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Research Article

Relationship Between Serum IgM Levels and Liver Function in Rubella and Measles Infection of Children Below Five Years in Nairobi County

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Abstract: Rubella and measles virus are two important diseases of children under 5 years of age and immunization is the main method of prevention of these diseases. Despite intervention through immunization, outbreaks of rubella and measles virus in Kenya are still reported in children. The main objective of current study was to investigate the correlation of liver function test and IgM assay, in measles and rubella viruses' infections in children under age of five years in Nairobi County. The study involved 235 subjects and was carried out at Kenyatta National Hospital, Mbagathi District Hospital and Mama Lucy Kibaki Hospital. Out of the 235 study subject who were qualitatively tested for both measles and rubella using IgM assay, only 3 (1.28%) were positive for measles and 5 (2.13%) positive for rubella. Liver function tests were analyzed for all the 235 study subjects. Among the liver function parameters, total protein and albumin showed a very strong negative correlation ($r = -0.932$ and $r = -1.000$ respectively) with measles IgM concentration; this was statistically significant at $p = 0.035$ and $p = 0.007$ respectively. Positive correlation was shown between measles IgM concentration and AST ($r = 0.247$), ALT ($r = 0.637$), ALP ($r = 0.935$), TBILI ($r = 0.719$) and DBILI ($r = 0.654$). This positive correlation was statistically significant for AST ($p = 0.032$) and ALT ($p = 0.021$). TP, ALB, ALP, TBILI and DBILI showed a negative correlation ($r = -0.316$, $r = -0.872$, $r = -0.804$, $r = -0.550$ and $r = -0.404$ respectively) with rubella IgM concentration which was statistically significant for TP and ALB at $p = 0.015$ and $p = 0.031$ respectively. Positive correlation was shown between rubella IgM concentration and AST ($r = 0.333$) and ALT ($r = 0.360$). This positive correlation was statistically significant for AST ($p = 0.044$) and ALT ($p = 0.028$). The study has established that the 2 diseases still affect children below the age of 5 years in Nairobi County. The metabolic and excretion functions of the liver for the studied population were affected by these viral infections as expressed by an increase in the mean levels of transaminases (AST = 206 iu/L, ALT = 202 iu/L) and bilirubin (TBILI = 43 µmol/L and DBILI = 30 µmol/L) in blood. Similar studies should be undertaken in all the counties in Kenya to establish the status of rubella and measles in children <5 years of age. Liver function tests should be included during the baseline study of the suspected cases of rubella or measles infection.

Keywords: Children <5 years, IgM, liver function test, measles, Nairobi, rubella

INTRODUCTION

Measles is highly contagious and can result in complications that include encephalitis, otitis media, blindness, pneumonia and diarrhea. Mortality is normally high in children with malnutrition particularly in developing countries including Kenya (WHO, 2009). On the other hand; rubella infection causes a relatively mild disease in children. The highly effective, safe and relatively inexpensive measles and rubella vaccines, protect individuals from infection and their widespread use can completely stop the spread of the viruses in populations and achieve and maintain high levels of immunity. From the reports of WHO some years back (WHO, 2000), it was estimated that 535,000 children died of measles, the majority in developing countries and this burden accounted for 5% of all under-5 mortalities. Laboratory confirmation of acute infection revealed more cases of rubella virus infection rather than measles (WHO, 2000). Rubella infection has been identified as a leading cause of birth defects commonly known as Congenital Rubella Syndrome (CRS). In the United States of America rubella virus was a common disease that occurred primarily among young children of 6-9 years until the live attenuated rubella vaccine was licensed (WHO, 2000). Introduction of the vaccine

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has helped to eradicate rubella virus and prevent its congenital infections (Huang *et al*., 2013). In this outbreak, rubella was detected using the case-based measles surveillance system. The number of confirmed rubella cases was 473 in 2010, 604 in 2011, 300 in 2012, 336 in 2013 and 646 in 2014 (LeBaron *et al*., 2009).

In developing countries, approximately 10-30% of measles cases require hospitalization and one in a thousand of these cases among children results in death from measles complications. Improving measles vaccination coverage and reducing measles-related deaths is a global imperative, particularly as it relates to the United Nation's Sustainable Development Goal 3 (SDG 3) that aims, to ensure healthy lives and promote wellbeing for all at all ages. The United Nations took the initiative to have measles and rubella routine vaccination to reduce child mortality. The infectiousness of measles and rubella easily leads to global spread and even countries that eliminated their indigenous transmission remain vulnerable to outbreaks. Despite having routine vaccination programmes, measles and rubella viruses continue to cause infections in susceptible persons brought about by low immunization coverage in some countries. Rubella vaccine is not given in most African countries (Hickman *et al*., 2011).

The current study aims at establishing the status of these two viral infections affecting children below the age of five years in the metropolitan county of Nairobi. On the other hand the study also aims at investigating the effect of these viral infections on liver functions.

MATERIALS AND METHODS

The study was carried out among children attending maternal child health clinic at Kenyatta National Hospital, Mbagathi District Hospital and Mama Lucy Kibaki Hospital. Clinical examination and recruitment of study subjects was done by the physician in each institution. The analytical work was done in Kenyatta National Hospital diagnostic laboratories. The design used was a cross sectional descriptive laboratory based study. IgM antibodies and liver function parameters were determined in blood of children suspected to have measles or rubella infection. The study population were children under 5 years of age brought to the maternal child healthcare clinics at Kenyatta National Hospital, Mbagathi Hospital and Mama Lucy Kibaki hospital to seek and receive various medical procedures.

The study included all children who presented at the study site with manifesting symptoms and signs consistent with infection of the measles or rubella viruses. The study excluded children who did not present with clinical symptoms of measles or rubella. Guardians/parents who accompanied the children to hospital were explained about the study and requested to give consent for the blood to be withdrawn from the children. The physician clinically examined the children for symptoms consistent with rubella and measles infection. The symptoms included the following: Fever, malaise, sneezing, rhinitis, congestion, conjunctivitis and cough and Koplik's spots (Barreto *et al*., 2006).

The investigator who is a qualified medical personell in the hospitals collected blood specimen from all children who met the inclusion criteria in the first appearance within the study period. The upper arm was tied with a tourniquet to locate a vein. A methylated spirit swab was used to sterilize the site for blood collection. A butterfly needle connected to a 5 mls syringe was used to draw blood from the vein. Approximately 3 mls of blood was drawn from each study subject. The needle was disconnected from the syringe and the blood put into a plain vacuitainer tube labelled with the study subject identification number.

Blood specimen was transported in a cool box and delivered to the laboratory. Clotted blood specimen in the plain vacuitainer were placed in the centrifuge buckets and then centrifuged at 3000 rpm for 3 min to separate the serum. (Tuck *et al*., 2009). The serum was harvested using pastuer pipettes and divided into two equal aliquots for IgM and liver function tests respectively. These serum specimens were stored at 4-8°C until the day of analysis. Analysis of the tests were done within 7 days after specimen collection. Quantitative analytical work included prepared internal quality control specimen and the analysis of the study subject specimen proceeded once the internal quality control target value had been attained for accuracy and precision.

The study subjects serum was used for the analysis of liver function parameters i.e., Total Protein (TP), Albumin (ALB), Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), Total Bilirubin (TBILI) and Direct Bilirubin (DBILI). The IgM immunological analysis was carried out to qualitatively determine the presence or absence of rubella and measles. IgM quantitative determination was carried out on the specimens that were positive for either rubella or measles.

The Enzygnost ®Anti measles virus/IgM immunoassay diagnostic kit (Dade Behring: Germany) and Enzygnost ®Anti Rubella virus/IgM immunoassay diagnostic kit (Dade Behring: Germany for qualitative detection and quantitative determination of IgM antibodies to measles/rubella virus in human serum and plasma was used for serological assay of Measles/Rubella IgM antibodies.

RESULTS

The study population had 235 study subjects comprising of 128 (54%) females and 107 (46%) males. The mean age of the study subject was 2.5 years. The

Table 1: Internal Quality Control (IQC) for the studied parameters of measles and rubella study in Kenya

	Assigned QC report			Study QC report
Parameter (unit)	Session	QC range	Mean	Mean
IgM (µiu/mL)	5	0.57-1.93	1.25	1.04
TP (g/L)	27	63.00-77.00	70.00	71.00
ALB (g/L)	27	41.00-49.00	45.00	42.00
AST (iu/L)	27	21.00-31.00	26.00	24.00
ALT (iu/L)	27	19.00-31.00	25.00	25.00
ALP (iu/L)	27	78.00-110.00	94.00	101.00
TBILI (µmol/L)	27	14.00-28.00	21.00	23.00
DBILI (µmol/L)	27	7.00-17.00	12.00	13.00

Table 2: Status of measles and rubella in children under 5 years of age in Nairobi

Virus	Number	Mean absorbance	Mean concentration (µiu/mL)	S.D.	Results
Measles	232	0.0715	-	0.056	Negative
	3	0.4130	921	473.000	Positive
Rubella	230	0.0703	-	0.059	Negative
	5	0.3190	1470	1271.000	Positive

S.D.: Standard deviation

distribution of the study subject within the study sites were 184, 29 and 22 from Kenyatta National Hospital, Mbagathi District hospital and Mama Lucy Kibaki Hospital respectively. This was categorized into two i.e., qualitative and quantitative, based on the analytical procedure carried out. The daily internal quality control for the qualitative analytical procedure for IgM was carried out using a positive and negative control. According to the classification of the reagent kit, a negative results was indicated if the absorbance was <0.1 and positive result if the absorbance was >0.2. Any absorbance value between 0.1 and 0.2 was indicated as discordant. The qualitative internal quality control results were achieved through the conversion of the absorbance into quantitative results as per the specification of the reagent kits for both measles and rubella. The quality control results are as indicated in Table 1.

The Internal Quality Control multi-sera was used to determine the session quality control results for the specific parameters that constitute the Liver Function Tests i.e., total protein, albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, total bilirubin and direct bilirubin. The Internal quality control results are as indicated in Table 1.

The session indicates how many times the analysis was carried during the analytical period of the study for both qualitative and quantitative analytical procedures. The immunological analysis was carried out in five sessions whilst the end point and UV enzymatic kinetic reaction analysis was carried out in 27 sessions as indicated in Table 1.

The assigned quality control result is what is indicated in the reagent kit against which the session internal quality control results are compared with. The study quality control results for the analyzed parameters were within the specified assigned QC range of mean ±2 Standard Deviations (SD) (QC range) as shown in Table 1.

Out of the 235 study subject who were qualitatively tested for both measles and rubella, only 3 (1.28%) were positive for measles and 5 (2.13%) positive for rubella. Three study subjects who were positive for measles came from Kenyatta National Hospital. Five Rubella positive cases were distributed as follows: two from Kenyatta National Hospital, two from Mama Lucy Kibaki Referral Hospital and one from Mbagathi District hospital. Positive results were those whose corrected absorbance was >0.2 whilst negative results were those whose corrected absorbance was <0.1. The mean corrected absorbance for the measles and rubella positive cases were 0.413 and 0.526 respectively as shown in Table 2. Two hundred and thirty-two and 230 subjects reacted negative for both measles and rubella with corrected mean absorbance of 0.0715 and 0.0703 respectively, as shown in Table 2.

Liver function tests were normal in 225 out of the 237 study subjects. The mean values for TP, ALB, AST, ALT, ALP, TBILI and DBILI were 65.4 g/L, 40 g/L, 18 iu/L, 28 iu/L, 253 iu/L, 13 µmol/L and 5 µmol/L, respectively (Table 3). The means value for the TP, ALB, AST, ALT, ALP, TBILI and DBILI for the eight study subjects who were positive for measles and rubella infection were; 67 g/L, 30 g/L, 206 iu/L, 202 iu/L, 246 iu/L, 43 µmol/L and 30 µmol/L, respectively (Table 3).

The means value for TP, ALB, AST, ALT, ALP, TBILI and DBILI for the 4 out of 225 study subjects who were negative for measles and rubella infection but had abnormal liver function tests results were; 80 g/L, 30 g/L, 295 iu/L, 282 iu/L, 263 iu/L, 18 µmol/L and 4 µmol/L respectively as shown in Table 3.

In order to determine the clinic-pathological effects of measles and rubella infection on liver function, results of study subjects who were negative for measles and rubella infection (n = 225) were statistically compared with those infected (n = 8) by the two diseases using paired samples t test. The mean levels of TP, ALB, ALP, TBILI and DBILI in measles and

Table 3: Clinic-pathological effects of measles and rubella infections in children under 5 years of age in Nairobi

Parameters	Number	TP (g/L)	ALB (g/L)	AST (iu/L)
Subjects without measles and rubella infection	225	65	40	18
Subjects with measles and rubella infection	8	67	30	206
Subjects with abnormal LFTS results without measles and rubella	4	80	30	295
Parameters	ALT (iu/L)	ALP (iu/L)	TBILI (µmol/L)	DBILI (µmol/L)
Subjects without measles and rubella infection	28	253	13	5
Subjects with measles and rubella infection	202	246	43	30
Subjects with abnormal LFTS results without measles and rubella	282	263	18	4

Table 4: Statistical comparison of liver function tests for the study subject infected and those not infected with measles and rubella

		Paired differences							
					95% confidence interval of the difference				
Study groups compared parameters		Mean	S.D.	S.E.M.	Lower	Upper	t	df	Sig. (2-tailed)
Pair 1	ntp-aftp	-8.28	21.27	8.04	-27.96	11.38	-1.03	6	0.343
Pair 2	nalb-afalb	-4.00	7.39	2.79	-10.83	2.83	-1.43	6	0.202
Pair 3	nast-afast	-189.42	92.06	34.79	-274.57	-104.28	-5.44	6	0.002
Pair 4	nalt-afalt	-159.85	152.69	57.71	-301.07	-18.63	-2.77	6	0.032
Pair 5	nalp-afalp	16.42	213.44	80.67	-180.97	213.83	0.20	6	0.845
Pair 6	ntbili-aftbili	-30.28	63.97	24.17	-89.44	28.87	-1.25	6	0.257
Pair 7	ndbili-afdbili	-29.71	59.39	22.44	-84.64	25.21	-1.32	6	0.234

n: Normal; af: Affected; df: Degree of freedom; S.D.: Standard deviation; S.E.M.: Standard error of mean; t: t-value

Table 5: Correlation between the liver function parameters and IgM serum concentration for measles and rubella

Pearson correlation statistics		TP	ALB	AST	ALT	ALP	TBILI	DBILI
Measles conc	Pearson correlation	-0.932	-1.000	0.247	0.637	0.935	0.719	0.654
	Sig. (2-tailed)	0.035	0.007	0.032	0.021	0.231	0.489	0.546
	N	3.000	3.000	3.000	3.000	3.000	3.000	3.000
Rubella conc	Pearson correlation	-0.316	-0.872	0.333	0.360	-0.804	-0.550	-0.404
	Sig. (2-tailed)	0.015	0.031	0.044	0.028	0.101	0.337	0.500
	N	5.000	5.000	5.000	5.000	5.000	5.000	5.000

N: Number; conc: Concentration; Sig.: Significance

rubella infected and non-infected subjects were not significantly different ($p = 0.343$, $p = 0.202$, $p = 0.845$, $p = 0.257$ and $p = 0.234$, respectively). The means difference of AST and ALT for the infected and non-infected study subject was statistically significant ($p = 0.002$ and $p = 0.032$ respectively) as shown in Table 4.

The correlation of liver function parameters and IgM serum concentration for measles and rubella infected study subjects is summarized in Table 5 above. Total protein and albumin showed a very strong negative correlation ($r = -0.932$ and $r = -1.000$ respectively) with measles IgM concentration which was statistically significant at $p = 0.035$ and $p = 0.07$ respectively. Positive correlation was shown between measles IgM concentration and AST ($r = 0.247$), ALT ($r = 0.637$), ALP ($r = 0.935$), TBILI ($r = 0.719$) and DBILI ($r = 0.654$). This positive correlation was statistically significant for AST ($p = 0.032$) and ALT ($p = 0.021$).

TP, ALB, ALP, TBILI and DBILI showed a negative correlation ($r = -0.316$, $r = -0.872$, $r = -0.804$, $r = -0.550$ and $r = -0.404$, respectively) with rubella IgM concentration which was statistically significant for TP and ALB at $p = 0.015$ and $p = 0.031$ respectively. Positive correlation was shown between rubella IgM concentration and AST ($r = 0.333$) and ALT ($r = 0.360$). This positive correlation was statistically significant for AST ($p = 0.044$) and ALT ($p = 0.028$).

DISCUSSION

Results of this study findings show that there were more children infected with rubella 5 (2.13%) than measles 3 (1.28%) in the study sites. These results represent the point prevalence of rubella and measles for the studied population. Although the results indicate a relatively low prevalence of the 2 diseases in the 2 hospitals, it is implied from this study that the 2 diseases do occur and should be considered in diseases control program, among the other important diseases that cause adverse effects on health status of the children. The low infection could be attributed to improved immunization programmes in Kenya as opposed to other regions quoted in literature. The findings of the current study presented low rate of rubella infection compared with other regions across Africa. A similar study carried out in North Western Nigeria produced a rubella infection rate of 2.6% which was in agreement with the findings of the current study (Omoleke and Udenenwu, 2016). A higher rate (12%) of rubella infection was reported in a study carried out in a neighbouring country (Ethiopia) in which the study population was in children below the age of 15 years (Etsehiwot, 2015). Low rubella infection rate of 1.3% was produced by a study carried out in Namibia involving children below 5 years of age (Emmy, 2015).

Several studies have been reported in literature concentrating on measles infection of children below 5

years of age (Ndode, 2015). Comparatively, the rate of measles infection expressed in the current study (1.28%) is lower than what has been expressed in other studies carried in other regions of Africa. A similar study carried out in Ghana expressed an infection rate of 6.9%, which was far much higher than what was expressed in the current study (Binka *et al*., 2007). In 2014, a relatively higher prevalence (2%) of measles in children under 5 years of age was reported in Nigeria (Duru *et al*., 2014).

In the present study measles and rubella virus were found to causean elevation of liver enzymes namely; Alanine Transferase (ALT), Aspartate Aminotransferase (AST) and Alkaline Phosphatase (ALP). Two hundred and twenty-five study subjects (94%) had normal liver function tests. Four study subjects who were negative for measles and rubella infection had elevated liver enzymes namely; Alanine Transferase (ALT), Alkaline Phosphatase (ALP), Aspartate Aminotransferase (AST). This suggests that there were other factors that caused elevation of liver enzyme in the children included in the study. Our results agree with those of Satoh *et al*. (2008), who also found that the transaminases were elevated in children who were negative for the studied viruses. Another study carried out in France was also in agreement with the findings of the current study that measles adversely affect the functions of the liver (Dinh *et al*., 2013). The findings of these three studies strongly suggests that the studied viruses affect the metabolic function of the liver that take place in the intracellular fluid of the hepatocytes. The appearance of elevated levels of the transaminases in the extracellular fluid further suggests that the viruses compromise the integrity of the cell membrane. Other studies have shown the effect of these diseases on liver function characterized by elevation of the liver transaminases (Premaratna *et al*., 2017; Minemura *et al*., 2014; Fisher *et al*., 2015).

The current study showed that the diseases cause hyperbilubinaemia. This implies a compromised bile excretion by the hepatocytes. Lambert (2007) reported similar findings of hyperbilubinaemia in children below five years infected by measles and rubella viruses. Our study did not show any effect of the viruses on the concentration of total protein and albumin among the study subject. There was no significance difference in total protein ($p = 0.343$) and albumin ($p = 0.202$) concentration of the study subjects found to have rubella and measles when compared statistically with those children who were negative for both viruses.

The study showed a positive correlation between some liver function tests and concentration of IgM for the infected subjects. The presence of rubella or measles infection automatically increases the concentration of IgM in the blood of the affected children. The severity of the disorders is consistent with an increase in the blood IgM concentration (Gastañaduy *et al*., 2016). Total protein and albumin of the study subjects who turned positive for measles showed a very strong negative correlation with measles IgM concentration which was statistically significant suggesting that a rise in IgM does not affect the concentration of proteins of the children with measles infection. The observed strong negative correlation between proteins and IgM blood concentration is in agreement with studies carried out by Sternfeld *et al*. (2010).

Significant positive correlation was established between the transaminases and IgM concentration in measles and rubella infections. It can therefore be stated that the severity of the studied viral infections results in an increase in the blood concentration of the IgM and consequently an increase in the concentration of the transaminases. Satoh *et al*. (2008), also found that all their study subjects who reacted positive for measles infection, showed an elevation of Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST). Similarly results of positive correlation between the IgM concentration and transaminases have been expressed in a study by Minemura *et al*. (2014). Elevated levels of total and direct bilirubin showed a positive correlation in both infections, but this was not statistically significant. This means therefore that hyperbilirubinaemia has no direct effect on the concentration of IgM.

CONCLUSION

The study has established that measles and rubella still affect children below the age of 5 years in Nairobi County. The rate of infection is low for the 2 diseases but there occurrence should not be ignored and they should be emphasized in disease control programmes. The metabolic and excretion functions of the liver for the studied population are affected by these viral infections as expressed by the elevated levels of transaminases and bilirubin blood levels concentrations. The two disorders have not been seen to affect the synthesis function of the liver for the studied children population since the proteins concentrations in blood are within the reference ranges quoted in literature. The current study showed that the studied viruses also compromise the excretory function of the hepatocytes which is expressed by hyperbilubinaemia of the blood specimens of the study subjects. Due to the significant positive correlation between the transaminases and the IgM concentration in the studied viral infection, it can be concluded that rubella and measles infection have an adverse effect on the metabolic activities of the hepatocytes of the studied population.

RECOMMENDATIONS

Similar studies to be under taken in all the counties in Kenya to establish the status of rubella and measles

in children below 5 years of age. Any child who present with signs and symptoms of measles or rubella should be investigated to avoid the spread of the virus. Liver function test should be included during the baseline study of the suspected cases of rubella or measles infection. It should also form part of the investigation to determine the prognosis of the positive cases of both viral infections.

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