Misdiagnosis of Dengue Fever and Co-infection With Malaria and Typhoid Fevers in Rural Areas in Southwest Nigeria

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Research Article

Keywords: Infection, Coinfection, IgM, IgG, NS1

DOI: https://doi.org/10.21203/rs.3.rs-292692/v1

Abstract

Background

Dengue and malaria have similar symptoms and arthropod vector and their mode of transmission coupled with differential diagnosis. Though typhoid fever differs from dengue and malaria by not having arthropod vector and different mode of transmission, it shares differential diagnosis with Dengue and Malaria which make misdiagnosis possible. This misdiagnosis of these three diseases has since been a major concern towards therapeutic administration because of their co-occurrence in many cases.

Methods

This study focused on the misdiagnosis of dengue fever for malaria or typhoid fever since the three have differential diagnosis and could co-occur. 741 samples were collected from malaria patient and 333 samples for typhoid fever outpatient at the health department facilities in rural communities of South West Nigeria. The samples were tested for dengue virus (DV) NS1 protein, anti DV IgM, anti DV IgG and RT-qPCR.

Result

Of all the samples tested 315 (29.4%) were positive to DV NS1 while 50 (6.7%) and 13 (3.9%) of 714 malaria samples and 333 typhoid samples respectively had Dengue fever co-infection. Co-infection of the three types of fever occurred in 5 (0.5%). A total of 54 (5%) DV cases were wrongly diagnosed for malaria while 14 (1.3%) DV cases was wrongly diagnosed as typhoid.

Conclusion

Conclusively, there was significant number of misdiagnosed cases of DV for either malaria or typhoid, hence it is recommended to include DV screening into routine hospital test especially in cases of malaria and typhoid negative by rapid diagnostic testing.

Introduction

Dengue and Malaria fevers are the most common arthropod-borne diseases caused by mosquito bite and they also have similar signs and symptoms. Typhoid fever, which is caused by *Salmonella typhi* and 3 types of *Salmonella paratyphi* also share similar symptoms with both malaria and dengue fevers. Co-infection of Malaria and Dengue was first reported in 2005 [1], while Orhe et al in 2003 report a co-infection of malaria and typhoid fever [2] and that the few cases that have been reported indicated that, co-infections maybe more severe than singles infection (Malaria or Dengue fever) [3], although there is a paucity of reports for Dengue and typhoid fevers co-infection. In most cases, it is common to first think of malaria diagnosis when feverish syndromes are observed in patients and secondly, typhoid fever will be suspected and even treated empirically. Dengue virus infection is rarely taken into consideration by the clinicians because the disease is not considered as endemic of which this could lead to fatal consequences. Hence, early diagnosis of Dengue infection will not only prevent complications such as Dengue Hemorrhagic fever (DHF) and Dengue Shock syndrome (DSS) but will also curtail unnecessary consumption of antimalaria drugs and antibiotics thereby reducing menace of antimicrobial resistance.

Dengue fever, also known as break bone fever, is an infectious tropical disease caused by the Dengue virus, a member of the Flaviviridae family [4]. About 390 million cases of Dengue infections are reported every year [5] and the virus is a cause of serious health problems in many tropical and subtropical areas of the world. Dengue hemorrhagic fever (DHF) first emerged as a public health problem in 1954, when the first epidemics occurred in other regions of the world in the 1980s and 1990s caused by all four serotypes of Dengue virus [6]. DHF and DSS, are major public health concerns because of their severe and often fatal disease in children as approximately 90% of DHF victims are children less than 15years of age [7].

Dengue virus is transmitted to humans by the bite of an infected Aedes mosquito mostly *Aedes Egypti* [8]. It primarily propagates in skin dendritic cells and replicate in target cells such as the monocytes or macrophages [9]. Symptoms include fever, headache, muscle and joint pains, and a characteristic skin rash that is similar to measles. In few cases, the disease progress into life-threatening DHF resulting in bleeding, low levels of blood platelets or blood and plasma leakage, or into dengue shock syndrome where low blood pressure occurs [10] and can lead to death. Malaria remains the deadliest infectious diseases in Africa and its parasites belongs to the genus Plasmodium. In humans, malaria is caused by *P. falciparum, P. malariae, P. ovale, P.knowlesi* [11]. Among the parasite known to transmit malaria, *P. falciparum* is the most common species identified (75%) followed P. vivax (20%) [12]. Although *P. falciparum* traditionally accounts for the majority of deaths while recent studies also suggests that *P. vivax* malaria can also be life-threatening [13]. Like in Dengue, symptoms of malaria include fever, headache, rash, vomit and joint pain.

Typhoid fever also remains an important public health problem in many developing countries of the world including Nigeria [14] about 11 million cases of typhoid fever occur annually with 600,000 deaths. In tropical Africa and some other developing countries enteric fever is rampant because of the low socio-economic and poor hygienic conditions in these regions. During the past few years in Nigeria, there have been a high incidence of typhoid fever creating fears or panic in any febrile illness which has led to drug abuse among populace especially chloramphenicol

Dengue, malaria and typhoid are three major public health concerns in tropical settings and developing countries. Few cases of Dengue-Malaria coinfection has been reported in Nigeria [15] not much of Dengue (DV) and typhoid has been reported. Moreover, concurrent infection with the three different infective agents especially DV and malaria lead to an overlap of their clinical features. This can pose a diagnostic challenge to the physician, especially in endemic areas [16]. There has also been reports of misdiagnosis of the of malaria and DV infections [17], which could be due to differential diagnosis of both infections. Although reports of DV and typhoid infection are sparse, it is therefore imperative to investigate the co-occurrence due to their differential diagnosis. This study is not aware of any study which investigated DV, malaria and typhoid co-infection and misdiagnosis in Nigeria. Hence this study investigated the frequency of co-occurrence of dengue, malaria and typhoid fevers in rural communities in South West Nigeria, as well as their possible misdiagnosis of dengue fever for malaria and/or typhoid fever.

Methods

Study Design

This study is a cross sectional research conducted in several health facilities in rural areas of South West, Nigeria.A cross section of the patients seeking diagnosis for malaria and typhoid were tested for Dengue Virus (DV) NS1,IgM, IgG, using ELISA and Reverse Transcriptase Polymerase Chain Reaction (RT-qPCR). The DV test was done independent of whether the patients are positive for malaria and typhoid or not.

Inclusion Criteria

This study involved all consenting out-patients that reported to health facilities for malaria and typhoid fever during the course of the research. Any sample testing positive to the different types of malaria parasite were included in the study and any sample testing positive to different causative agents of typhoid fever was included in the study or both diseases All collected sample must have been tested in the facility and result registered in the facility register. These samples were then tested for dengue NS1 used as a first line marker for dengue virus. All samples testing positive for dengue NSI were again tested for anti DV IgM, IgG and RT-PCR.

Sample collection

5 ml of blood was aseptically collected from patients (n=1074) seeking malaria and/or typhoid diagnosis in the health institutions in rural areas of South West Nigeria from October to September in the year sampled. The blood samples were collected into EDTA bottles from each participant by a trained phlebotomist using needle and syringe and were immediately transported in cold chain to the Microbiology Laboratory.Each bottle was labeled indicating their age,sex and location.Blood samples were shared into 2 EDTA bottles and one to be used for DV ELISA and the other for malaria and typhoid.

Test for Malaria

Malaria testing was done in the clinics using the Rapid Diagnostics Testing after which samples were immediately shipped to the laboratory and confirmed using the Giemsa staining technique.

Test for Typhoid Fever

Typhoid fever was tested in theclinical laboratory using the slide agglutination and typhoid RDT, samples were shipped to the laboratory for confirmation using the tube agglutination technique as adapted to the use of microtiter plate, all the patients were made to come back a week after the first test for a second sample collection used for paired sample testing [18].

Enzyme Linked Immunosorbent Assay

Blood samples for ELISA was immediately centrifuged at 3000 rpm (Beckman Microfuge centrifuge centrifuge) and sera separated from the whole blood and immediately used for ELISA. Sera stored in the refrigerator were brought out and allowed to attain room temperature as well as all the reagents. Sera were dispensed into the antibody impregnated ELISA microplate and the test carried out as described by the manufacturer of the ELISA test kits (Melsin Medicals, China). ELISA kits used included ELISA NS1, IgM and IgG for research. ELISA plates

were loaded into the microplate reader (Molecular devices, USA) at optical density of 450nm, absorbance were generated and analyzed using the myassays software to generate the concentration of each sample in each of the parameters for analysis.

RNA Extraction

RNA was extracted using the Norgen Biotek total RNA extraction kit. 100 ml of non-coagulating whole blood was collected into well-labeled RNAse free microfuge tubes and 350 lysis buffer added to the blood in the microfuge tubes and the extraction procedure carried out as directed by the manufacturer (Norgen Biotek, Ontario Canada). All samples testing positive to DV NS1, IgM and IgG had their RNA extracted RT-PCR.

RT- PCR procedure

RT-qPCR was carried out on all samples testing positive to dengue NS1 by ELISA technique after RNA extraction. A PCR reaction mixture was set up using the MAXIMA SYBR green with ROX RT-PRCR master mix to achieve a total volume of 25ml using the hot start as described by the manufacturer. The primers used were obtained from already published research [19] which are universal primers targeting 3' untranslated region of all complete genome sequences of dengue virus available in GenBank (n=3,305)DENV_F- GCATATTGACGCTGGGARAGAC, DENV_R1-3 -TTCTGTGCCTGGAATGATGCTG, DENV_R4- YTCTGTGCCTGGATWGATGTTG) and probe (DENV_P- CAGAGATCCTGCTGTC). Hence all 4 types of DEV will be detected. The primers were sent to Inqaba Biotech, South Africa for synthesis. The PCR mixtures were put into the thermocycler (Biorad icycler, (Biorad USA). The PCR program was as follows- UDG pretreatment 50°C 2 mins for 1 cycle, initial denaturation 95°C for 10 mins 1 cycle, denaturation at 95°C for 15 sec 40 cycle, annealing at 60°C for 30 sec 40 cycle and extension at 72°C for 30 sec 40 cycles. Data acquisition was then done and analyzed with the icycler software for CT values.

Results

A total of 1074 blood samples were collected from different health facilities in different rural locations in South West Nigeria of which 741 (69%) blood samples were positive for malaria parasites, 333 (31%) were positive to typhoid fever while from the malaria and typhoid positive samples, 315 (29.4%) were positive to dengue using the NS1 protein (Fig. 1). From DV NS1 results, 80 (25.4%) of the total samples were positive to anti DV IgM and 20 (6.3%) positive to anti DV IgG while 287 (91.1%) samples were positive for DV by RT-PCR (Table 1) confirmation. Of the total number of 741 confirmed malaria cases, 50 (6.7%) also had DV NSI (co-infection) {t = 5.8540) and also confirmed by RT-PCR, There was 13 (3.9%) typhoid- DV co-infection (t = 9.3611) from the 333 samples positive to typhoid fever, while malaria/typhoid co-infection with DV had 5 (0.5%) samples positive (p = 0.9296 and p-0.9432 respectively). A total of 54 DV positive samples were wrongly diagnosed as malaria parasites while 14 (1.3%) samples positive for DV weremisdiagnosed as typhoid fever (χ = 86.877, p = 0.0000001), showing an association between all misdiagnosed samples.Age group distribution shows that age groups 21–26, 27–32 and 15–20 have the highest number of all samples positive for all infections (Fig. 1). Age group 39–44 years had the highest number of DV malaria co-infection, however, age group 27–32 and 33–38 were higher for DV typhoid co-infection while 27–32 and 33–38 years bracket has the highest positive cases for the 3 co-infection. These age brackets also has the highest number of DV misdiagnosis with 15 cases respectively after age group 39–44 which had 20 cases. Age group 27–32 and 33–38 had the highest misdiagnosed samples for DV with 6 samples respectively. Figure 2 shows sex distribution to malaria, typhoid, DV and all their co-infections. Males were more infected with malaria parasites 412 (55.6%) while females were 329 (44.4%). For typhoid 218 (65.5%) were females while males 115 (34.5%) were positive. DV NS1 had 200 (63.5%) positive males and 115 (36.5%) positive samples were females. Other DV parameters also followed the same trend. Monthly distribution shows that the months of October, September, August, July, and June had the highest number of positive cases to malaria and DV, samples positive to typhoid fever did not show a particular distribution pattern (Table 3). November and June has the highest number of co-infection cases with Malaria/DV(t= -0.639, p = 0.537) as compared to others, while September has the highest number of co-infection for the 3 parameters (t = 0.905, p = 0.387) and October and March had the highest number of typhoid and DV co-infection (t = 1.008, p = 0.537) (Fig. 1). The concentration of the NS1 protein detected by ELISA technique as analyzed by the myassays microplate software was moderate andevenly distributed across all samples positive for DV NS1 (mean = 6.25mM) irrespective of sex, age or month of sample collection (Fig. II), the DV anti IgM concentration was also (mean = 41.94) with men having higher concentration and age distribution shows that adults of age groups 33–38, 37–44 and 27–32 having higher concentration (Fig. III).The Anti DV IgG also vary like the IgM with a mean of 51.72 (Fig. IV).

Discussion

This study is a cross-sectional and comparative analysis of DV, malaria and typhoid fever in co-infection in rural settings of South West Nigeria, with misdiagnosis of dengue fever for malaria or typhoid fever. DV fever co-infection with malaria and typhoid fevers was analyzed using 4 different parameters which included NS1, IgM, IgG antibodies and later confirmed with RT-PCR. The NS1 is first protein to be

produced in the infection, which ensures the first early window is not missed in the DV infection, the IgM is the first antibody to be produced in response to an infection while the IgG will remain even in convalescence. A combination of all these ensures that no case is missed during the period of the study. The RT-PCR is used to validate all the results from the serological analysis and that any DV missed by ELISA technique will be captured by RT-PCR and at the same time quantifying the antigen in each sample. Of the total 315 DV NS1 positive samples, 287 samples were RT-PCR positive, thereby confirming that 28 samples though came in contact with DV but has not yet established enough antigen to be detected by PCR, which thereby confirms the usefulness of the NS1 protein in detecting dengue infection. This study generally reveals a high incidence of Malaria/DV co-infection as well as Malaria typhoid but the trio co-infection was not significant. A study of prevalence of concurrent dengue and malaria was reported by Charrel et al.[1] to have 0% prevalence in Netherlands, which oppose the result from this study. This reason for this may be due to geographical variation and high level of mosquito control in Netherlands, which is lacking in Nigeria. In addition, the mosquito vector for the two diseases have different habitats, malaria mosquito vector has its habitat in the forest [16] while Dengue mosquito vector main habitat is in the city [19]. Hence, overlapping of the habitat may not be easily available in Netherlands as is the case in Nigeria. Significant low Malaria-Dengue concurrent rate can be expected [20]. Dengue-Malaria co-infection has been referred to as uncommon phenomenon in the temperate regions. However, reports showed that the highest dengue-Malaria reported was 23.21% found in Pakistan while as low as 0.01% was found in Senegal [21]. Another study conducted in Brazil recorded 2.8% [7]. The report from Pakistan was similar to that from this study which is as a result of similar geographic conditions of both regions. The Senegal report also opposed results from this study and a major factor responsible for that is due to the time of the year and city the Senegal sampling was done, since both countries are in sub-Saharan Africa as indicated by the 2.84% Dengue virus and malarial concurrent infection within Ilorin metropolis In Nigeria [22]. Okoror et al. [23] also reported a prevalence of a high prevalence of DV infection (57.5%) in selected rural communities in South West Nigeria

since all the hospitals do not officially screen for DV, and the differential diagnois DV, malaria and typhoid despite similar clinical presentations makes misdiagnosis not unusual. Therefore, co-infections may give rise to wrong diagnosis especially in areas where the clinician depends on empirical treatment. Moreover, the treatment regimens for these coinfections are not the same as those for mono-infections. Hence, a delay in implementing the appropriate treatment regimen for these different infections due to poor diagnosis can result in fatal consequences in compromising the patient's health.

Age group distribution revealed that age group 21–26 through to 39–40 have the highest prevalence of Malaria/DV co-infection and they were statistically significant ($p = 0.9296$: CI = 0.05). These age group also had the highest prevalence for malaria alone as well as for typhoid. The reason for this may be attributed to active (working class) which are found in this age range and their outdoor engagement on a day to day routine, making contact with mosquito unavoidable [24]. The study is also supported by Okoror et al [25] who reported the endemic nature of typhoid in Nigeria. In addition to this, sex distribution shows that more males were more infected with Malaria as compared to females and also Malaria DV co-infection was more in males compared to females, as well as typhoid DV coinfection. The overall infection also show similar pattern of sexual distribution. This was also reported by Dhanya et al. [26], though more males have been shown to have more outdoor activities than their female counterparts.

The distribution of Malaria/DV and Typhoid monthly, show that the months of November and June had the highest Malaria/DV co-infection distribution while October and March showed the highest co-infection distribution for typhoid and DV with significant statistical difference from other months. This coincides with period of high rainfall and progression to dry season for malaria/DV infection and the period of high breed of mosquitoes. For typhoid/DV co-infection the months of highest prevalence coincides with period of high rainfall as these are the period of lowest hygiene due to high flooding which increases incidence of typhoid fever, and high proliferation of mosquitoes leading to high incidence of DV. Some authors have also reported both seasonal and monthly distribution of Malaria/DV co-infection. Dhanya et al. [26] in an India study reported a monthly distribution of Malaria and Dengue co-infection and reported their highest prevalence was between July and December which is in agreement with some of the months reported in this study. Savargaonkail et al.[24] also reported similar distribution in India. Total samples for malaria, typhoid and DV also follow similar pattern of distribution. Other factors that may have influenced this distribution includes rainfall fluctuation, humidity, and temperature [27, 28].

The concentration of NS1 protein, which was evenly distributed across the study population further goes to confirm the high prevalence of DV in the population and their misdiagnosis for malaria and typhoid fever. This is more importantly noticed with the high anti DV IgM and IgG which however was distributed along sex and age. The high concentration noticed in males goes to establish the earlier claims that males are more involved with out-door activities in the study population and therefore more exposed to the vector.

Conclusion

In conclusion this research showed that lots of dengue positive samples are misdiagnosed for malaria and typhoid fevers and as such dengue testing should be incorporated to national testing scheme especially in areas where high dengue infection has been reported like in

this study population so as not to compromise the patients' health. The importance of this paper can not be undermined because of the public health implication of undermining or misdiagnosis of dengue for malaria or typhoid, a situation which could endanger the health of the population because of the like progression of dengue fever to DSS leading to death.

List Of Abbreviations

NS1, DV, DV IgG, DV IgM, RT-QPCR, DHF, DSS, ELISA, EDTA, RDT, RNA, PCR, MAXIMA, SYBR, ROX, RT-PRCR, DENV, UDG, CT

Declarations

Conflict of Interest

We declare no conflict of interest. Author did not receive any form of financial assistance whatsoever.

Ethical Clearance

Ethical approval was granted by Ethical Review committee of the Joseph Ayo Babalola University, Ikeji-Arakeji, Nigeria. All participants in this study agreed to participate through filling of questionnaire.

Consent for Publication

Not applicable

Competing Interest

We declare no competing interest.

Funding

Authors received no funding from anywhere, but study was carried out from their personal purse.

Acknowledgement

We acknowledge the contribution of all our project students who were involved in sample collection during this study.

Availability of Data Materials

Not applicable

Author contribution

LEO conceived the study and was involved from writing of proposal through ethical defense and sample collection, laboratory analysis and to writing up of the paper. EOB was involved in supervision of laboratory analysis and writing of the final paper. OMU was involved in sample collection and laboratory analysis, EOA participated in sample collection and laboratory analysis, SKO and BO were involved in final data analysis.

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Tables

Table I: Age distribution of Dengue fever, Malaria and typhoid fever in some rural settlement in South West Nigeria

Age Group	Number Positive										
	Malaria	**Typhoid**	**DV NSI**	**DV IgM**	**DV IgG**	**DV PCR**	**Malaria/ DV**	**Typhoid/DV**	**Malaria/DV/Typhoid**	**Wrong diagnosis Malaria**	**Wrong diagnosis Typhoid**
15-20	110	53	48	21	9	46	0	0	0	0	0
21-26	135	49	48	27	5	48	10	5	1	3	1
27-32	115	61	36	10	0	34	9	5	2	15	6
33-38	101	61	37	8	2	34	9	0	1	15	6
39-44	97	44	45	8	3	40	22	0	1	20	1
45-50	86	25	39	6	1	30	0	0	0	1	0
51-56	62	21	41	0	0	36	0	2	0	0	0
57-62	35	19	21	0	0	19	0	1	0	0	0
Total	741	333	315	80	20	287	50	13	5	54	14

Table II: Sex distribution of Dengue fever, Malaria and typhoid fever in some rural settlement in South West Nigeria

Gender	Number Positive										
	Malaria	**Typhoid**	**DV NSI**	**DV IgM**	**DV IgG**	**DV PCR**	**Malaria/ DV**	**Typhoid/DV**	**Malaria/DV/Typhoid**	**Wrong diagnosis Malaria**	**Wrong diagnosis Typhoid**
Male	412	115	200	54	10	151	35	7	4	37	3
Female	329	218	115	26	10	136	15	8	1	17	3
Total	741	333	315	80	20	287	50	15	5	54	6

Table III: Monthly distribution of Dengue fever, Malaria and typhoid fever in some rural settlement in South West Nigeria

Month	**Dengue**	**Typhoid**	**Malaria**
October	41	44	87
November	20	12	44
December	12	10	39
January	12	10	27
February	16	12	27
March	29	29	46
April	35	28	67
May	41	39	71
June	40	39	90
July	38	38	93
August	28	27	81
September	21	27	69
Total	**333**	**315**	**741**