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Correlation of parasite density and biochemical parameters in children with malaria infection in Calabar, South-South Nigeria

Akpan Uwem Okon[1*], Bassey Iya Eze[1], Uwaetteh Akanimoh Emmanuel[2], Inyang Wisdom Marcus[3] and Usoro Chinyere Adanna[1]

Abstract

Background: Malaria parasitemia is associated with premature, excessive hemolysis, induction of oxidative stress, and derangement in metabolism of iron, proteins, and some electrolytes. This study aims to evaluate the effects of malaria infection on ascorbic acid (AA), uric acid (UA), iron, transferrin, albumin, total iron-binding capacity (TIBC), calcium, and magnesium levels in malaria infection.

Results: Among the 50 malaria-infected children, 12 had severe parasitemia (*PD* ≥ 10,000 parasites/μl), 16 had moderate parasitemia (*PD*: 2000 to < 10,000 parasites/μl), and 22 children had mild parasitemia (*PD* < 2000 parasites/μl). The AA, iron, transferrin, and TIBC levels were significantly lower and UA and Mg higher in malaria-infected children compared with the controls. Ascorbic acid correlated negatively with UA and PD in malaria-infected children. Iron correlated positively with albumin, transferrin, and TIBC in malaria-infected children, while Ca correlated negatively with Mg levels.

Conclusion: Malaria infection in children is associated with reduced AA and iron parameters and increased UA and Mg levels; hence, vitamin C and iron supplementation could be useful in malaria therapy.

Keywords: Uric acid, Ascorbic acid, Iron, Albumin, Malaria, Parasitemia, Parasite density

Background

One of the major consequences of malaria in children is premature and excessive hemolysis of parasitized red cells which consequently leads to anemia and may trigger inflammatory responses that could be detrimental to the host, by contributing to metabolic derangements [1].

Infection with malaria parasite directly generates large quantities of reactive oxygen species (ROS) by inflammatory cytokines recruited during infection leading to oxidative stress. The damaging effects of oxidative stress are normally limited by antioxidants that scavenge reactive oxygen species in the body [2]. However, low dietary intakes of vitamin C or reduced synthesis of non-dietary antioxidants such as albumin, glutathione, and uric acid are likely to result in an oxidant-antioxidant imbalance that may exacerbates inflammation and tissue damage [3].

Decrease levels of ascorbic acid have been reported in malaria-infected children [4] and have been attributed to increased utilization of plasma antioxidants during malaria pathogenesis.

Malaria-infected RBCs has been shown to accumulate excess hypoxanthine and xanthine from human plasma

*Correspondence: akpauwem11@gmail.com

[1] Department of Clinical Chemistry & Immunology, University of Calabar, Calabar, Cross River State PMB 1115, Nigeria
Full list of author information is available at the end of the article

[1, 5] which is degraded by plasma xanthine oxidase to uric acid upon schizont rupture [6].

Increased uric acid levels in parallel with clinical severity have been reported in malaria-infected children [7, 8]. Other studies have shown that elevated levels of xanthine oxidase and liver enzymes are biochemical features of *Plasmodium falciparum* parasitemia in Nigerian children [9].

Iron is a very essential mineral needed by the body to help make hemoglobin, process cell division, stimulate brain cell growth, build muscle cells, and strengthen the immune system. Iron deficiency in primary school children has a significant impact on their immune system, cognitive skills, and learning achievement [10]. Malaria has been reported to cause profound disturbances in physiological iron distribution and utilization, through mechanisms that include hemolysis, release of haem, dyserythropoiesis, anemia, deposition of iron in macrophages, and inhibition of dietary iron absorption. These effects have significant consequences. Malarial anemia is a major global health problem, especially in children, which remains incompletely understood and is not straightforward to treat. Malaria and iron have a complex but important relationship. However, how the parasite acquires its iron from its mammalian host remains unclear, but iron chelators can inhibit pathogen growth in vitro and in animal models [11]. Some authors have associated malaria acquisition and severity (or *P. falciparum* virulence) to the concentrations of macro-minerals (Mg, Na, K, Ca, and P) and micro-minerals (Fe, Zn, Se, Cu, and Co) in children [12, 13]. Iron, Fe, is an essential micronutrient necessary for the transportation of respiratory gases via hemoglobin in the red blood cells. On the other hand, magnesium, Mg, is mainly found in intracellular fluid and in bones about 60% complexes with calcium. Magnesium functions in the activation of many enzymes requiring ATP — alkaline phosphatase, hexokinase, fructokinase, phosphofructokinase, adenyl cyclase, etc. Magnesium also plays an active role in the metabolism of sodium, potassium, and calcium. It acts on the heart, blood vessels, nerves, muscles, and gut [14].

Calcium (Ca) on the other hand is considered an essential nutrient for human body, whereby bones and the teeth in the body are strengthened as a result of the presence of calcium, due to its relevance in maintaining health and nutrition of the body. During malaria infection, most noticeable symptom is reduction in calcium level. Clinical symptoms associated with malaria like sweating, shivering, fever, and high pulse rate are most times cause a reduction in calcium levels [15].

The actual relationship between uric acid, ascorbic acid, and severity of malaria infection is still uncertain as these parameters may serve as useful indicators of the degree of parasitemia in children with *Plasmodium falciparum* infection. The study therefore assessed uric acid, ascorbic acid, calcium, magnesium, albumin, and some iron parameters in children with malaria infection in Calabar, Nigeria, and the effect of malaria parasite density on the levels of these parameters.

Methods

Study location

The study was conducted at the University of Calabar Teaching Hospital, Calabar, Cross River State from June, 2021, to October, 2021. Calabar is the capital city of Cross River State which is divided into Calabar Municipal and Calabar South Local Governments and is located at the coastal south-south area (4°57′N 8°19′E) of Nigeria.

Study design

This was a cross-sectional study involved malaria-infected children as test subjects and apparently healthy children as controls.

Inclusion and exclusion criteria

Children whose parents/guardians gave consent, with confirmed cases of falciparum malaria in the last 3 days, were recruited as test subjects, while apparently healthy children with no history of falciparum malaria in the last 3 days and no history of hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) infections and whose parents/guardians gave consent were recruited as controls. Individuals whose parents/guardians did not give consent and those with chronic system or organ illness and on malaria medication were excluded from the study.

Selection of subjects

A total of eighty (80) subjects were enrolled into the study. Fifty (50) children with microscopy confirmed malaria infection aged 15 years, and thirty (30) apparently healthy children without malaria parasitemia were recruited into the study.

Sample collection

Three milliliters (3 ml) of peripheral blood was collected asceptically from the subjects by venipuncture into a plain sample container. An aliquot of the sample from the syringe was used to prepare thick and thin blood films on an appropriately labeled clean grease-free slide. The samples in plain containers were allowed to clot and retract after which there were spun at 5000 rpm for 5 min. Sera were collected and stored at −20 °C in appropriate sample vials for assay of biochemical parameters.

Laboratory methods

Identification of malaria parasite by Giemsa staining technique

Giemsa staining procedure was used for detection and quantification of malaria parasites in thick films. To ensure that proper staining results are achieved, a positive smear of malaria parasite was included with each new batch of working Giemsa stain. Thick and thin blood smears were allowed to air-dry and thin blood smear fixed with absolute alcohol. They were stained using 10% of the Giemsa stock stain for 10 min [16].

Calculation of parasite density

Parasite densities were recorded as a ratio of parasites to white blood cells (WBC) in thick films. *Plasmodium* parasites were counted against 200 WBC on the thick film. A total of 500 WBCs were counted where less than 9 parasites were counted after counting against 200 WBC.

Parasite densities (parasite/µl of whole blood) were then calculated as follows: (number of parasites counted/WBC counted) × WBC count per µl of blood.

Parasite densities for all participants were calculated using assumed WBC counts of 8.0 × 10^9/L of blood, determined by the World Health Organization (WHO) to be used conveniently in facilities which lack the tools to determine patients' absolute full blood count value.

Malaria parasite densities of infected children were grouped into three categories: severe, moderate, and mild. Those classified with severe malaria had a parasite density of ≥ 10,000 parasites/µl, those with moderate malaria, a parasite density of 2000 to < 10,000 parasites/µl; and mild malaria, a parasite density of < 2000 parasites/µl [16].

Biochemical analyses

Serum uric acid assay was performed using uricase enzymatic colorimetric method [17] with kit obtained from the Giesse Diagnostics™, Montecelio, Rome, Italy. Serum ascorbic acid was estimated by the 2, 4-dinitrophenyldrazine method reported by Thurnham and Stephen (1979) [18]. Serum calcium (Ca) level was estimated by modified ortho-cresolphthalein complexone [19] using calcium commercial kit (AGAPPE) from Switzerland. Magnesium was estimated using test kit for quantitative determination of Mg in biological fluids obtained from the GIESSE Diagnostics, Rome, Italy. Serum albumin was estimated using the colorimetric bromocresol green (BCG) method with kit obtained from the Giesse Diagnostics, Rome, Italy. All tests except serum iron were run on Optima DIGITAL COLORIMETER Model AC 114 (THE OPTIMA COMPANY LIMITED, London, UK). Serum iron was estimated using the atomic absorption spectrophotometry with 230ATS Atomic Absorption Spectrometer (Buck Scientific Instruments LLC, 58 Fort Point St, Norwalk, CT 06855, USA).

All samples and reagents were brought to room temperature prior to analysis. The test was performed according to manufacturer's instructions.

Statistical analysis

The Student *t*-test was used to compare the mean difference between groups. One-way analysis of variance (ANOVA) was used to determine variations within and among groups. LSD post hoc analysis was used to determine variations between group means. Pearson's correlation coefficient was used to determine associations between variables. Statistical significance was set at probability, $P < 0.05$. All data obtained were analyzed using Statistical Package for the Social Sciences (SPSS) version 20.0 software.

Results

The serum uric acid, ascorbic acid, iron, albumin, transferrin, TIBC, Ca, and Mg levels in malaria-infected children and controls are shown in Table 1. The mean serum ascorbic acid, iron, transferrin, and TIBC were significantly lower in malaria-infected subjects compared to the controls, while the mean serum uric acid and magnesium levels were significantly higher in the test subjects than in the controls.

The serum uric acid, ascorbic acid, iron, albumin, transferrin, TIBC, Ca, and Mg levels in children with mild, moderate, and severe malaria are shown in Table 2. There was a significant variation in the levels of uric acid, ascorbic acid, iron, albumin, transferrin, TIBC, calcium,

Table 1 Serum uric acid, ascorbic acid, iron, albumin, transferrin, TIBC, Ca, and Mg levels in malaria-infected children and controls

Parameter	Malaria $N = 50$	Controls $N = 30$	t-cal	*p*-value
Age (years)	6.01 ± 4.46	7.52 ± 3.72	1.63	0.110
Uric acid (mg/dl)	5.57 ± 1.64	4.30 ± 0.70	4.80	0.001*
Ascorbic acid (mg/dl)	0.196 ± 0.05	0.774 ± 0.05	12.24	0.001*
Iron (µg/dl)	63.94 ± 28.04	117.53 ± 10.57	10.03	0.000*
Albumin (g/dl)	3.67 ± 0.73	3.87 ± 0.50	1.319	0.191*
Transferrin (mg/dl)	127.70 ± 56.07	235.23 ± 21.06	10.07	0.000*
TIBC (µg/dl)	191.62 ± 84.20	352.80 ± 31.71	10.05	0.000*
Calcium (mmol/l)	2.08 ± 0.37	2.18 ± 0.23	1.33	0.187
Magnesium (mmol/l)	3.55 ± 1.19	2.06 ± 0.45	6.57	0.000*

Values are expressed as mean ± SD. *Significant at $P < 0.05$, *TIBC*, total iron-binding capacity; *t-cal*, calculated *t*-value

Table 2 Uric acid, ascorbic acid, iron, albumin, transferrin, TIBC, Ca, and Mg levels in children with mild, moderate, and severe malaria

Parameter	Mild malaria $N = 22$	Moderate malaria $N = 16$	Severe malaria $N = 12$	F-cal	*p*-value
PD (parasites/µl)	895.32 ± 378.99	5120.31 ± 1917.43	11290.25 ± 728.67	309.29	0.192
Uric acid (mg/dl)	4.46 ± 0.70	5.41 ± 0.67	7.82 ± 1.58	46.83	0.000*
Ascorbic acid (mg/dl)	0.242 ± 0.03	0.175 ± 0.01	0.142 ± 0.01	89.88	0.000*
Iron (µg/dl)	106.18 ± 13.42	64.33 ± 12.90	63.94 ± 28.04	116.29	0.000*
Albumin (g/dl)	4.18 ± 0.51	4.02 ± 0.55	2.95 ± 0.42	29.94	0.000*
Transferrin (mg/dl)	212.18 ± 26.81	128.38 ± 26.00	75.28 ± 17.79	115.32	0.000*
TIBC (µg/dl)	318.55 ± 40.25	192.57 ± 39.01	112.94 ± 26.68	115.50	0.000*
Calcium (mmol/l)	2.33 ± 0.32	1.86 ± 0.25	2.13 ± 0.42	12.66	0.000*
Magnesium (mmol/l)	2.48 ± 0.87	4.08 ± 0.66	4.67 ± 1.23	26.52	0.000*

Values are expressed as mean ± SD. *Significant at $P < 0.05$, *TIBC* Total iron-binding capacity; *PD* Parasite density

and magnesium in children with mild, moderate, and severe malaria.

Table 3 shows a comparison of uric acid, ascorbic acid, iron, albumin, transferrin, TIBC, calcium, and magnesium levels in children with mild, moderate, and severe malaria using LSD post hoc analysis. Uric acid and Mg were significantly lower in children with mild malaria compared to those with moderate malaria, while ascorbic acid, iron, albumin, transferrin, TIBC, and calcium were significantly higher in children with mild malaria

Table 3 Uric acid, ascorbic acid, iron, albumin, transferrin, TIBC, Ca, and Mg levels in children with mild, moderate, and severe malaria using LSD post hoc analysis

Parameter	Groups		Mean diff.	Std. error	*p*-value
	Mild malaria ($n = 22$)	Moderate malaria ($n = 16$)			
Uric acid	4.46 ± 0.70	5.41 ± 0.67	0.95	0.32	0.005
Ascorbate	0.242 ± 0.03	0.175 ± 0.01	0.07	0.01	0.000
Iron	106.18 ± 13.42	64.33 ± 12.90	41.85	4.37	0.000
Albumin	4.18 ± 0.51	4.02 ± 0.55	0.16	0.18	0.383
Transferrin	212.18 ± 26.81	128.38 ± 26.00	83.80	8.77	0.000
TIBC	318.55 ± 40.25	192.57 ± 39.01	125.97	13.16	0.000
Ca	2.33 ± 0.32	1.86 ± 0.25	0.47	0.94	0.000
Mg	2.48 ± 0.87	4.08 ± 0.66	−1.59	0.26	0.000
	Mild malaria ($n = 22$)	Severe malaria ($n = 12$)			
Uric acid	4.46 ± 0.70	7.82 ± 1.58	3.36	0.35	0.000
Ascorbate	0.242 ± 0.03	0.142 ± 0.01	0.10	0.01	0.000
Iron	106.18 ± 13.42	37.67 ± 8.91	68.52	4.49	0.000
Albumin	4.18 ± 0.51	2.95 ± 0.42	1.23	0.19	0.000
Transferrin	212.18 ± 26.81	75.28 ± 17.77	136.90	9.02	0.000
TIBC	318.55 ± 40.25	112.94 ± 26.68	205.60	13.53	0.000
Ca	2.33 ± 0.32	2.13 ± 0.42	0.21	0.14	0.131
Mg	2.48 ± 0.87	4.67 ± 1.22	−2.19	0.37	0.000
	Moderate malaria ($n = 16$)	Severe malaria ($n = 12$)			
Uric acid	5.41 ± 0.67	7.82 ± 1.58	2.41	0.37	0.000
Ascorbate	0.175 ± 0.01	0.142 ± 0.01	0.03	0.01	0.000
Iron	64.33 ± 12.90	37.67 ± 8.91	26.67	3.77	0.000
Albumin	4.02 ± 0.55	2.95 ± 0.42	1.07	0.16	0.000
Transferrin	128.38 ± 26.00	75.28 ± 17.77	53.10	7.57	0.000
TIBC	192.57 ± 39.01	112.94 ± 26.68	79.63	11.35	0.000
Ca	1.86 ± 0.25	2.13 ± 0.42	−0.26	0.13	0.051
Mg	4.08 ± 0.66	4.67 ± 1.22	−0.59	0.36	0.103

*Significant at $P < 0.05$, *TIBC* Total iron-binding capacity, *PD* Parasite density

compared to those with moderate malaria. Ascorbic acid, iron, albumin, transferrin, TIBC, and calcium were significantly lower in children with severe malaria than those with mild malaria. Ascorbic acid, iron, albumin, transferrin, and TIBC were significantly higher in children with moderate malaria than those with severe malaria.

Table 4 shows the correlation of parasite density against serum ascorbic acid in malaria-infected children where a negative correlation was observed. It also shows the correlation of parasite density against uric acid levels in malaria-infected children where a positive correlation was observed, while ascorbic acid correlated negatively with uric acid. Iron correlated positively with albumin, transferrin, and TIBC, respectively. Albumin correlated positively with transferrin and TIBC respectively, while calcium correlated negatively with magnesium.

Discussion

Electrolyte imbalances, mineral disturbances, and antioxidant unrest are known to be common clinical manifestations in several infectious diseases including malaria [15]. In this study, the serum ascorbic acid concentration was significantly lower in the malaria-infected children than in the controls studied. This may be attributed to increased oxidative stress as a result of the release of more free radicals (reactive oxidative species, ROS) in falciparum malaria infection [20]. To counteract this oxidative stress, plasma antioxidants are transferred to the erythrocyte membrane where they are rapidly utilized and destroyed during the infection, hence the decrease in serum ascorbic acid concentrations as observed in this study [3]. There was also a progressive decrease in serum ascorbic acid concentration with increase in malaria parasite density. This finding is in agreement with previous reports [21]. Falciparum malaria has also been known to be associated with depressed immune function, as evidenced by earlier reports [22]. This depressed immunity could also be a contributing factor to the low ascorbic acid levels seen in children. Ascorbic acid supplementation has been shown to result in significant improvement in serum ascorbic acid concentration [23]; hence, supplemental doses of ascorbic acid in malaria-infected children may therefore be important in boosting their developing immune system and protect them from the destructive action of oxidant compounds released during red cell rupture that accompanies infection by the malaria parasite. The serum uric acid concentration was significantly higher in the malaria-infected children than in the control subjects. This increase may be as a result of accumulation of high concentrations of uric acid precursors: hypoxanthine and xanthine in *Plasmodium*-infected erythrocytes. Upon the rupture of these erythrocytes, the uric acid precursors are degraded into uric acid by the host enzymes [1]. It was also observed that serum uric acid concentration increased significantly with increase in the severity of malaria parasitemia. This is due to the excessive accumulation of uric acid precursors and progressive destruction of red blood cells by the malaria parasites during the infection [23]. In our study, the level of Mg in *P. falciparum* malaria infection was reduced. This observation agrees with earlier study of Onyesom et al. [24] who reported low levels of Mg in the serum of infected children in Delta State, Nigeria, and Cote d'Ivoire, respectively. *P. falciparum*, the causative agent of malaria, has the capacity of adhering to blood vessels in a process called cyto-adherence. This cyto-adherence leads to obstruction of microcirculation resulting in malfunction of several organs and immune system breakdown. The consequence of this process could modify micronutrient levels including Mg and Fe in serum of infected subjects. Also, *P. falciparum* binds, invades, and destroys RBCs. In these processes, serum concentration of Fe is depleted, and intracellular levels of Mg are also reduced [12]. The results of this study according to parasite density also showed that serum concentrations of Ca and Mg were significantly reduced in moderate parasitemia when compared to mild parasitemia. This observation may be justified by the fact that in the course of infection, nutrients move from circulation to the tissues causing a reduction from circulation [25]. The reduction in calcium may also be caused by the clinical manifestation of malaria, which affects neuromuscular excitability, nerve conduction, and muscular contraction. Luong and Nguyen [26] also found that losses in Ca can be caused during digestive and renal problems following malaria infection. This renal insufficiency in malaria can cause an increase in urinary excretion of minerals such as calcium. Ndako and colleagues [15] also reported that trophozoites concentrate calcium in their internal compartment for

Table 4 Correlation of biochemical parameters in malaria-infected children

Parameter	Index	*r*-value	*p*-value
Ascorbate	Uric acid	−0.667	0.000*
	PD	−0.835	0.000*
PD	Uric acid	0.779	0.026*
Iron	Albumin	0.726	0.000*
	Transferrin	1.000	0.000*
	TIBC	1.000	0.000*
Albumin	Transferrin	0.726	0.010*
	TIBC	0.725	0.001*
Transferrin	TIBC	1.000	0.000*
Calcium	Magnesium	−0.641	0.000*

*Significant at $P < 0.05$, *PD*, parasite density, *r*-value — correlation coefficient

metabolism, thereby resulting in hypocalcemia observed in our study. Our study observed a significant reduction in serum Fe, transferrin, and TIBC in the infected children than in the controls. These observations are similar to earlier reports by Desmansya et al. [27] who reported low levels of serum Fe, transferrin, ferritin, and TIBC in children aged 5–11 years in North Maluku. Erythropoietic iron requirement is met largely through recycling of senescent red blood cells through reticuloendothelial macrophages, where iron is repackaged onto transferrin for transport to the bone marrow. Malaria-induced destruction of infected and noninfected red blood cells both stresses and impedes the capacity of reticuloendothelial macrophages to recycle iron back to the bone marrow. This subsequently causes low iron status which may account for the reduction in Fe, transferrin, and TIBC observed in this study. We also report significant reduction in serum albumin levels as the malaria infection progresses from mild to severe parasitemia. This agrees with the findings by earlier researchers who reported low levels of total protein and albumin in malaria-infected children aged 1–15 years [20]. Impairment of hepatic function associated with severe malaria may be responsible for the progressive low albumin levels observed in this study. Also, serum albumin is a negative acute phase protein, whose concentration reduces as a result of malaria infection probably due to an increase in its transcapillary escape rate. Serum ascorbic acid correlated negatively with uric acid concentrations in the malaria-infected children. This is similar to earlier report by Lisa et al. that vitamins like ascorbic acid may improve uric acid excretion in urine rather than lowering its production [28]. Parasite density correlated negatively with serum ascorbic acid concentration and positively with serum uric acid concentration, as the infection progresses from mild to severe states.

Conclusions

Severe *Plasmodium falciparum* infection in children may be associated with reduction in ascorbic acid and iron parameters and increase in uric acid and magnesium levels; hence, vitamin C and iron supplementation could be of therapeutic importance after malaria therapy.

Abbreviations

ROS: Reactive oxygen species; TIBC: Total iron-binding capacity; PD: Parasite density; AA: Ascorbic acid; UA: Uric acid; LSD: Least significant difference.

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Authors' contributions

UO, conceptualize the research, data collection, laboratory analyses, and initial manuscript writing and review. IE, conceptualize the research, statistical analyses, and manuscript review. AE, data collection, laboratory analyses, and final review of manuscript. WM, data collection, statistical analyses, and final review of manuscript. CA, conceptualize the research, laboratory analyses, and final review of manuscript. The authors read and approved the final manuscript.

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Availability of data and materials

Data obtained from this study will not be shared as it is against the ethical policies of the Health and Research Ethical Committee of the University of Calabar Teaching Hospital, Calabar, on research carried out on human subjects so as to maintain the participants' confidentiality.

Declarations

Ethics approval and consent to participate

Written informed consent was obtained from parents/guardians of the participants before sample collection. The purpose and nature of the research were explained to the parents/guardians of the participants, and they gave their consent. Ethical approval was given by the Health and Research Ethical Committee of the University of Calabar Teaching Hospital, Calabar, Cross River State, Nigeria. Informed written consent was given by the participants before being enrolled into the study. All experiments were performed in accordance with the ethical standards laid down in the Helsinki Declaration of 1975, as revised in 2000.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Clinical Chemistry & Immunology, University of Calabar, Calabar, Cross River State PMB 1115, Nigeria. [2]Department of Chemical Pathology, Faculty of Basic Medical Sciences, Obafemi Awolowo University, Ile-Ife, Nigeria. [3]Faculty of Medicine, University of Calabar, Calabar, Cross River State PMB 1115, Nigeria.

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