Congenital rubella syndrome: pattern and presentation in a southern Nigerian tertiary hospital

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Background: **Congenital rubella syndrome (CRS) resulting from maternal rubella infection can result in miscarriages, still birth and rubella infection of the infant. The aim of this study was to evaluate the pattern and presentation of CRS over an 8-year period as seen in the University of Port-Harcourt Teaching Hospital (UPTH), Nigeria.**

Methods: **The medical records of all cases of CRS presenting to the Pediatric Department of UPTH from January 2000 to December 2007 were reviewed.**

Results: **There were 16 394 babies delivered in UPTH from January 2000 to December 2007. Of these babies, 19 were clinically diagnosed as having CRS, but none had laboratory confirmation. They had a mean age of 5.1 ±3.2 months (range: 1-11 months). Seventy-five percent of their mothers had presumed rubella infection during the first trimester of pregnancy. Cataract was noticed to be the most prominent systemic manifestation in 18 of the 19 babies. Other common manifestations included hearing impairment (n=14), microcephaly (n=13), patent ductus arteriosus (n=11), and low birth weight (n=10). A surge was observed in the number of babies with CRS from 2004 to 2007; however, this was not statistically significant (χ^2=8.68, P=0.28). Unfortunately, long-term outcome of the 19 babies was not available.**

Conclusion: **CRS is commonly diagnosed at our center. Thus, mounting effective surveillance for CRS and considering the inclusion of rubella vaccine in Nigeria are of extreme importance.**

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Key words: **congenital rubella syndrome; maternal infection; national program on immunization**

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Introduction

Congenital rubella syndrome (CRS) resulting from maternal rubella infection, especially in the first trimester, affects an estimated 100 000 infants each year worldwide.[1] Immunization has reduced its occurrence in the developed world, though it remains a problem in countries with poor immunization coverage like Nigeria. It is a major global cause of preventable hearing impairment and blindness.[2,3] Since rubella vaccine was licensed, the World Health Organization Expanded Program on Immunization has not made global recommendations regarding rubella vaccination.[4-6] However, recent WHO recommendations encourage all countries not routinely immunizing against rubella to quantify the burden of disease due to CRS and to consider universal rubella vaccination in children and ensure immunity of women of childbearing age.[6-8] Also, it is recommended that countries undertaking measles elimination with greater than 80% of measles immunization coverage should take the opportunity to eliminate rubella as well through use of measles-rubella or measles mumps-rubella vaccine in their childhood immunization program.[6]

In 2007, the WHO reported that 123 countries had national rubella vaccination program.[9] The vaccine is available only in the private sector in some countries.[10] The problem with this is that the prevalence of CRS can be increased with only partial immunization coverage by shifting disease to adulthood.[11] No country in sub-Saharan Africa has included rubella vaccines in their national immunization program[10] and rubella serology which is essential for reliable rubella surveillance is not available in most countries of sub-Saharan Africa.[12] Data on CRS in Africa are very limited as only small numbers of clinically diagnosed cases have been reported.[12] The largest reported CRS case series followed simultaneous epidemics of rubella and measles in Harare, Zimbabwe after an influx of

refugees in the 1970s.[13] In Nigeria, routine screening of antenatal women for rubella immunity is not available. Nigeria does not include rubella immunization in the national program on immunization even though measles immunization is routinely administered to infants from 9 months of age. It is important to routinely screen mothers for rubella antibodies during prenatal care, which will prevent rubella in subsequent pregnancies and is also essential for the control and elimination of CRS.

This study aimed to evaluate retrospectively the pattern and systemic manifestations of CRS in the University of Port-Harcourt Teaching Hospital (UPTH) and to discuss the necessity to include rubella vaccine in the national program on immunization.

Methods

This retrospective study surveyed medical records of children who were seen at the Pediatric Department of UPTH, Nigeria from January 2000 to December 2007. The teaching hospital is the only tertiary hospital located in the metropolis of Port Harcourt, the capital of Rivers State, one of the Niger Delta states in Nigeria. It is the nerve center of the famous Nigerian oil industry with a population of 5 689 087 and an area of 21 850 km^2. It has a population of about 541 115.[14] The hospital serves as a general/referral center for neighboring states. The babies in this study were delivered in this hospital. The presence of maculopapular body rashes which disappeared on the third day were considered to be suggestive of rubella rash in the mothers. Information on maternal rash was obtained from the case notes of the babies. There was no evidence of exclusion of CRS-like syndrome (cytomegalovirus/toxoplasmosis infection) from the case notes.

CRS was classified as clinically confirmed or probable according to the following case definitions.[15] Clinically confirmed CRS case: an infant with either 2 major criteria, e.g., congenital cataract, congenital heart disease, auditory impairment, or 1 major criterion and 1 minor criterion, e.g., hepatomegaly, microcephaly, severe developmental delay, failure to thrive (weight for age below the third percentile, and thrombocytopenia ($<150\times10^9$/L). Probable CRS case: an infant with heart disease, suspected hearing impairment, or at least one eye sign consistent with a diagnosis of CRS (cataracts, microphthalmos, congenital glaucoma). The CRS cases were identified by retrospective chart review. Distraction testing (head turn to sound) was applied in all the babies with hearing impairment.

Data were analyzed using SPSS version 14. The Chi-square test was used to test the relationship between variables. $P<0.05$ was considered statistically significant.

Table 1. Time of appearance of body rashes in the mother

Time of appearance of rash/fever (weeks of gestation)	Number of cases*	%
4 weeks before conception	1	5.3
Conception to 8 weeks†	9	47.4
8 weeks to 12 weeks	3	15.8
12 weeks to 24 weeks	2	10.5
24 weeks to 36 weeks	1	5.3

*: no rash in 3 cases; †: time of conception was estimated from the last menstrual period.

Table 2. Anthropometric measurement of the 19 infants with congenital rubella syndrome at birth

Parameters	Number
Birth weight (kg)	
1.5-1.9	3
2.0-2.4	8
2.5-3.0	8
Length (cm)	
47	5
48	6
49	4
50	4
Occipito-frontal circumference (cm)	
30	3
31	4
32	6
33	3
35	2
37	1

Table 3. Systemic manifestations of congenital rubella syndrome

Clinical manifestations	Number of cases	%
Cataract	18	94.7
Hearing impairment	14	73.9
Microcephaly	13	68.4
Patent ductus arteriosus	11	57.9
Low birth weight	10	52.6
Ventricular septal defect	4	21.1
Hepatosplenomegaly	4	21.1
Thrombocytopenia	2	10.5
Glaucoma	1	5.3

Table 4. Annual incidence of clinically diagnosed cases of congenital rubella syndrome in this study

Year	Positive number (%)	Negative number (%)
2000	0 (0.0)	1600 (9.8)
2001	3 (15.8)	2095 (12.8)
2002	1 (5.3)	1985 (12.1)
2003	0 (0.0)	1882 (11.5)
2004	2 (10.5)	1787 (10.9)
2005	3 (15.8)	2297 (14.0)
2006	5 (26.3)	2430 (14.8)
2007	5 (26.3)	2295 (14.0)
Total	19 (100.0)	16371 (100.0)

$\chi^2=8.68$; $P=0.28$.

Results

There were 16 394 babies delivered in the UPTH from January 2000 to December 2007. Of these babies, 19 were clinically diagnosed as having CRS, with an incidence of 1.2 per 1000 live births. None of them had laboratory confirmation because serology was not available. All were infants with a mean age of 5.1±3.2 months (range: 1-11 months). There were 12 males and 7 females giving a male to female ratio of 1.7:1. Seventy-five percent of the mothers had a history of presumptive rubella during the first trimester of pregnancy evidenced clinically by the appearance of body rashes (Table 1). The anthropometric measurements of the study group are shown in Table 2. Eleven of the 19 babies with CRS were low birth weight; the mean birth weight was 2.4± 0.5 kg (range: 1.7-3.5 kg). The mean length and occipito-frontal circumference (OFC) of the babies were 48.4±1.1 cm and 32.2±1.8 cm, respectively. Cataract was noticed to be the most prominent systemic manifestation in 18 of the 19 CRS babies recorded, and hearing impairment in 14. Bony changes were not documented in all babies. Other clinical manifestations of the babies are shown in Table 3. There was a surge in the number of babies with CRS from 2004 to 2007; however, this was not statistically significant (χ^2=8.68, P=0.28) (Table 4). Unfortunately, long-term outcome of these infants was not available.

Discussion

In this study, 19 infants were clinically diagnosed with CRS in an 8-year period in a tertiary hospital in Nigeria. In our study, three quarters of apparent maternal infections occurred in the first trimester of pregnancy, which is in keeping with the pattern reported elsewhere.[16] Infection during the first trimester of pregnancy carries a significant risk of abortion and teratogenic effects.[16] The severity of the damage to the fetus depends upon the virulence of the organism and the timing of fetal infection. In surviving infants, the clinical manifestations of CRS are numerous: deafness, cardiac disease, mental retardation, eye defects and insulin dependent diabetes mellitus.[16] Early diagnosis will facilitate early intervention for specific disabilities.

Rubella infection causes high morbidity in infants, especially ocular manifestation. Rubella cataract is the most common ocular sign; it accounts for 94.7% of cases in our study. Congenital glaucoma is an infrequent finding following maternal rubella.[17] It is, therefore, not surprising to have only 1 (5.6%) case of glaucoma in our series.

In this study, 14 of the 19 babies with CRS had hearing impairment. Previous studies on the etiological factors for deafness indicated maternal rubella as a high risk prenatal factor for congenital deafness.[18] Peckham et al[19] studied children with sensorineural deafness and found 24% had CRS. In another study on 75 children with deafness due to embryopathy from maternal rubella, 15 children showed an interauricular auditory functional asymmetry, which is one of the elements of etiological diagnosis and enables better adaptation of a hearing aid for rubella-induced deafness.[20] A Nigerian study found that 26 of 267 deaf children had clinical features suggestive of CRS.[21] Distraction testing was used to diagnose hearing impairment in our series, but it may not be very accurate. Two newer objective methods used to test infant hearing in industrialized countries are otoacoustic emission (OAE) and auditory brainstem response (ABR), which have been shown to have a sensitivity of 90% and a specificity of 91% for hospital screening of neonates.[22,23] These newer screening tests are not available in our facility.

Cardiovascular defects with maternal infection occur between the 3rd and 12th week of gestation, and the most common defects include patent ductus arteriosus, stenosis of the pulmonary artery and its branches, and septal defects.[18] In our study, patent ductus arteriosus occurred in over half the cases. Diagnosis was based on clinical manifestation of a continuous murmur at the left upper sternal border and echocardiographic findings. This finding is similar to previous reports.[17,18]

Brain damage in congenital rubella infection also occurs between the 3rd and 16th week of gestation, causing mild to severe mental retardation with microcephaly and spastic diplegia.[24] Gross structural malformations are rare; instead, there are ischemic damage and variable microcephaly. In our study, 13 (68.4%) of the cases were microcephalic, which is consistent with the concept that the virus can infect the neuroepithelium and reduce cell proliferation.[24]

A constant feature of CRS is fetal growth retardation, perhaps due to reduced or slower cell division in infected cells. In a study,[24] birth weights were 65% of control values, and cell counts of organs from CRS autopsy material revealed that the number of parenchymal cells in the heart, liver, pancreas, and adrenals were reduced by 30%-80%. Our results showed that 11 (57.9%) of the patients were low birth weight. The low birth weight in patients with congenital rubella infection may be due to placental impairment and vascular insufficiency.[24]

The incidence of clinically diagnosed CRS in our study was 1.2 per 1000 live births which compares favorably with 0.8 per 1000 live births in a Ghanaian

study.[25] CRS has not previously been reported from West Africa, although two reports from Nigeria found that 9 of 41 infants with patent ductus arteriosus[26] and 67 of 267 deaf children[21] had additional clinical features suggestive of CRS.

Limitation of this study was that only clinical diagnosis was used for both maternal rubella infection and CRS because serology is not available. It is possible that many cases of CRS were missed because the study was retrospective and not all CRS patients might have obvious clinical manifestations.

In conclusion, many conditions with significant disease burdens compete for limited public health attention and funding. The burden of disease due to CRS is not well appreciated. The disability burden from blindness, deafness, mental retardation, and cardiac defects may be partly due to CRS that has not been diagnosed. Because the burden of chronic disability due to congenital fetal infection causes serious multisystemic malformations resulting in severe morbidity and mortality, there is a need to mount effective CRS surveillance. All infants with unexplained microcephaly, hearing impairment, cataract, glaucoma, patent ductus arteriosus, splenomegaly, thrombocytopenia or radiolucent bone disease should be investigated even if maternal immunity to rubella was documented prior to or during pregnancy. Also, vaccination against rubella to prevent infection should be recommended for all women of childbearing age who do not have documented proof of prior immunization and who do not demonstrate antibodies from natural infection or prior immunization. Pregnant mothers should have routine screening for rubella during antenatal care and susceptible mothers should be offered rubella immunization after delivery. Proper immunization nearly always prevents the disease. A greater awareness of various aspects of CRS in our country is the need of hours. Combination of mumps, measles and rubella will be cost effective and attractive. We therefore recommend universal screening and follow-up vaccination of susceptible females and include rubella immunization in the routine national program on immunization with either single or combined vaccination.

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