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Non-Classical symptoms of malaria in parts of South Eastern Nigeria: A Preliminary Report

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Abstract

Malaria is associated with varied symptoms some of which are not documented or recognized. This study is a preliminary report on non-classical symptoms of malaria among a cross-section of 200 consenting patients in parts of South Eastern Nigeria. Socio-Clinico data was collected using structured pre-tested questionnaire. Malaria status was confirmed using Rapid Diagnostic Test. Data was analyzed with Chi-square at P<0.05 significance. Most of the study patients were 30-39 years (50.0%) and males (40.0%). All reported experiencing fever at onset of illness with 175 (87.5%) reporting non-classical symptoms particularly bitterness of the taste buds (5.0%), mostly as double symptoms (32.5%) or multiple symptoms (37.5%). About 133/175 (76%) tested malaria positive. Non-classical symptoms were significantly associated with period of last malaria treatment and current malaria status respectively (P<0.05). There is need to further investigate the dynamics, patterns, consistency and host factors involvement of non-classical symptoms of malaria and potential implications for malaria elimination plans.

Keywords: Malaria, Non-classical symptoms, Clinical recognition, Diagnosis.

INTRODUCTION

Malaria is still a major global public health problem particularly in tropical developing countries. The disease has a broad spectrum of clinical features that vary from asymptomatic infection to severe disease [1,2], associated with anemia, jaundice, coma, plaquetopenia, respiratory distress, and cerebral malaria. Between asymptomatic presentation and severe cases lies the clinical spectrum of non-severe malaria.

Worldwide, it is estimated that 300-500 million people are infected with malaria each year; resulting in about 1.5-2.7 million deaths annually [3,4]. Malaria which is caused by obligate intra-eryrthrocytic protozoa of the genus plasmodium are of four species; *P. falciparum*, *P. viviax, P. ovale* and *P. malaria*. Plasmodium is primarily transmitted to humans via the bite of an infected female Anopheles mosquito. However, infections can also occur through exposure to infected blood products (transfusion malaria) and by congenital transmission [5,6].

Patients with malaria typically become symptomatic a few-weeks after infection, although the host's previous exposure or immunity to malaria affects the symptomatology and incubation period [7]. In addition, each plasmodium species has a typical incubation period. Importantly, virtually all patients with malaria complain of fever and headache. Other classical/clinical symptoms include; cough, fatigue, malaise, chills, arthralgia, myalgia. And less common malarial symptoms are anorexia and lethargy, nausea, vomiting, diarrhea and jaundice [7].

Prompt and accurate treatment of malaria requires that malaria should be recognized promptly and accurately. Clinical diagnosis based on which most treatments in malaria endemic areas particularly sub-Saharan Africa are made rely on presentation or report of symptoms such as fever, headache, chills, joint pains, vomiting etc. [8-10]. These symptoms over the years have been implied in the case definition of malaria [8]. However, these symptoms are not specific for malaria alone but for other illnesses also prevalent in malaria endemic areas. This overlap of common documented and otherwise classical symptoms of malaria with other illnesses is chiefly responsible for over treatment of malaria in endemic areas [11]. It is noteworthy that while the WHO has recommended test before malaria treatment, people in poor endemic areas particularly sub-Saharan Africa still treat malaria based on recognition of symptoms as well as clinical diagnosis without confirmation with microscopy or rapid diagnostic tests (RDTs). In these areas,

diagnosis may not be readily available or maybe expensive for the inhabitants who are exposed or at risk of the disease.

Although malaria has earned a lot of global interest, much is not known about some other undocumented or unrecognized symptoms often presented by patients suffering malaria in endemic areas. Sometimes, these symptoms manifest without the common classical symptoms of malaria, while most times are accompanied by some classical symptoms. These symptoms which we now refer to as non-classical symptoms of malaria can lead to differential diagnosis dilemmas in endemic areas while in non-endemic areas may confuse clinicians that are not familiar with them. Proper profiling, characterization and documentation of these non-classical symptoms may be useful for defining new criteria or algorithms for malaria recognition, clinical diagnosis as well as new case definition based on more specific and distinct sets of malaria symptoms. This will help in better malaria management in poor endemic areas where laboratory diagnosis may not be readily available or may be expensive. It may also have some useful implications for strategies towards malaria elimination.

This paper is therefore a preliminary report on studies on non-classical symptoms of malaria in parts of South Eastern Nigeria

MATERIALS AND METHODS

Study Design

This is a cross-sectional study which involved all subjects receiving health examinations for malaria and related illnesses at the out-patient clinic of the Federal Medical Centre Owerri, South Eastern Nigeria. In total, 227 individuals were selected, but 200 subjects were finally included for further analysis.

Study Setting

The Study was carried out in Federal Medical Center (FMC) Owerri, South Eastern Nigeria. The Federal Medical Center is a tertiary health center serving Imo State and parts of South Eastern Nigeria. South Eastern Nigeria is located between latitude 5° 101 and 5° 511 North, longitudes 6° 351 and 70281 East with a population density of 458 persons/km^2. There are two main climate regimes: a dry season and a wet season. The mean annual rainfall is between 1,800 and 2,500 millimeters per year. The maximum and minimum temperatures are 31.9°C and 22.5°C respectively while the daily sunshine rate is about 4.4 h. Average relative humidity is about 74% occurring mostly during the wet season, while the rate of evaporation and evapotranspiration are 3.0 mm/day and 136 mm/month respectively. The vegetation is typically rain forest. These areas experience stable malaria transmission all year round with most of the population experiencing malaria infection and expressing different clinical manifestations.

Study Population and sample size

The study population consisted of individuals of all age groups attending outpatient clinics due to suspected malaria at the FMC Owerri South Eastern Nigeria. Sampling was conducted for a period of Four months among these individuals. Firstly, on each sampling day, the patients were grouped into 5 strata; each stratum consisted of people within a particular age range, for instance, people ≤18, 19-29, 29-30...≥50. Subsequently, the individuals in each stratum were selected using balloting. Ballot papers written “YES” and “NO” were picked by them. Those who picked “yes” were pre-selected while those that picked “no” were not selected. Further, only those who reported experiencing "hot body" (fever) at the onset of illness were finally selected. This process was used until 227 individuals were selected. However, 27 of them declined giving written consent. Therefore, 200 consenting individuals were finally selected for the study

Data Collection

Structured pretested questionnaire was used to collect socio demographic and clinical data including information pertaining symptoms experienced by the study patients. Prior to data collection, the study was first introduced, the objectives elucidated, and informed written consent sought and obtained from the 200 study patients. Research assistants administered the questionnaires but elicited them in English, Igbo or "Pidgin English" depending on the choice of the patients. The assistants administered the questionnaires in-person and stayed on hand to clarify points of confusion. They collected the questionnaires immediately after completion and identification numbers (ID) assigned which were also recorded on the questionnaire. The parents/ guardians of children or those who could not complete the questionnaires themselves did so on their behalves.

Malaria Rapid Diagnostic Tests (RDTs)

Rapid Diagnostic Tests were carried out to confirm the malaria status of the study patients by qualified health personnel on the spot soon after the questionnaire was completed. The tests were carried out using SD Bioline Malaria Ag P.F/P.F/P.V test Kit, product No.O5FK120 manufactured by standard Diagnostic, Inc Korea Republic. The expiry dates of the test kits were carefully checked, and it was confirmed that the seals were not broken. Each patient's ID were labeled on the cassette, to enable easy documentation. The fourth finger was disinfected with alcohol and allowed to air dry after which it was pricked with lancet to obtain a capillary blood. The first drop of blood was wiped with dry cotton while subsequent drops were drawn with capillary tube. The drawn whole blood was transferred into the sample well marked (s) on the cassette. The test results were read within 15-30minutes as instructed by the manufacturer and recorded in the questionnaire of the respective patients. Those who were malaria positive were prescribed appropriate malaria treatments by the consulting clinicians while further referrals were done for those who needed it.

Data Analysis

Descriptive methods were used to summarize the data characteristics. Frequency distribution tables were constructed for all class variables and data were expressed as percentage of distribution. Chi-square test was used to analyze the level of significance which was interpreted as calculated value > tabulated value at $p<0.05$.

Ethical approval

Ethical approval was given by the Ethical Committee of the School of Health Technology, Federal University of Technology Owerri, Nigeria. Permission was also sought and obtained from the management of Federal Medical Centre Owerri, South Eastern Nigeria. Informed written consent was sought and obtained from all the participants before they could take part in the study.

RESULTS

A total of 200 participants were involved in the study (Table 1), out of which 80 (40.0 %) were males and 120 (60.0 %) were females. The age distribution of participants was such that participants 18 years and below were 55 (27.5%), participants between 19-29 years were 10(50%), participants between 30-39years were 100 (50.0%), those 40-49 years were 30 (15.0%) and those who were 50 years and above were 5 (2.5%). Out of the 200 participants studied, those who reported non-classical symptoms were 175 (87.5%), out of which 70 (40.0%) were males and 105 (60.0%) were females. All the study participants (100%) reported experiencing fever at the onset of illness.

Table 2 shows the non-classical symptoms reported by the study patients with suspected malaria. These non-classical symptoms were grouped into single symptoms; including nightmare (1.0%), bitterness of taste buds (5.0%), mouth blusters (4.0%), sore throat (5.0%), pain in the eye (1.5%) and pimples (1.0%). Some participants reported experiencing double symptoms as follows; bitterness of taste buds and mouth blisters (18.5%) and sore throat and mouth blisters (4.0%). Most of the participants reported experiencing multiple symptoms; bitterness of taste buds, nightmare, mouth blisters and pains in the eye 45 (22.5%) and mouth blisters, sore throat and bitterness of taste buds (15.0%). However, 25 (12.5%) of the participants did not present any non-classical symptoms.

Table 3 presents the relationship between non-classical symptoms associated with malaria and period of last malaria treatment. About 14 (40.0%) participants with single symptoms had treated malaria in less than three months, 8 (22.9%) participants with single symptoms had treated malaria between three and six months while 13 (37.1%) participants with single symptoms had treated malaria in more than six months before the study. Also, among participants with double symptoms, about 9 (13.8%) participants had malaria treatment in less than three months before the study, 11 (16.9%) participants had malaria treatment within three to six months before the study while 45 (69.3%) participants had malaria treatment in more than six months before the study. Among participants with multiple symptoms, about 9 (12.0%) had malaria treatment in less than three months before the study, 10 (13.3%) had malaria treatment within three to six months before the study and 56 (74.7%) had malaria treatment in more than six months before the study. There was a significant relationship between non-classical symptoms of malaria and period of last malaria treatment ($\chi 2 = 18.14$, P=0.001, df=4).

The relationship between non-classical symptoms associated with malaria and malaria status of study patients is depicted in Table 4. Twenty-two (22 (69.8%)) of the study patients with single symptoms tested positive for malaria while 13 (37.2%) participants with single symptoms tested negative for malaria. About 55 (84.6%) participants with double symptoms tested positive for malaria while 10 (15.4%) participants with double symptoms tested negative for malaria. Furthermore, 56 (74.6%) participants with multiple symptoms tested positive for malaria while 19 (25.4%) participants with multiple symptoms tested negative. Statistical analysis shows a significant relationship between non-classical malaria symptoms and malaria status of the study patients ($\chi^2 = 5.948$, P=0.051, df = 2).

Table 1: Socio-Clinico Characteristics of Study Patients

Variable	Frequency	Percentage
Age (yrs)		
≤18	55	27.5
19-29	10	5.0
30-39	100	50.0
40-49	30	15.0
≥50	5	2.5
Total	**200**	**100.0**
Sex of Participants		
Male	80	40.0
Female	120	60.0
Total	**200**	**100.0**
Non- Classical symptoms		
No. Reporting Non-Classical Symptoms	175	87.5
No. Not reporting Non-Classical Symptoms	25	12.5
Total	**200**	**100**
Experienced Fever		
Yes	200	100
No	0	0.0
Total	**200**	**100**
Confirmed Malaria Status (N-175)		
Positive	133	76.0
Negative	42	24.0
Total	**175**	**100**

Table 2: Self-Reported Malaria Associated Non-Classical Symptoms by Study Patients

Form of symptom	Symptoms	Frequency	Percentage
Single Symptom			
n = 35(17.5%)	Nightmare	2	1.0
	Bitterness of taste buds	10	5.0
	Mouth blisters	8	4.0
	Sore throat	10	5.0
	Pain on the eye	3	1.5
	Pimples	2	1.0
Double Symptoms			
n = 65(32.5%)	Bitterness of taste buds + Score throat	20	10.0
	Bitterness of taste buds + Mouth blisters	37	18.5
	Sore throat + Mouth blisters	8	4.0
Multiple symptoms n=75(37.5%)	Bitterness of taste buds +Nightmare + Mouth blister +pain in the eye	45	22.5
	Mouth blisters +sore throat + Bitterness of taste buds	30	15.0
None n=25(12.5%)	Did not report Non-classical symptom	25	12.5

Table 3: Relationship Between Reported Non-Classical Symptoms and Period of Last Malaria Treatment

		Last period of malaria treatment		
Symptoms	**Total (%)**	**Treatment in less than 3 months**	**Treatment within 3 -6 months**	**Treatment in more than 6months**
Single Symptom				
Nightmare	2(1.0)	1(50.0)	1(50.0)	0 (0.0)
Bitterness of taste buds	10(5.0)	2 (20.0)	2(20.0)	6(40.0)
Mouth blisters	8(4.0)	2 (25.0)	3(37.5)	3(37.5)
Sore throat	10(5.0)	4(40.0)	2(20.0)	4(40.0)
Pain in the eye	3(1.5)	3(100.0)	0(0.0)	0(0.0)
Pimples	2(1.0)	2(100.0)	0(0.0)	0(0.0)
Total	**35(17.5)**	**14(40.0)**	**8(22.9)**	**13(37.0)**
Double Symptoms				
Bitterness of tastes buds + Sore throat	20(10.0)	4(20.0)	4(20.0)	12(60.0)
Bitterness of tastes buds +mouthblisters	37(18.5)	5(13.5)	7(18.9)	25(67.6)
Sore throat + mouth blisters	8(4.0)	0(0.0)	0(0.0)	8(100.0)
Total	**65(32.5)**	**9(13.8)**	**11(16.9)**	**45(69.3)**

Multiple symptoms				
Bitterness of taste buds +Nightmare + Mouth blister +pain in the eye	45(22.5)	3(6.6)	3(6.6)	39(86.8)
Mouth blisters + bitterness of taste buds+ sore throat	30(15.0)	6(20.0)	7(23.3)	27(56.7)
Total	**75(37.5)**	**9(12.0)**	**10(13.3)**	**56(74.7)**

X^2= 18.14, P = 0.001, d.f = 4

Table 4: Relationship Between Reported Non-Classical Symptoms and Current Malaria Status

		Malaria status	
Symptoms	**Total (%)**	**Positive (+)**	**Negative (-)**
Single symptoms			
Nightmare	2(1.0)	1(50.0)	1(50.0)
Bitterness of taste buds	10(5.7)	7(90.0)	3(30.0
Mouth blisters	8(4.5)	6(75.0)	4(25.0)
Sore throat	10(5.7)	6(60.0)	4(40.0)
Pan in the eyes	3(1.7)	1(33.3)	2(66.7)
Pimples	2(1.3)	1(50.0)	1(50.0)
Total	**35(20.0)**	**22(62.8)**	**13(37.2)**
Double Symptoms			
Bitterness of taste buds +sore throat	20(11.4)	17(85.0	3(15.0)
Bitterness of taste buds +mouth blisters	37(21.1)	32(86.5)	5(13.5)
Sore throat + mouth blister	8 (4.6)	6(75.0)	2(25.0)
Total	**65(37.1)**	**55(84.6)**	**10(15.4)**
Multiple Symptoms			
Bitterness of taste buds +Nightmare + Mouth blister +pain in the eye	45(25.7)	37(82.2)	8(17.8)
Mouth blisters + sore throat + bitterness of taste buds	30(17.2)	19(63.3)	11(36.7)
Total	**75(42.9)**	**56(74.6)**	**19(25.4)**

χ^2 = 5.948, P=0.051, df = 2.

DISCUSSION

Malaria is an infection that generates series of clinical symptoms. These symptoms have been widely reported in many clinical and experimental studies and can therefore be referred to as the classical symptoms of malaria because they are documented and normally used to recognize the disease. However, there are other symptoms often presented or reported by many in malaria endemic areas when they suffer from malaria. Most of these symptoms have not been reported and are therefore not documented/ recognized and not normally recommended for malaria recognition. These symptoms can therefore be referred to as non-classical. This study reports for the first time, to the best of our knowledge, these non-classical symptoms of malaria. Many of the study patients who visited the clinic in South Eastern Nigeria on suspicion of malaria presented these non-classical symptoms mostly as double or multiple symptoms in addition to fever. Experience of fever in malaria endemic areas is usually a basis for suspecting malaria [1,7], which usually requires confirmation either with a combination of other symptoms (clinical algorithm) [10] or as recommended, by appropriate tests (microscopy, RDT, PCR etc.) [8]. Some of our study patients with fever were confirmed malaria negative, indicating that their fever may be of other etiologies. However, majority of those presenting the non-classical symptoms in addition with experiencing fever at the onset of their illness were also confirmed malaria positive. The most prominent of these non-classical symptoms was bitterness of the taste buds which occurred either as a single symptom or in combination with other symptoms in form of double or multiple symptoms. Bitterness of the taste buds during infections is thought to be an inflammatory reaction by the host's natural defense against toxic substances released in the body during that infection [12]. Malaria is associated with the release of toxins into the victim's blood stream during infection which in turn induces agents of inflammatory response [13]. During infections like malaria and certain inflammatory conditions, specific cytokines like the tumor necrosis factor α (TNF – α) is released by the body to fight the infections [14]. The role of these cytokines is primarily to initiate and maintain immune response resulting in inflammation. A previous study has shown that the taste bud cells express TNF receptors making them potential targets of TNF; and further suggested that TNF preferentially modulate bitter taste responses [15]. This may account for the mechanism behind bitterness of the taste buds during malaria infections as reported by our study patients. Other studies have also associated high level of TNF with increased malaria parasite density in parts of sub Saharan Africa [16-18].

Other non-classical symptoms reported by the study patients include mouth sores, nightmare, sore throat and pains in the eye. Fewer people reported these as single symptoms but more as double or multiple symptoms mostly in combination with bitterness of taste buds.

Mouth blisters were reported by participants, but these sores were seen in participants who had experienced fever during the onset of disease. Mouth blisters also known as cold sores or fever blisters are almost only associated with certain febrile viral infections such as herpes simplex at the primary stage [19]. These sores which appear as clusters of tiny blisters on the lip may not be a direct symptom of malaria but may be induced by fever which also results from inflammatory response. The underlying mechanism causing mouth blisters is not clear and there are little or no previous reports associating mouth sores with malaria. It is however important that further investigations be carried out to corroborate this report or otherwise on whether mouth blisters can result from malaria infections in malaria endemic areas as well as to understand the mechanism that causes it.

Nightmare was reported more by participants with multiple symptoms. Previous reports had associated malaria with nightmares and dreamy state as during world war II, a US military clinician noted characteristically confusional form of psychosis, dreamy state, nightmare as well as bizarre delusions associated with both severe and mild form of malaria [20]. A previous study had also reported nightmares and dreamy state among patients suffering malaria during malaria epidemic on the Macedonia front during the World War 1 between 1916 and 1918 [21]. However, the real association of nightmare and dreamy state with malaria have also been challenged [20].

Sore throat was mostly reported by patients presenting double and multiple symptoms. Sore throat may have manifested as a sub-symptom of malaria secondary to primary symptom of pharyngeal congestion that may feature as cough [21]. Constant coughing irritates the throat and can result to pains and sores in the throat. Whereas coughing has been reported to be a manifestation of the pulmonary involvement of malaria [22], sore throat has been reported as a respiratory symptom in a study among Amazonian patients with malaria [23].

Pains in the eye was observed in this study as a single symptom and occurred in form of multiple symptoms among other symptoms. Eye pain is not usually associated with malaria except that some headaches may induce pains in the eye. It is noteworthy that headache is a classical symptom of malaria [24]. Among our study patients however, it is not certain if the eye pains they experienced was because of malaria induced headache. Even though the proportion of those reporting pain in the eye in this study was small, it is also important to investigate further to know if this is a recurring manifestation during malaria illness in this and other endemic areas.

Most of the study patients who reported the non-classical symptoms were those who had not treated malaria for a long time (six months before the study). This may suggest that these individuals have been exposed to infections for some time before manifesting the symptoms later on, they may have been asymptomatic for a while. In high transmission areas, asymptomatic malaria is very common [25], and occurs as a result of either low density parasiteamia [26], or partial or semi immunity acquired because of repeated exposure to infections [27]. Whichever the case may be, which our study did not go further to confirm, manifestation of these symptoms may suggest that over the period of exposure, parasite density may have increased to a level that enabled clinical manifestation as has also been previously observed [28,29]. Acquired partial immunity for some reasons may be good enough to prevent progression to severe disease or complicated malaria but not necessarily, as may be the case here, to prevent manifestation of clinical symptoms of uncomplicated malaria [27,30]. Importantly too, as is the case of the classical symptoms of malaria, immune response may have also played a role in the manifestation of these non-classical symptoms. These aspects also require further investigation to understand the role of parasite density as well as immunity in the manifestation of these non-classical symptoms.

CONCLUSION

Malaria is a complex disease that presents with multiple symptoms. The classical symptoms of malaria based on which

clinical recognition/ differential diagnosis and treatment are made are not specific to malaria but also to other illnesses prevalent in malaria endemic areas. This has resulted in a lot of over diagnosis and overtreatment of malaria particularly in poor endemic areas where conventional confirmatory diagnosis may not be readily available. Despite recommendations for confirmatory testing before treatment of malaria, people in malaria endemic areas particularly sub-Saharan Africa still go ahead to treat malaria based on symptoms they recognize and associate with malaria. These may pose hindrances to the expected goals of the malaria elimination efforts in these areas. However, inhabitants in malaria endemic areas also present with other symptoms or manifestations that are not documented as reported in this study. These are the non-classical symptoms of malaria because they are not recognized and used for clinical recognition and differential diagnosis of malaria. But some of these symptoms are unique and can be added to the profile of malaria symptoms and manifestations if properly investigated, specifically associated with the disease (if found consistent in other endemic areas), characterized and documented. This is very important in deriving new sets of criteria or algorithms for the clinical recognition and differential diagnosis of malaria particularly in poor endemic areas. It will also help clinicians in both endemic and non-endemic areas not to be confused in taking decisions when they encounter such symptoms. In this study, majority of those who reported the non-classical symptoms particularly as double and multiple symptoms were confirmed malaria positive. Further investigations will focus on determining the dynamics, pattern and consistency of association with malaria of these non-classical symptoms in malaria endemic areas. The implications for efforts towards malaria elimination may be far reaching.

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Conflict of Interest

We declare that we have no conflict of interest.

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