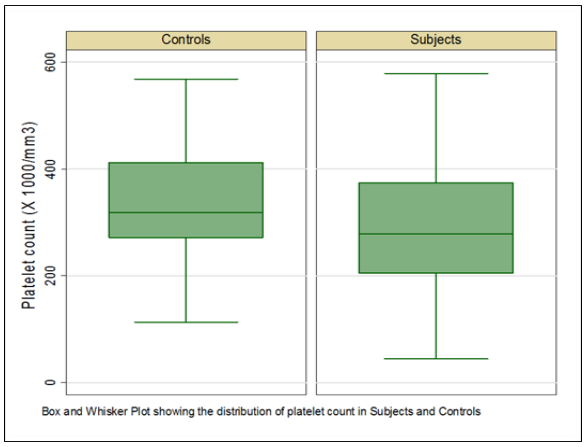

Figure 1. Comparison of platelet count in subjects and controls.

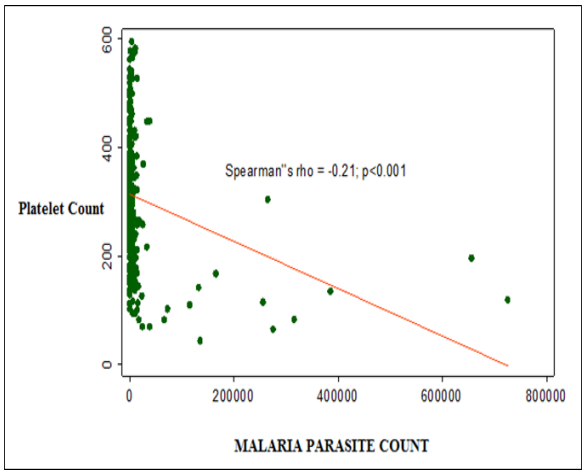

Figure 2. relationship between malaria parasite count and platelet count in subject

Table 3. Platelet count in subjects with uncomplicated versus severe malaria.

CLINICAL MALARIA	PLATELET(x 10^9/L)		P- value
	Range	Mean ± SD	
Uncomplicated	70 – 596	313.95 ± 117.98	
Severe	44- 565	192.54 ±141.62	P < 0.001

Table 4. Pattern of thrombocytopenia in malaria as seen in subjects

Platelet count x10^9/L	SUBJECTS				Total		P-value
	UNCOMPLICATED MALARIA		SEVERE MALARIA				
	n	%	n	%	n	%	
>100	153	(98.1)	18	(75)	171	(95)	
<100	3	(1.9)	6	(25.0)	9	(5)	0.001
Total	156	(100.0)	24	(100.0)	180	(100.0)	

Table 5. The distribution of platelet count versus malaria parasite count in subjects.

Platelet count (x 10^9/L)	n (180)	Malaria parasite count (/uL)	
		Range	(Mean ± SD)
< 50	1	135,000*	135,000
50 – <100	8	5500 – 315,000	93,750 ± 126,057
100 – <150	14	2500 – 725,500	127,036 ± 205,915
>150	157	500 - 655500	12,443 ± 57,358

*Only one subject had a platelet count less than 50 x 10^9/L.

DISCUSSION

In this study, the platelet count in the control children was higher than that observed in the children infected with malaria. This is an observation similar to that made by Akingbola **et al** (13) and Iwalokun **et al** (17) in Lagos, Nigeria, and in agreement with other studies which have reported decreasing platelet count values with malaria in individuals of all races. Quantitative and qualitative changes in the platelets occur in malaria with an attendant reduction in platelet count values (2). These have been consistently noted to occur in platelets during malaria infection and serve to re-inforce the adverse effect of malaria parasitaemia on platelet count.

Table 6. Clinical characteristics of severe malaria in subjects in relationship with thrombocytopenia (< 100 x 10^9/l)

Variable*	No n (%)	Yes n (%)	p-value
Prostration	4 (16.7)	20 (83.3)	0.206
Impaired consciousness	21 (87.5)	3 (12.5)	0.285
Hyperpyrexia	4 (16.7)	20 (83.3)	1.000
Respiratory distress	16 (66.7)	8 (33.3)	0.050
Multiple convulsions	21 (87.5)	3 (12.5)	0.285
Jaundice	22 (91.7)	2 (8.3)	0.394
Haemoglobinuria	23 (95.8)	1 (4.2)	0.555
Severe anaemia	17 (70.8)	7 (29.2)	0.195
Hypoglycemia	18 (75.0)	6 (25.0)	0.102

*Many subjects had more than one characteristic at presentation

Children below five years of age constituted a greater percentage of those presenting with manifestations of severe malaria and with thrombocytopenia. The older children with relatively greater acquired malarial immunity had less severe manifestations, including thrombocytopenia. A similar observation that platelet count depression was age related, and more pronounced in children under five years was made by Jeremiah and Uko (16) in port-harcourt, eastern Nigeria. Many studies have documented this trend mostly in endemic areas, which are a larger part of Africa, Asia and South America (3-6,13,17). This is associated with the degree of malarial immunity that is yet to be acquired in early childhood in such population. This indicates the need for sustained efforts at malaria control programmes and for prompt treatment of malaria in this age group, especially in endemic regions like Nigeria. Other studies in the western part of Nigeria showed a different observation that platelet count depression in malaria showed no correlation with age and malaria related immune status of the child (18,26). This may be related to the malaria related immune status of children in this endemic region.

No significant gender difference in normal platelet counts was seen in these children. A similar observation was documented by Quinto **et al** (18) and Onwukeme **et al** (19) but contrasting to reports by Taylor **et al** (20) in Dublin, Ireland. Taylor **et al** (20) found a higher platelet count in girls than boys. The age range of the children in this study was lower than that of the Irish children and may explain the observed difference. Taylor **et al** (20) recruited adolescent children up to nineteen years of age, and it is documented that in older children, the haematological parameters including platelet count tend towards adult values with remarkable gender differences (20,21). The peri-pubertal rise which occurs in girls is related to the onset of menstruation and may perhaps, have been partly responsible for the higher values observed in the Dublin study. Generally, as noted in this study, platelet count values are not significantly affected by gender in childhood populations.

The prevalence of thrombocytopenia in malaria is seen to be higher among non-immune children, who are yet to develop full malarial immunity, as compared to those living in endemic regions. The immunity of children in endemic regions seems to confer a protective role against the development of severe manifestations, including thrombocytopenia (22-24). This may be a possible reason for the observed low prevalence of thrombocytopenia in children presenting in current study.

Children with severe manifestations of malaria such as severe anaemia, hyperpyrexia and prostration had significantly lower platelet counts than those with uncomplicated malaria in this study similar to previous reports in other Nigerian children by Akingbola **et al** (13) and Iwalokun **et al** (17). Reduction in platelet count values, which is a more frequent finding in severe forms of malaria, would have been responsible for the lower platelet counts seen in the children in this study.

Three of the study subjects presented with uncomplicated malaria and thrombocytopenia with no remarkable clinical symptom or sign except fever. Adedapo **et al** (25) and Iwalokun **et al** (17) both in Ibadan, made such observations. It is possible that these children may have haboured malaria parasitaemia for a prolonged period with no symptoms, prior to the development of symptomatic illness and presentation in hospital. The adverse effect of such chronic low grade parasitaemia on platelet counts levels may have been responsible for the thrombocytopenia seen in the children at presentation. This suggests that the absence of features of complicated malaria in a malaria endemic region like Nigeria, does not completely exclude the possibility of thrombocytopenia in malaria.

Most children with thrombocytopenia, presented with more than one clinical symptom or sign of severe malaria. This finding was similar to reports from other studies (13,16,24). There were no significant independent predictors of thrombocytopenia in this study, in contrast to observations by Gerardin **et al** (26) and Iwalokun **et al** (17). They documented altered sensorium (cerebral malaria), as an independent variable that predicts thrombocytopenia in severe malaria and attributed this to platelet sequestration in the cerebral microvasculature (13). This finding was however not observed in this study. The reason may be because the above studies were done a decade ago, and included a greater percentage of children who presented with cerebral malaria. The present study documented a lower percentage of children presenting with cerebral malaria, with no significant relationship with thrombocytopenia. This may be as a result of the improved awareness of parents and caregivers in malaria treatment and preventive measures put in place by the Government in the past decade (3,4). This probably prompts more timely presentation of children to the health facilities for treatment.

The trend of an inverse relationship between the parasite density and the platelet counts of subjects in present study was similar to observations by few other authors (27,38), but in contrast to the study by Mohanty **et al** (29) who found no correlation at all between the parasite density and the platelet count. A consistent linear relationship between parasite density and platelet count has not been firmly established, but generally, higher parasite counts are associated with a more marked depression of platelet count. The reduced platelet lifespan and platelet destruction in acute malaria, which partly results from the binding of malaria antigen unto platelets is perhaps responsible for the above findings. This observation was found to be irrespective of the malaria transmission level or specie in the areas studied (8,11,13,29).

Bleeding manifestations from thrombocytopenia in malaria was not a finding in this study. This was similar to other reports of the rarity of this in malaria (30,31). The postulated mechanism for this haemostatic response is the activation of hypersensitive platelets which seems to play a beneficial role in thrombocytopenia in malaria.

CONCLUSION

In conclusion, there was a negative correlation between the malaria parasite density and the platelet count. Subjects with severe manifestations of malaria had significantly lower platelet counts than those with uncomplicated malaria and there was no significant difference in platelet count based on gender in children. It would be beneficial whenever possible to monitor platelet counts in children presenting with malaria, especially in endemic regions, more-so those presenting with clinical features of severe disease.

COMPETING INTEREST

None of the authors had conflict of interests in this study.

AUTHORS' CONTRIBUTION

UEE and EEM conceived the idea for the study. UEE co-ordinated specimen collection and analysis of clinical specimen. IEE and EIJ participated in the study design and manuscript writing. All authors read and approved the final manuscript.

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