Incidence Of Concurrent Malaria And Typhoid Fever Infections In Febrile Patients In Jos, Plateau State Nigeria.

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Abstract: Malaria and typhoid fever are major aetiological considerations in both acute and prolonged fever of unknown origin (PUO) in the tropics. Because of the high prevalence of malaria and typhoid fever in Nigeria, co-infections are common. This study investigated the incidence of *Salmonella enterica* serovar *typhi* and *Plasmodium* species in febrile patients in Jos, Nigeria. A total of 300 each of blood and stool samples were collected from patients presenting febrile conditions suggestive of malaria and typhoid fever and analyzed using parasitological, agglutination (Widal) and stool culture techniques. All isolates were identified as *Salmonella enteric* serovar *typhi* using standard microbiological techniques. The results revealed that 162(54%) patients were positive for malaria parasites out of which 68(42%) had typhoid fever by Widal test and 9(5.6%) by stool culture test. A correlation analysis showed a strong relationship between malaria parasite and *Salmonella typhi* both by Widal test (r=0.98) and by stool culture (r=0.91) tests. The result showed that malaria is more likely to cause fever than typhoid infection. It is therefore pertinent to suggest that every treatment of fever should be preceded by appropriate laboratory diagnosis that can establish the actual aetiology. The use of widal test alone in the diagnosis of typhoid fever is unreliable, misleading and should be discouraged. Culture technique still remains the gold standard in the diagnosis of typhoid fever and should be embraced. In the absence of culture facilities, widal test can be used provided judicious interpretation of the test result is made against a background of pertinent information. Also where culture facilities are lacking and patients show positive for malaria and widal test, malaria should be treated first. Only when malaria has been ruled out should such patients be treated for typhoid fever.

Index Terms: Co-infection, Febrile Patients, Malaria, *Plasmodium spp., Salmonella spp.,* Typhoid

1 INTRODUCTION

Malaria is a mosquito-borne infectious disease of humans and other animals caused by parasitic protozoans of the genus *Plasmodium*. Commonly, the disease is transmitted via a bite from an infected female *Anopheles* mosquito, which introduces the organisms from its saliva into a person's circulatory system. In the blood, the protists travel to the liver to mature and reproduce [1]. The presentation may include headache, fever, shivering, joint pain, vomiting, hemolytic anemia, jaundice, hemoglobin in the urine, retinal damage, and convulsions [2], and in severe cases can progress to coma or death. The disease is widespread in tropical and subtropical regions in a broad band around the equator, including much of Sub-Saharan Africa, Asia, and the Americas [3]. Five species of *Plasmodium* can infect and be transmitted by humans.

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The vast majority of deaths are caused by *P. falciparum* and *P. vivax*, while *P. ovale*, and *P. malariae* cause a generally milder form of malaria that is rarely fatal[4]. The zoonotic species *P. knowlesi*, prevalent in Southeast Asia, causes malaria in macaques but can also cause severe infections in humans [5]. Malaria is prevalent in tropical and subtropical regions because rainfall, warm temperatures, and stagnant waters provide habitats ideal for mosquito larvae. The World Health Organization has estimated that in 2010, there were 219 million documented cases of malaria. That year, the disease killed between 660,000 and 1.2 million people [6], many of whom were children in Africa [7]. The actual number of deaths is not known with certainty, as accurate data is unavailable in many rural areas, and many cases are undocumented. Malaria is commonly associated with poverty and may also be a major hindrance to economic development [8],[9],[10]. On the other hand, typhoid fever is a common worldwide bacterial disease transmitted by the ingestion of food or water contaminated with the faeces of an infected person, which contain the bacterium *Salmonella enterica* serovar *typhi* [11]. It is a systemic infectious disease characterized by an acute illness, the first typical manifestations of which are fever, headache, abdominal pain, relative bradycardia, splenomegaly, and leucopenia [12],[13]. An estimated 16–33 million cases of typhoid fever occur annually. Its incidence is highest in children and young adults between 5 and 19 years old [14]. These cases as of 2010 caused about 190,000 deaths up from 137,000 in 1990 [15]. Historically, in the pre-antibiotic era, the case fatality rate of typhoid fever was 10-20%. Today, with prompt treatment, it is less than 1% [16]. The disease has received various names, such as gastric fever, abdominal typhus, infantile remittant fever, slow fever, nervous fever and pythogenic fever. Humans are the only reservoir and host for typhoid fever and disease is transmitted via faecally contaminated water and food in endemic areas especially by carriers handling food [17]. Malaria and typhoid fever remain diseases of major public health importance in the tropics, causing significant morbidity

and mortality [9]. As a result, they constitute the two important diagnoses to be ruled out in the diagnosis of fever in the tropics [18]. Their high endemicity has made them become almost a house-hold name to every Nigerian [19]. Both malaria and typhoid share social circumstances that are imperative to their transmission. Therefore, a person living in such an environment is at great risk of contracting both infections either concurrently or as an acute infection superimposed on a chronic one [18]. An association between malaria and typhoid fever was first described in the medical literature when it was named typhomalarial fever by the United States Army doctor J.J. Woodward in the middle of the 19th Century during the American Civil War [21],[22]. In the last two decades, this relationship has been substantiated by studies from Africa and India [10,][22],[23],[24],[25],[26]. However, the actual and precise underlying mechanism to explain the association between the two infections is still uncertain, although there are few postulations which explain why malaria may predispose to *Salmonella* bacteremia and sepsis [18]. It has been shown that antibody response to O antigen of *Salmonella typhi* was markedly reduced in acute episode of malaria compared with that in controls where humoral immunity is transiently impaired [27]. It has also been demonstrated in a murine model of infection with *Salmonella murium* that haemolysis which occur in malaria may predispose to gram-negative organism as what has been seen in haemolytic disease caused by sickle cell disease and bartonellosis [28]. While high prevalence of malaria is an established fact, it is only within the last decade that an unusually high number of illnesses have been diagnosed as malaria co-existing with typhoid fever. Nigeria is highly endemic with both infections such that they have become almost a household name to every Nigerian. Because of this high prevalence, it is common to see patients undergoing treatment even when their diagnosis has not been confirmed [29]. Also, most clinicians are used to linking every symptom and sign to a single pathology; this is misleading as both diseases share similar sypmtomatology [18],[24]. Clinical syndromes produced by both diseases often present with diagnostic difficulties and in some cases could lead to diagnostic confusion [26]. Although, the diseases have been associated with major negative impact in Nigeria such as high medical cost, decreased manpower, repulsion to investment and tourism and many others [10],[30],[31], treatment has not been accompanied with definitive laboratory diagnosis. As a result, the present study investigated the incidence of concurrent malaria and typhoid fever infection in febrile patients from two hospitals in Jos, Plateau State Nigeria as well as established the advantage of stool culture over widal agglutination test in the diagnosis of typhoid fever.

2 MATERIALS AND METHOD

2.1 Study Area

The study was conducted in two hospitals in Jos North. Jos North is the capital city of Plateau state in Nigeria. Jos is located in an area covering about 9400km of the crystalline complex in North Central Nigeria. Its average elevation is about 1250m above mean sea level and has an average annual rainfall of about 1,400mm. There is always large influx of people including foreigners to the city due to the economic viability. The hospitals used were Plateau State Specialist Hospital and Eldin Specialist Hospital. Plateau State Specialist Hospital (PSSH), Jos (formally known as Plateau Hospital) is located at Old Bukuru road Jos, plateau state. The hospital stands on its own, serving as a referral centre for other general and cottage hospitals within the state and hence, opens to the inhabitants of plateau state. Eldin Specialist Hospital on the other hand, is situated in Dodon Dutse Street, Jos. It is accessible to people living around the area and caters majorly for women.

2.2 Study Population

A total of 300 patients (male, n=117 and female, n=183) presenting febrile conditions suggestive of malaria or typhoid in Plateau State Specialist Hospital (n=192) and Eldin Specialist Hospital (n=108) were recruited for the study. It included individuals of all ages and sexes.

2.3 Sample Collection

Samples used in this study were blood and stool samples. A total of 600 samples were collected including 300 blood and 300 stool samples. About 5 ml of blood samples were aseptically collected by venepuncture [32] from each patient into plain tubes. Stool samples were collected into sterile bottles. Also structured questionnaires were administered and sociodemorgraphic information of each patient was obtained.

2.4 Laboratory Analysis

2.4.1 Parasitological examination of blood samples

A thick blood film for each blood sample was made on clean grease-free glass slide and stained by the Giemsa Staining Technique as described by Ochei and Kolhatkar [33]. Just before use, the commercially prepared Giemsa stain was diluted 1 in 10 by adding 5 ml of stain to 45 ml buffered distilled water (pH 7.0) and mixed. The blood films were flooded with freshly diluted Giemsa stain for 30 minutes. The stain was then washed off and slide allowed to air-dry in a draining rack after the underside was cleaned with cotton wool. The dried smear was examined on at least 100 high powered microscope fields before considered as negative. The presence of any peripheral parasitaemia at least one per 100 thick fields was considered significant as the entire patient presented with fever.

2.4.1 Widal agglutination test for *Salmonella* antibodies

Widal agglutination test was performed on each blood sample using the Widal agglutination kit (Biotech lab, United States) containing somatic (O) and flagella (H) antigens of *Salmonella typhi* and *Salmonella paratyphi* A-C. A negative saline control was introduced in each batch of test. The procedure used was as described by Ochei and Kolhatkar [33]. Drops of sera from each patient were made on a clean tile, mixed with the antigens rocked for 3 minutes and observed for agglutination. A positive Widal test was considered as one that gave a reaction titre of 1/80 or greater in a single test.

2.4.2 Bacteriological examination of stool samples

A small portion of each stool sample was inoculated on previously dried surface of *Salmonella-Shigella* agar using sterile wire loop. The plates were incubated aerobically at 37 ^{o}C for 24 hours after which they were observed for growth. Isolates were identified as *Salmonella enteric* serovar *typhi* using standard microbiological techniques [33].

3 RESULTS

A total of 300 febrile patients were screened for malarial and typhoid fever infections. Out of this number, the results showed that 162(54%) were positive for malaria parasite infection. The incidence of malaria parasite infection was higher in females (30.33%) than males (23.67%). With respect to age, malaria parasite infection rates were highest (18.33%) among patients within 20-29 years of age and least (1%) among patients who were 60 years old and above. Of the 162 patients who were positive for malaria parasite test, 68(42%) and 9(5.6%) showed co-infection with typhoid fever by widal test and stool culture respectively. The rate of co-infection with respect to widal test was higher in females (61.8%) than males (38.2%), while stool culture showed that male patients were more co-infected that female patients with co-infection rates of 55.6% and 44.4% respectively. With respect to age, co-infection was highest (22 of 68) among patients within the age bracket 20-29 years and least (0 of 68) among those 60 years of age and above by widal test. There was a strong relationship by correlation analysis between malaria parasite infection and typhoid fever both by widal test (r=0.98) and stool culture (r=0.91). Details of the study results are as shown in the tables 1-4 below:

4 DISCUSSION

Malaria and typhoid fever infections continue to be major diseases of public health concerns, especially in the tropics, and are known to present clinically similar symptoms with fever being the major presentation [26]. Nigeria, like other tropical and sub-tropical countries, is an area of high endemicity for both infections [24]. As a result, people living in Nigeria are at risk of contracting both diseases either concurrently or as an acute infection superimposed on a chronic one [18].

Table 1: Age and Sex Distribution of Malaria in febrile patients in Jos, Plateau State Nigeria.

Age group	Total examined	Male		Female		Total (%) Positive
		No. examine	No. positive	No. examined	No. positive	
0-9	66	30	15	36	18	33(11.00)
10-19	58	23	15	35	19	34(11.33)
20-29	90	40	29	50	26	55(18.33)
30-39	34	8	4	26	12	16(5.33)
40-49	24	7	5	17	9	14(4.67)
50-59	13	6	2	7	5	7(2.33)
≥60	15	3	1	12	2	3(1.00)
Total	300	117	71	183	91	162(53.99)

Table 2: Age and Sex Distribution of Patients co-infected with Malaria and Typhoid fever by Widal Test in febrile patients in Jos, Plateau State Nigeria.

Age group	Total examined	Male		Female		Total (%) Positive
		No. examine	No. positive	No. examined	No. positive	
0-9	33	15	5	18	8	13(39.40)
10-19	34	15	7	19	8	15(44.10)
20-29	55	29	9	26	13	22(40.00)
30-39	16	4	1	12	7	8(50.00)
40-49	14	5	4	9	4	8(57.10)
50-59	7	2	0	5	2	2(28.60)
≥60	3	1	0	2	0	0(0.00)
Total	162	71	26	91	42	68(42.00)

Table 3: Age and Sex Distribution of Patients co-infected with Malaria and Typhoid fever by Stool Culture in febrile patients in Jos, Plateau State Nigeria.

Age group	Total examined	Male Positive	Female Positive	Total (%) Positive
0-9	33	1	1	2(6.10)
10-19	34	1	2	3(8.80)
20-29	55	3	0	3(5.50)
30-39	16	0	0	0(0.00)
40-49	14	0	1	1(7.10)
50-59	7	0	0	0(0.00)
≥60	3	0	0	0(0.00)
Total	**162**	**5**	**4**	**9(5.60)**

Table 4: Co-infection of Malaria and Typhoid fever with respect to Widal test and Stool culture compared in febrile patients in Jos, Plateau State Nigeria.

Age group	Total positive for Malaria	Total positive for Typhoid	
		Widal	Stool Culture
0-9	33	13(39.40)	2(6.10)
10-19	34	15(44.10)	3(8.80)
20-29	55	22(40.00)	3(5.50)
30-39	16	8(50.00)	0(0.00)
40-49	14	8(57.10)	1(7.10)
50-59	7	2(28.60)	0(0.00)
≥60	3	0(0.00)	0(0.00)
Total	**162**	**68(42.00)**	**9(5.60)**

This study revealed that of the 300 patients screened, 162(54%) were positive for malaria whereas only 68(22.67%) to 77(25.67%) were positive for typhoid fever. This shows that malaria is more likely to cause fever than typhoid, although both share fever in their symptomatology. This result is in agreement with the findings of Igbeneghu *et al.* in Ibadan, who observed 50.4% of malaria against 4.7% of typhoid fever [19]. However, the result varies with the findings of Nwuzo *et al*. in Abakaliki, Opara *et al.* in Owerri and Igharo *et al.* in Ondo, who observed higher prevalent rates of typhoid than malaria in febrile patients; the prevalent rates were (21.20% typhoid vs. 13.20% malaria) [10], (42% typhoid vs. 39% malaria) [22] and (73.9% typhoid vs. 37.6% malaria) [26] respectively. The variation in the results could be attributed to differences in the environmental conditions of the studied population. Factors such as poor hygiene resulting to faecal contamination, lack of potable water as well as inadequate breeding grounds for mosquitoes could have contributed to reasons why they observed higher rates of typhoid fever infections than malaria. In Jos North, the large influx of people could have created adequate opportunities for mosquitoes to breed. Also most sources of drinking water in Jos North are tap and borehole. There are less surface waters used for drinking that could be open to faecal contamination. Jos North environment is also more hygienic especially as the present Plateau State government insists that every household should have good toilet systems, minimizing uncontrolled defaecation in the nearby bushes which is the major source of faecal contamination of surface running waters with the bacteria that causes typhoid fever infections. Furthermore, the result revealed a very strong relationship between malaria and typhoid fever infections both by widal test and stool culture. However, there were considerably higher rates of concurrent malaria and typhoid fever infections by widal test (42%) compared to the stool culture technique (5.6%). This is to be expected as widal test, being a serological test, only proves exposure to a certain antigen; it does not tell if infection is

recent or not [18]. Also there could be possible cross-reactivity with other antigens having common somatic or flagella recognition proteins [26]. Therefore, widal test which has been used for decades in Nigeria for the diagnosis of typhoid fever infections only leads to false positive and overestimated results [18]. Cross-reactivity between malaria parasite antibodies and widal antigens has been reported to have led to over-diagnosis of typhoid fever [34], [35]. The result is in conformity with the findings of Uneke [9], and Keong and Sulaiman [18]. Also, Ammah *et al.* in Cameroon reported that out of 200 patients with fever, 17% had concurrent malaria and typhoid fever based on bacteriological proven diagnosis as compared to 47.9% based on widal test [23]. Samal and Sahu described 52 patients with malaria positive in the peripheral blood smear, out of whom eight cases had positive widal tests but the blood culture were negative for *Salmonella typhi* in all; all the cases were cured with antimalarial therapy [36]. Other studies in agreement with this result are those of Mbuh *et al.* (0.5% culture vs. 10.1% widal test) [29], Igbeneghu *et al.* (0.8% culture vs. 21% widal test) [19] and Nwuzo *et al.* (6.1% culture vs. 42.4% widal test) [10]. However, although culture technique remains the gold standard in typhoid fever diagnosis as supported by this study, widal test is still of significant diagnostic value provided judicious interpretations of the test results are made against backgrounds of pertinent information [9].

5 CONCLUSION

There is a strong relationship as revealed by this study, between malaria and typhoid fever infections as both share some social circumstances and diagnostic symptomatology. Also revealed is the fact that typhoid fever has been over-diagnosed by widal test and many patients have been placed on antibiotics against typhoid fever when it is not called for. This is because malaria parasite antibodies may cross-react with widal antigens, leading to overestimation of typhoid fever infections [23], [35]. Silently shown by this study is the fact that most febrile patients neither had malaria nor typhoid fever. Therefore, a high index of suspicion is necessary to diagnose a co-infection as most clinicians are used to linking every symptom and sign to a single pathology, undermining the fact that both malaria and typhoid fever may present with mimicking symptoms [18]. It is therefore pertinent to suggest that every treatment of fever should be preceded by adequate laboratory diagnosis that can establish the actual aetiology. The use of widal test alone in the diagnosis of typhoid fever is unreliable, misleading and should be discouraged. Culture technique still remains the gold standard in the diagnosis of typhoid fever and should be embraced. In the absence of culture facilities, widal test can be used provided judicious interpretation of the test result is made against the background of pertinent information. Also where culture facilities are lacking and patients show positive for malaria and widal test, malaria should be treated first. Only when malaria has been ruled out should such patients be treated for typhoid fever [19]. Also suggested are other preventive measures such as personal and environmental hygiene, use of mosquito treated nets and insecticides. All cases of typhoid fever should be identified and promptly treated to avoid further transmission.

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