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Serological Survey of Dengue Virus Immunoglobulin M Among Febrile Patients in Kaduna Metropolis, Nigeria

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Abstract - The purposes of this research were to determine the prevalence of dengue virus in the study population, to determine the relationship between the occurrence of dengue virus IgM and potential risk factors and to determine the association between the occurrence of dengue virus and some symptoms. In this study, blood specimen were collected from 340 subjects with febrile complaints attending hospitals in Kaduna metropolis, Nigeria and who gave their consent to participate. Serological determination of dengue virus IgM was carried out using enzyme linked immunosorbent assay technique. Structured questionnaires were also administered to obtain data on demographic, risk factors, and symptoms of illness. A total of 6 subjects were positive for dengue virus IgM giving a prevalence of 1.8%. There was no statistically significant association between the occurrence of dengue virus IgM and potential risk factors, demographic factors and symptoms of the illness. The occurrence of dengue virus in the study population was confirmed.

Keywords: Serological; Dengue; Virus; IgM; Febrile; Kaduna

Introduction

The dengue virus is single stranded, positive sense RNA virus which belong to the family Flaviviridae, genus Flavivirus (Gubler, 1997; Rodenhuis-Zybert *et al.*, 2010). Other members of the same genus include yellow fever virus, West Nile virus, St. Louis encephalitis virus, Japanese encephalitis virus, tick-borne encephalitis virus, Kyasanur forest disease virus, and Omsk haemorrhagic fever virus (Gould and Solomon, 2008). Most are transmitted by arthropods (mosquitoes or ticks); therefore, also referred to as arboviruses (arthropod-borne viruses) (Gould and Solomon, 2008). The clinical outcomes of dengue virus infection could vary from asymptomatic, mild febrile dengue fever (DF) to severe and life threatening dengue haemorrhagic fever (DHF)/dengue shock syndrome (DSS) (Gunther *et al.*, 2007).

Typically, people infected with dengue virus are asymptomatic (80%) or only have mild symptoms such as an uncomplicated fever (WHO, 2009; Whitehorn and Farrar, 2010). Others have more severe symptoms (5%), and in a small proportion it is life-threatening (Whitehorn and Farrar, 2010; Reiter, 2010). The incubation period ranges from 3–14 days, but most often is 4–7 days (Gubler, 2010). Therefore, travellers returning from endemic areas are unlikely to have dengue if fever or other symptoms start more than 14 days after arriving home (Ranjit and Kissoon, 2010). Children often experience symptoms similar to those of the common cold and gastroenteritis (Varatharaj, 2010) but are more susceptible to the severe complications (Ranjit and Kissoon, 2010).

Dengue has emerged in recent decades and become a worldwide public problem, particularly in Asia-Pacific and Americas-Caribbean regions (Gubler and Clark, 1995; Gubler, 2004; Halstead, 2008). In Africa, the epidemiology and public health effects of dengue is not clear (Amarasinghe *et al.*, 2011). *Aedes spp.* mosquitoes are widely distributed in Africa and can serve as vectors of dengue virus (Amarasinghe *et al.*, 2011). When their distribution is combined with rapid population growth, unplanned urbanization and increase in international travel, extensive transmission of dengue virus is likely in Africa (Gubler, 2004; United Nations, 2009). Over the past five decades, cases of epidemic or sporadic dengue have been reported in sub-Saharan Africa (WHO, 2009). Although sporadic cases of DHF have been reported in a few countries in Africa,

no outbreaks have been reported (Gubler and Clark, 1995). However, when compared with the Asia-Pacific and Americas-Caribbean regions, the epidemiology of dengue in Africa has not been defined.

A study in Nigeria determined the prevalence of flavivirus infection among 1,816 children and adults in urban and rural areas from samples were collected mainly during the early 1970s (Fagbami *et al.*, 1977). Virus-specific haemagglutination inhibition testing showed that the prevalence of immunity was 38% for dengue virus-1 infection, 45% for dengue virus-1 infection, 43% for yellow fever virus infection and 49% for West Nile virus infection (Fagbami *et al.*, 1977). Serum specimens were also tested by suckling mouse neutralization of dengue virus – 2. The authors concluded that because a high proportion of specimens with antibody to dengue virus – 2 were confirmed by neutralization and because many had only monotypic antibody, the prevalence results were not likely confounded by cross-reactive antibodies to other flaviviruses. Another study by Baba *et al.* (2009) revealed the prevalence of dengue virus IgG in rain forest and wooded savannah areas of Nigeria was 69.0%. In addition, the study by Fagbemi *et al.* (1977) showed an increase in prevalence of antibodies against dengue virus with age. These suggest endemic infection.

Materials and Methods

Study area

Kaduna State occupies part of the central position of the northern part of Nigeria (with Kaduna as its capital) and shares boundaries with Niger State to the west, Zamfara, Katsina and Kano states to the north, Bauchi and Plateau states to the east and FCT Abuja and Nasarawa State to the south. Kaduna State lies at latitude 10°20' north and longitude 7°45' east. The state occupies an area of approximately 48,473.2 square kilometres and has a population of more than 6 million people (KGIS, 2008). Four hospitals were selected from Kaduna metropolis and used for the study.

Study population and ethical clearance

Referred-patients with febrile illnesses who sent to the laboratory for malaria test were recruited for the study. Ethical consent was sought and obtained from the ethical committee of Kaduna State Ministry of Health and from all hospitals in this research.

Inclusion and exclusion criteria

Patients attending the hospital during the period of the research who were referred to the hospital laboratory for malaria test and who gave their consent to participate were included in study. Non febrile patients and patients referred for malaria test who did not give their consent to participate in the study were excluded.

Sample collection

A total of 340 serum samples were collected from febrile patients. About 5ml of blood was collected by venipuncture. The blood was allowed to clot at room temperature and the serum was carefully collected after centrifugation at 2,000 rpm for 10 minutes and stored at –4ºC for further analysis.

Detection of dengue virus IgM and determination of risk factors associated with dengue virus infection

An IgM capture ELISA (MAC–ELISA) as previously described by Vorndam and Kuno (1977) was used for dengue virus IgM detection. A set of standard questionnaire was used to collect demographic data, clinical history and dengue risk factors. The questionnaires were divided into three sections. Section A required demographic such as age, gender, highest educational level attained, marital status and occupation from the patients. Section B required some clinical data such as symptoms of fever, headache, muscle and joint pains, cold, abdominal discomfort, diarrhoea, vomiting and rash. Section C attempted to uncover the exposure of the patients to risk factors such as use of mosquito nets, use of insecticides, presence of gutters or bushes close to residential area, sleeping in the afternoon, leaving of doors open in the early mornings and evenings, frequency of anti-malaria drug use and current use of anti-malaria drug predisposing to

dengue virus infection. The questionnaire was administered using the discussion method during which the researcher asks the patients questions contained in the questionnaire and thick as appropriate. The information gathered was recorded.

Results and Discussion

Prevalence of dengue virus

Figure 1 presents the prevalence of dengue virus IgM in the study population. Out of the 340 samples studied, 6 (1.8%) patients were sero-positive for dengue virus IgM and 334 samples (98.2%) were sero-negative for dengue virus. Although, the prevalence of dengue virus IgM obtained in this study was quite low, it has brought to lime light the occurrence of the virus within Kaduna metropolis, Nigeria. A positive case of dengue virus in a community is epidemiologic importance as mosquitoes can transmit the virus from an infected person to a high proportion of susceptible individuals within the same environment. The result of this study is in line with previous studies by Dawurung *et al.* (2010) with a prevalence of 2.2% and Baba *et al.* (2009) with prevalence of 0.67%.

Relationship between occurrence of dengue virus IgM and potential risk factors

The relationships between some potential risk factors and the occurrence of dengue virus IgM in the study population are presented in Table 1. The risk factors considered including the use of mosquito bed net, the use of insecticides, presence of gutters or bush around house, sleeping in the afternoon, and the use of insecticide/bed net in the afternoon. There was no significant association between the presence of these factors and the occurrence of dengue virus IgM ($p>0.05$). However, odds ratio analysis shows that those who did not use mosquito bed nets at night are at 1.275 times more likely to be infected with dengue virus than those who use. Patients with gutters and/or bush close to their residential areas are 1.3 times likely to get dengue virus infection (Table 1). The relationship between the occurrence of the dengue virus IgM and risk factors was not significant as their p-values were greater than 0.05. This could be due to the fact that the total number of the study samples infected with dengue virus was quite small.

Table 1. Relationship between the occurrence of dengue virus IgM and potential risk factors

	Dengue virus IgM					
Risk factors	Total	Positive(%)	Negative(%)	p-value	OR	CI 95%
Use of mosquito net						
No	208	4(1.9)	204(98.1)	0.781	1.275	0.230-7.058
Yes	132	2(1.5)	130(98.5)			
Use of insecticides						
No	120	2(1.7)	118(98.3)	0.919	0.951	0.165-5.071
Yes	220	4(1.8)	216(98.2)			
Gutters/bush around house						
Yes	205	4(2.0)	201(98.0)	0.748	1.323	0.239-7.328
No	135	2(1.5)	133(98.5)			
Sleep in the afternoon						
Yes	245	4(1.6)	241(98.4)	0.766	0.772	0.139-4.285
No	95	2(2.1)	93(97.9)			
Use of insecticides in the afternoon						
No	218	3(1.4)	215(98.6)	0.368	0.363	0.036-3.617
Yes	27	1(3.7)	26(96.3)			

Note**:** OR = odds ratio, CI = Confidence interval

Primary protection against infection with dengue virus depends on the control of mosquitoes (Mahyoub *et al.*, 2013). Such control measures include the use of insecticide treated mosquito bed nets, spraying of insecticides and other measures to reduce the reproduction and multiplication of mosquito vectors of disease and reduce their number in the environment to the

extent that they do not spread disease (WHO, 1990). In Africa, *Aedes aegypti* breeds primarily in natural containers such as trees, holes and leaf axils and artificial containers (Rozendaal, 1997). Therefore, the need for effective environmental management cannot be overemphasized. Insecticide treated bed nets can be effectively used to protect infants and night workers while sleeping in day time since the vector specie bite during the day time, early morning or late afternoon.

Relationship between the occurrence of dengue Virus IgM and demographic factors

The relationship between the occurrence of dengue virus IgM and demographic factors are presented in Tables 2 to 4. The demographic factors considered including age, gender, highest educational level attained, marital status, and occupation. There was no significant association between the occurrence of dengue virus IgM and these demographic factors ($p>0.05$). However, odds ration analysis shows that, age group 41-50 was 1.605 times more likely of having dengue virus IgM than other age groups (Table 3). Females were 2.877 times more likely to have dengue virus IgM positive than males. Considering highest educational level attained, patients with primary education were at 2.430 times more likely to have dengue virus IgM positive compared with those with other levels of education (Table 4.). According to marital status, those who were married had the likelihood of 2.048 times of being dengue cases than those who were single and widowed (Table 4).

The relationship between the occurrence of dengue virus IgM and occupation was not significant (Chi-square = 3.081 and p = 0.379) (Table 4). Dengue infection is not peculiar to any age group or sex (Dawurung *et al.*, 2010) indicating that everyone is at risk of contracting the disease. However, with regards to gender distribution, the prevalence of dengue virus IgM in females (2.3%) was higher than that of males (0.8%) and odds ratio analysis shows that females were 3 times more likely to come down with dengue virus infection than males. This could be due to the fact that *Aedes sp* breeds in human dwelling and surroundings and women are more likely to remain in and around the home, carrying out domestic activities during the day when the mosquitoes are most active, feeding indoors and outdoors. This agrees with previous research by Shu-yuan, (2007), Dawurung *et al.* (2010), and Idris *et al.* (2010). With regards to highest educational level attained, those with tertiary education had the least percentage occurrence of dengue virus IgM (0.0%). Dengue transmission by *Aedes aegypti* has been associated with poor hygienic conditions, which in turn may be associated with low socio economic levels and to low schooling of the house dwellers (Rodriguez-Figueroa *et al.*, 1995). In Kenya, the use of insecticide-impregnated bed nets was significantly related to mother's educational level (Marsh *et al.*, 1996).

Table 2. Relationship between the occurrence of dengue virus IgM and demographic factors (age and gender)

Demographic Factors	Dengue virus IgM					
	Total	Positive (%)	Negative (%)	P-value	OR	C.I.
Age						
1 – 10	66	1(1.5)	65(98.5)	0.864	0.828	0.095-7.206
Others	274	5(1.8)	269(98.2)			
11 – 20	56	1(1.8)	55(98.2)	0.990	1.015	0.116-8.854
Others	284	5(1.8)	279(98.2)			
21 – 30	87	1(1.1)	86(98.9)	0.613	0.577	0.066-5.006
Others	253	5(2.0)	248(98.0)			
31 – 40	54	1(1.9)	53(98.1)	0.958	1.060	0.121-9.259
Others	286	5(1.7)	281(98.3)			
41 – 50	38	1(2.6)	37(97.4)	0.667	1.605	0.183-14.118
Others	302	5(1.7)	297(98.3)			
>50	39	1(2.6)	38(97.4)	0.687	1.558	0.177-13.691
Others	301	5(1.7)	296(98.3)			
Gender						
Female	217	5(2.3)	212(97.7)	0.316	2.877	0.332-24.914
Male	123	1(0.8)	122(99.2)			

Note: OR = odds ratio, C.I. = Confidence interval

Table 3. Relationship between the occurrence of dengue virus IgM and some demographic factors (educational level and marital status)

Demographic factors	Dengue virus IgM					
	Total	Positive(%)	Negative(%)	p-value	OR	CI 95%
Educational level						
Tertiary	65	0(0.0)	65(100.0)	0.230		
Others	275	6(2.2)	269(97.8)			
Secondary	105	2(1.9)	103(98.1)	0.896	1.121	0.202-6.220
Others	235	4(1.7)	231(98.3)			
Primary	59	2(3.4)	57(96.6)	0.297	2.430	0.435-13.585
Others	281	4(1.4)	277(98.6)			
Quranic	55	1(1.8)	54(98.2)	0.974	1.037	0.119-9.053
Others	285	5(1.8)	280(98.2)			
Informal	56	1(1.8)	55(98.2)	0.990	1.015	0.116-8.854
Others	284	5(1.8)	279(98.2)			
Marital Status						
Single	163	2(1.2)	161(98.8)	0.470	0.537	0.097-2.973
Others	177	4(2.3)	173(97.7)			
Married	169	4(2.4)	165(97.6)	0.402	2.048	0.370-11.336
Others	171	2(1.2)	169(98.8)			
Widowed	8	0(0.0)	8(100.0)	0.701		
Others	332	6(1.8)	326(98.2)			

Note: OR = odds ratio, CI = Confidence interval

Table 4. Relationship between the occurrence of dengue virus IgM and occupation

Demographic factor	Dengue virus IgM				
	Total	Positive(%)	Negative(%)	Chi-square	P-value
Occupation					
Civil servant	29	0(0.0)	29(100.0)		
Self employed	32	0(0.0)	32(100.0)		
Military	53	0(0.0)	53(100.0)		
Others	226	6(2.7)	220(97.3)	3.081	0.379

Occurrence of dengue virus in relation to some symptoms

The relationships between the occurrence of dengue virus IgM and some symptoms were also assessed. The symptoms include fever, headache, muscle and joint pains, cold, abdominal discomfort, diarrhoea, vomiting and rash. The association between the occurrence of dengue virus IgM and the presence of these symptoms in the study population was not significant ($p>0.05$). However, odds ratio analysis revealed that the 253 patients with fever were at 1.743 odds of having dengue virus IgM than those without fever. One hundred and seventy seven patients with abdominal discomfort were at 1.861 odds of being dengue cases than those who did not have abdominal discomfort. The 55 patients with diarrhoea were 2.651 times more likely to be dengue cases than those who do not have diarrhoea (Table 5). People with fever, diarrhoea and abdominal discomfort had higher percentage occurrences of dengue virus IgM positive and were more likely to have dengue virus IgM than those who did not display these symptoms. Similar clinical manifestations have been reported in different studies (Ayyub *et al.*, 2006; Shahin *et al.*, 2009). This is of immense public health importance because people who present with these symptoms at clinics and hospitals are presumably treated for malaria especially in malaria endemic country like Nigeria (FMH, 2001).

Table 5. Occurrence of dengue virus IgM in relation to some symptoms

	Dengue virus IgM					
Symptoms	Total	Positive(%)	Negative(%)	p-value	OR	CI 95%
Fever						
Yes	253	5(2.0)	248(98.0)	0.613	1.743	0.200-15.050
No	87	1(1.1)	86(98.9)			
Headache						
Yes	241	4(1.7)	237(98.3)	0.819	0.819	0.147-4.543
No	99	2(2.0)	97(98.0)			
Muscle and joint pains						
Yes	220	4(1.8)	216(98.2)	0.919	1.093	0.197-6.054
No	120	2(1.7)	118(98.3)			
Cold						
Yes	142	1(0.7)	141(99.3)	0.208	0.274	0.032-2.369
No	198	5(2.5)	193(97.5)			
Abdominal discomfort						
Yes	177	4(2.3)	173(97.7)	0.470	1.861	0.336-10.300
No	163	2(1.2)	161(98.8)			
Diarrhoea						
Yes	55	2(3.6)	53(3.6)	0.250	2.651	0.473-14.842
No	285	4(1.4)	281(98.6)			
Vomiting						
Yes	74	1(1.4)	73(98.6)	0.760	0.715	0.082-6.217
No	266	5(1.9)	261(98.1			
Rash						
Yes	7	0(0.0)	7(100.0)	0.720		
No	333	6(1.8)	327(98.2)			

Note: OR = odds ratio, CI = Confidence interval

Conclusions

In this study, the occurrence of dengue virus in the study population has been confirmed. Therefore, as the clinical symptoms associated with dengue virus infection are indistinguishable from many other febrile illnesses such as malaria, typhoid, and other virus diseases; therefore, specific diagnostic tests assume critical importance in the identification of febrile illnesses within the study area.

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